

CLINICAL TRIAL PROTOCOL

PHOSPHATE Trial

Pragmatic randomised trial of High Or Standard PHosphAte Targets in End-stage kidney disease

Short title: PHOSPHATE Study

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Protocol Number: AKTN 17.02

Trial Registration: Clinicaltrials.gov NCT03573089

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This protocol has been prepared in accordance with the SPIRIT statement: www.spirit-statement.org/

Sponsor Signatory:



Dr Thomas F Hiemstra
PHOSPHATE Global Trial Management Committee

4th April 2019
Date

Site Principal Investigator Agreement

The following statements refer to the current and future approved versions of the PHOSPHATE trial protocol.

- I agree the Intellectual Property contained within this protocol belongs to The University of Queensland and that the protocol will only be used, distributed or discussed in the context of conducting of the PHOSPHATE trial.
- I have read this protocol and agree that it contains all necessary details for carrying out the study as described.
- I will conduct this protocol as outlined herein, including all statements regarding confidentiality.
- I will make all reasonable efforts to complete the study within the time designated.
- I will provide copies of the protocol and all information provided by the Trial Management Committee (TMC) or the Regional Coordinating Centre representative to site study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study.
- I understand that the study may be terminated or enrolment suspended at any time, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.
- I agree to conduct this study in full accordance with all applicable regulations and the principles of the International Conference on Harmonization guidelines on Good Clinical Practice (ICH GCP).

Site Principal Investigator Name: _____

Site Principal Investigator Signature: _____

Date Signed: _____

STUDY SYNOPSIS

Title	Pragmatic randomised trial of High Or Standard PHosphAte Targets in End-stage kidney disease (PHOSPHATE)
Short Title	PHOSPHATE study
Clinical Phase	III
Principal Investigators	Prof Thomas Hiemstra, Prof Patrick Mark Prof Alastair Hutchison A/Prof Ron Wald, A/Prof Mike Walsh A/Prof Sunil Badve, Prof Suetonia Palmer,
Trial Sponsors	Australia and New Zealand: The University of Queensland acting through Australasian Kidney Trials Network (AKTN) The United Kingdom: Cambridge Clinical Trials Unit Canada: Applied Health Research Centre
Sample Size	3,600
Recruitment Period	3 years
Follow up	Until 1,190 study endpoints have been achieved
Study Duration	5 years
Concise Background	Hyperphosphataemia is highly prevalent in patients with End Stage Kidney Disease (ESKD) and associated with increased mortality risk. Clinical Practice Guidelines suggest lowering elevated phosphate levels towards the normal range (level 2C suggestion). However, trial data demonstrating that treatments that lower serum phosphate will improve patient-centred outcomes are lacking.
Study Design	Investigator-initiated, international, multi-centre, prospective, randomised, open-label, parallel-group, superiority, and pragmatic large simple trial (LST).
Primary Study Objective	To determine if, compared to a strategy of liberalised serum phosphate control, intensive phosphate lowering aimed at reduction of serum phosphate concentration towards the normal level (≤ 1.50

	mmol/L) reduces the risk of fatal or non-fatal major adverse cardiovascular events in ESKD patients receiving dialysis.
Primary Outcome Measure	Time to a composite endpoint of cardiovascular death, non-fatal myocardial infarction, coronary revascularization, stroke, or peripheral arterial event.

Secondary Outcome Measures	<ul style="list-style-type: none"> ● Time to individual components of the primary composite endpoint, ● Time to all-cause death, ● All cause hospitalisation, ● Utility-based quality of life EQ-5D-5L
Inclusion Criteria	<ol style="list-style-type: none"> 1. Age ≥ 45 years, or Age ≥ 18 years with diabetes, 2. ESKD treated with haemodialysis, or peritoneal dialysis, for at least 3 months, 3. Prescribed at least one phosphate-lowering medication at any dose. 4. Able to provide informed consent
Exclusion Criteria	<ol style="list-style-type: none"> 1. Elective kidney transplantation scheduled, 2. Concomitant major illness / comorbidity that may result in death in the next 6 months in the view of the treating physician, 3. Participation in an interventional study that is likely to affect serum phosphate concentration.
Treatment Description	<p><u>Experimental intervention:</u> Strategy of intensive serum phosphate reduction to ≤ 1.50 mmol/L</p> <p><u>Control intervention:</u> Strategy of liberalised serum phosphate control.</p> <p>In the intensive phosphate control arm, phosphate-lowering treatments will be used for normalisation of serum phosphate concentration (≤ 1.50 mmol/L). In the liberalised phosphate control arm, phosphate-lowering medications will be discontinued and phosphate-lowering treatments will be used only if serum phosphate concentration exceeds 2.50 mmol/L. In both trial arms, phosphate-lowering treatments, including dietary phosphate restriction, phosphate-lowering medications and optimisation of dialysis regimen will be at the treating physician's discretion and local practice.</p>

Safety Monitoring	Study endpoints including of cardiovascular death, all-cause death, non-fatal myocardial infarction, coronary revascularisation, stroke, peripheral arterial events and all cause hospitalisation plus Serious Adverse Events rated as possibly or probably related to the randomised study treatment will be reported to and monitored by the DSMB.
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ABBREVIATIONS

1,25 (OH) ₂ D	1,25-dihydroxyvitamin D
ADR	Adverse Drug Reactions
AKTN	Australasian Kidney Trials Network
ANZ	Australia and New Zealand
AVCC	Australian Vice Chancellors' Committee
CARI	Caring for Australasians with Renal Insufficiency;
CI	Confidence interval
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease Mineral and Bone Disorder
CSN	Canadian Society of Nephrology;
DSMB	Data Safety Monitoring Board
ESKD	End-stage kidney disease
FGF-23	Fibroblast growth factor 23
GCP	Good Clinical Practice
GMC	Global Trial Management Committee
HR	Hazard ratio
ICH	International Committee for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
KDIGO	Kidney Disease: Improving Global Outcomes
LST	Large simple trial
MBS	Medical Benefits Scheme
mg/dL	Milligrams per decilitre
mmol/L	millimoles per litre
NHMRC	National Health and Medical Research Council
NKF KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PBS	Pharmaceutical Benefits Scheme
PICF	Participant Information and Consent Form
PO ₄	Phosphate
RCC	Regional Coordinating Centre
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SD	Standard deviation
SONG	Standardised Outcomes in Nephrology
SPRINT	Systolic Blood Pressure Intervention Trial
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TARGET	Two phosphAte taRGETs in End-stage renal disease Trial
TMC	Trial Management Committee
UK	United Kingdom
USA	United State of America

1. ADMINISTRATION INFORMATION

1.1 *Trial/Study Registration*

The trial has been registered on ClinicalTrial.gov Registry [NCT03573089](https://clinicaltrials.gov/ct2/show/study/NCT03573089).

1.2 *Funding*

The study is funded from number of sources including country and state-based government funding bodies, non-restricted pharmaceutical company grants and national kidney disease bodies. Further funding will be sourced based on the success of pending applications and trial/country requirements.

1.3 *Roles and Responsibilities*

1.3.1 Protocol Development

The study protocol has been developed by the Global Trial Management Committee comprising of investigators from Australia, New Zealand, Canada and the United Kingdom.

1.3.2 Study Sponsor

The Regional Coordinating Centres are responsible for establishing a suitable study sponsor within their own region.

The AKTN will be responsible for convening and managing the Global Trial Management Committee. AKTN will also be responsible for developing and maintaining charters for the Global Trial Management Committee, and Data and Safety Monitoring Board.

AKTN will be responsible for reporting to the Global Trial Management Committee who in turn will be responsible for the oversight of the study.

1.3.3 Global Trial Management Committee (GMC)

The Global Trial Management Committee (GMC) has ultimate responsibility for the study and will oversee the trial. The GMC will be responsible for study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The GMC will have ultimate authority over these activities. The project funders will not have any role in these activities.

Alterations to the Charters may be made by the GMC, providing members have received one week's notice of the proposed changes, and the changes are approved at a duly constituted meeting by a majority vote representing a minimum of fifty-one percent of the eligible voting members.

Table 1.1. PHOSPHATE Global Trial Management Committee Membership

Dr Thomas Hiemstra (co-chair)	University of Cambridge, United Kingdom
Professor Patrick Mark	University of Glasgow, United Kingdom
Professor Alastair Hutchison	University of Manchester, United Kingdom
A/Prof Ron Wald (co-chair)	St Michael's Hospital, Toronto, Canada
A/Prof Michael Walsh	McMaster University, Hamilton, Canada
A/Prof Sunil Badve	St George Hospital, Sydney, Australia
Prof Suetonia Palmer	University of Otago, Christchurch, New Zealand

1.3.4 Regional Trial Management Committees (TMCs)

Each region will have a Trial Management Committee led by the Regional Chief Investigator, which will report to the Global Trial Management Committee and the Central Coordinating Centre. The Trial Management Committees will have responsibility for the delivery of the trial in their region and are answerable to the Global Trial Management Committee.

Each region will have a Regional Coordinating Centre (RCC) consisting of the Regional Coordinator and Project Lead for that region. The Regional Coordinating Centres will be responsible for managing and supporting the activities of the Trial Management Committee and regional trial activities.

Figure 1.1 PHOSPHATE Study Global Governance Structure



1.4 Publication policy

To qualify for authorship a contributor is expected to:

- Have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, or the creation of new software used in the work, or have drafted the work and substantially revised it; AND
- Have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND
- Have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

All contributors who meet the first criterion will be given the opportunity to qualify for authorship.

2. STUDY OVERVIEW

Hyperphosphataemia is highly prevalent in patients with end-stage kidney disease (ESKD) and associated with increased mortality risk. The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for chronic kidney disease–mineral and bone disorder (CKD-MBD) *suggest* lowering elevated phosphate levels towards the normal range (level 2C suggestion)^{1,2}. However, trial data demonstrating that treatments that lower serum phosphate prevent patient-centred outcomes are lacking^{1,2}.

The primary objective of the Pragmatic randomised trial of High Or Standard PHosphAte Targets in End-stage kidney disease (PHOSPHATE Study) is to test the hypothesis that phosphate-lowering treatment to reduce serum phosphate level towards the normal level (≤ 1.5 mmol/L) reduces fatal and non-fatal major cardiovascular events in patients receiving dialysis compared to a strategy of liberalised phosphate control with phosphate-lowering treatment for serum phosphate levels ≤ 2.5 mmol/L.

The PHOSPHATE Study is an investigator-initiated, international, multi-centre, prospective, randomised, open-label, parallel-group, superiority, and pragmatic large simple trial (LST). A total of 3600 adult participants (≥ 45 years or ≥ 18 years with diabetes) with ESKD receiving haemodialysis or peritoneal dialysis for at least 3 months and who are prescribed at least one phosphate lowering medication will be recruited from renal units in Australia, New Zealand, Canada and the UK.

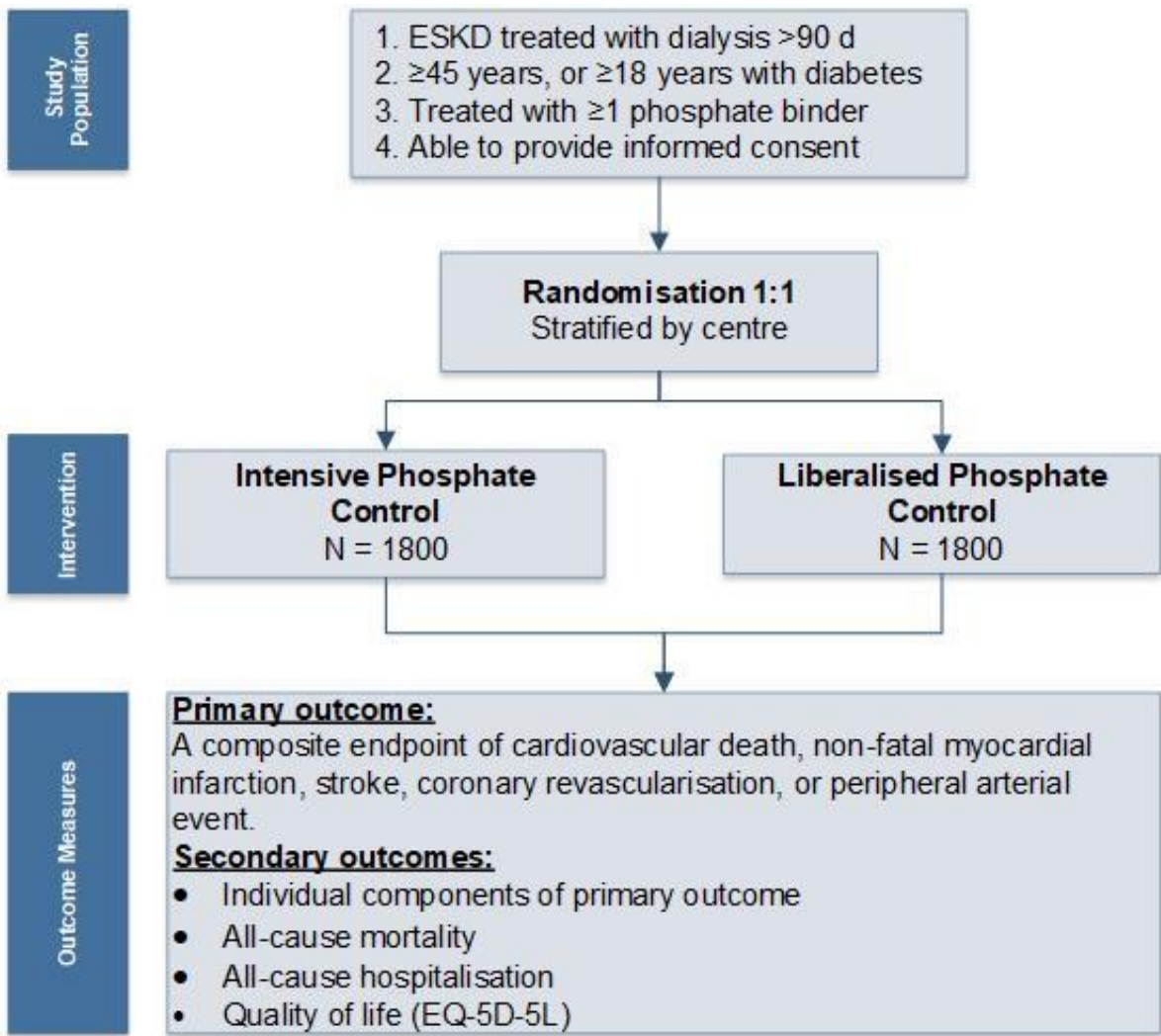
The primary outcome measure is time to a composite endpoint of cardiovascular death or non-fatal major cardiovascular event (myocardial infarction, coronary revascularisation, stroke or peripheral arterial event). The secondary outcome measures are (a) time to a composite of all-cause mortality, (b) individual components of the composite outcomes, (c) quality of life using EQ-5D-5L.

The participants will be randomised to either an intensive phosphate control - phosphate-lowering treatments aimed to intensively lower serum phosphate

concentration towards normal level (≤ 1.50 mmol/L) or to a strategy of liberalised phosphate control – which will be achieved by discontinuation of all phosphate-lowering medications and commence phosphate-lowering treatments only if serum phosphate concentration exceeds 2.50 mmol/L.

All participants will be assessed by their treating nephrologists at 1-3 monthly intervals, which is the standard practice. This is an event-driven trial, and the trial will continue until a total of 1,190 primary endpoint events have occurred. The planned follow-up for the study is unlikely to exceed 5 years from recruitment of the first participant. Participants may be withdrawn from the study earlier if they transfer to another dialysis unit which is not an active study site, or withdraw consent.

Figure 2.1: The study schema



3. BACKGROUND AND RATIONALE

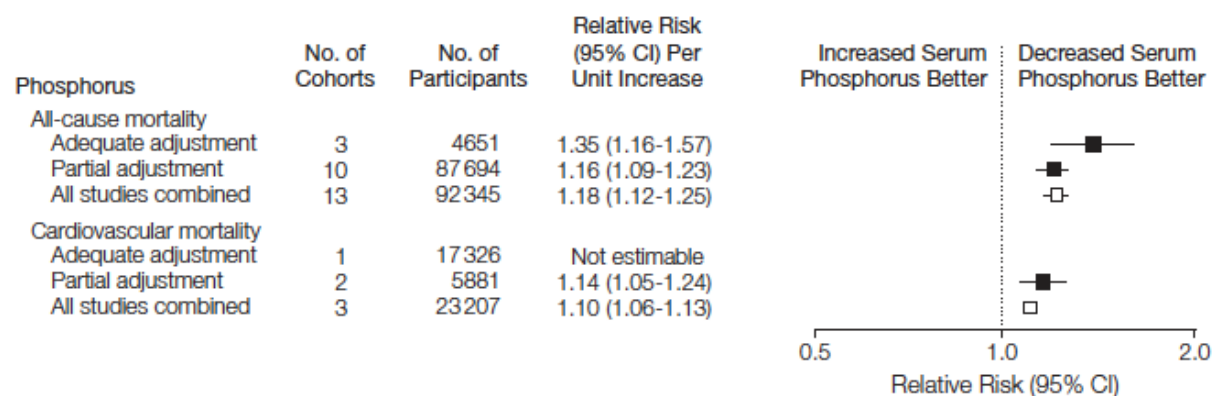
3.1 Outcomes in ESKD patients receiving dialysis

Over three million people worldwide are currently living with ESKD and require renal replacement therapy^{3, 4}. The need for dialysis is projected to double globally by 2030. Although dialysis is a life-sustaining therapy, the death rate among ESKD patients receiving dialysis is unacceptably high at 13 per 100 person-years⁵. Despite the annual cost of more than \$34 billion in United States alone⁶, the age-adjusted mortality rates of dialysis patients is 10 to 100 times higher than that of the general population^{7, 8}. Furthermore, ESKD patients suffer from impaired taste, loss of appetite, malnutrition, and poor quality of life.⁹

3.2 Hyperphosphataemia is associated with increased risk of mortality

Hyperphosphataemia, an inevitable consequence of impaired phosphate homeostasis, is highly prevalent in ESKD patients who require dialysis.^{10, 11} Hyperphosphataemia is a major ‘non-traditional’ risk factor for the excess mortality in ESKD patients.¹² In a systematic review of cohort studies, Palmer et al showed that, every 1 mg/dL (0.323 mmol/L) increase in serum phosphate concentration was associated with 18% and 10% increased risks of all-cause and cardiovascular mortality, respectively (Figure 3.1).¹³

Figure 3.1. Summary estimates for mortality for serum phosphate¹³



Numerous pre-clinical and clinical studies have shown that hyperphosphataemia is associated with the following outcomes: (1) atherosclerotic coronary artery disease, (2) heart failure, (3) left ventricular hypertrophy, (4) calcification of the tunica media of the arterial wall, (5) calcification of cardiac valves and other soft tissues, (6) increased secretion of the phosphaturic hormone, FGF-23, by osteocytes and osteoblasts, (7) decreased serum concentration of 1,25 (OH)₂D, and (8) secondary hyperparathyroidism leading to high-turnover bone disease¹².

3.3 Treatment of hyperphosphataemia in ESKD

Due to these consistently observed associations of hyperphosphataemia with adverse outcomes, all major clinical guidelines, including the KDIGO Clinical Practice

Guidelines for CKD-MBD recommend lowering serum phosphate concentration (Table 3.1).

Table 3.1. Target serum phosphate concentration

Guideline	Target serum phosphate concentration	Level/grade of evidence
NKF KDOQI 2003 ¹⁴	1.13 to 1.78 mmol/L	'Evidence'-based
CARI 2006 ¹⁵	<1.60 mmol/L	Level-III evidence
CSN 2006 ¹⁶	Within the normal range	Grade C
KDIGO 2009 ¹⁷ and 2017 update ²	Lowering elevated levels toward the normal range	2C
UK Renal Association 2015 ¹⁸	0.90 to 1.50 mmol/L	2C

Abbreviations NKF KDOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative; CARI: Caring for Australasians with Renal Insufficiency; CSN: Canadian Society of Nephrology; KDIGO: Kidney Disease: Improving Global Outcomes

The management of hyperphosphataemia in ESKD involves: (1) removal of phosphate by dialysis and residual kidney function, (2) dietary phosphate restriction, and (3) oral phosphate-lowering medications (also commonly known as phosphate-binders). Of these, the first two measures are usually limited in their effects,^{19, 20} such that phosphate-lowering medications are generally prescribed in about 88% of ESKD patients for more complete correction of hyperphosphataemia.²¹

3.4 Requirement for Serum Phosphate Comparison

3.4.1 RCT-level evidence that lower serum phosphate concentrations improve patient-centred outcomes is absent

The strategy to normalise serum phosphate levels has not previously been subjected to rigorous testing in a long term RCT. The KDIGO CKD-MBD Guidelines are entirely based on *low* certainty evidence from large *observational cohort* and *pre-clinical* studies. A network meta-analysis of 77 RCTs (12,562 patients), conducted by Palmer et al demonstrated no high-quality and long-term trials of relevance to phosphate-lowering medications to target serum levels and mortality¹³. Nearly all included trials were comparisons of different phosphate-lowering medications using identical serum phosphate targets, and not comparisons of targeting different phosphate levels. Risks of bias, as assessed by the Cochrane Tool, were frequently high risk, suggesting that the evidence was less certain and had reduced usefulness in clinical decision making. The meta-analysis showed that, compared to placebo, despite their phosphate-lowering effect, there was insufficient evidence that phosphate-lowering treatment reduced mortality.¹² It should be noted that the median sample size was 40 and the median follow-up was 6 months. Furthermore, the median all-cause and cardiovascular mortality rates were only 3.0 and 0.1 per 100

person-years, suggesting that the trials included a relatively low-risk cohort of patients and may not be representative of wider clinical practice.

Palmer et al. further evaluated the correlation between the effects of phosphate-lowering medications on phosphate reduction and mortality in another systematic review.¹³ This study showed that there was no detectable or consistent association between the treatment-induced reduction in serum phosphate (measured as either end-of-study serum phosphate or achievement of a lower serum phosphate target) and mortality. Therefore, evidence for serum phosphate as a valid surrogate endpoint in ESKD is currently insufficient to reliably inform care. In view of low certainty evidence and widespread prescribing, the KDIGO Clinical Practice Guidelines explicitly highlighted the need for a “prospective trial comparing two different phosphate targets”². In addition, this topic has been prioritised by the UK Kidney Research Consortium as one of the 3 top priority questions in nephrology to be advanced to national funding bodies and endorsed by the UK Government²².

3.4.2 Treatment with phosphate-lowering medications is associated with significantly increased pill burden and non-adherence, and poor quality of life

The median daily pill burden in dialysis patients is 19, and phosphate-lowering medications account for 50% of the total pill burden.¹⁴ In a large study, 64%, 37%, 20%, and 10% of haemodialysis patients were taking ≥ 6 , ≥ 9 , ≥ 12 , and ≥ 15 phosphate-lowering medication pills per day, respectively.¹⁵ Self-reported adherence to phosphate-lowering medications varies between 38% to 55%.^{14, 16} Higher pill burden is associated with lower quality of life in ESKD patients.¹⁴

3.4.3 Phosphate-lowering medications are associated with substantial adverse effects

Common adverse effects of phosphate-lowering medications are described in Table 3.2.¹⁷

Table 3.2. Common adverse effects of phosphate-lowering medications

Drug	Adverse effects
Aluminium hydroxide	Potential risk of dementia, microcytic anaemia, osteomalacia, gastrointestinal effects, need to monitor serum aluminium
Calcium carbonate	Gastrointestinal effects (22%), hypercalcaemia (10%), possible vascular calcification, dry mouth, unpalatable
Sevelamer	Gastrointestinal effects (38%), metabolic acidosis (34%)
Lanthanum	Gastrointestinal effects (8%), peripheral oedema (24%), myalgia (21%)
Sucroferric oxyhydroxide	Diarrhoea (6% to 24%), darkening of stools (12% to 16%)

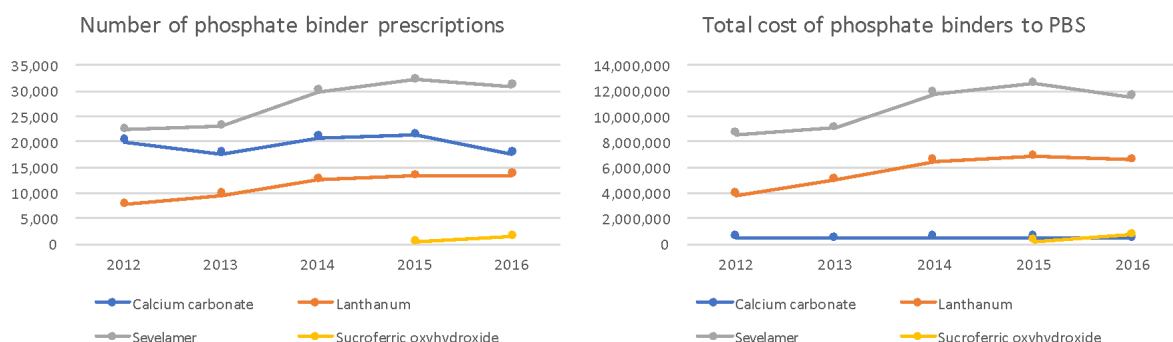
3.4.4 Serum phosphate is a biomarker with little or no relevance to patients

In a study conducted by using the nominal group technique involving 82 patients and caregivers in Australia and Canada, biochemical outcomes, including phosphate, ranked low on their priorities for outcomes.¹⁸ Patients described biochemical outcomes as “objective” measures “doctors tell you about” but are not “necessarily experienced” by patients. This study and an international Delphi survey (involving 1,181 participants: 202 patients/caregivers, 979 health professionals; from 73 countries) clearly showed that biochemical markers may have lower relevance to patients or their caregivers, and health professionals.¹⁹

3.4.5 Phosphate-lowering medications are a significant financial burden to patients and governments

In Australia, between 2012 and 2016, total PBS spending on all Pharmaceutical Benefit Scheme (PBS)-listed phosphate binders was A\$84,978,017 (Figure 3.2). Between 2012 and 2016, the total number of phosphate-lowering medication prescriptions and total PBS spending of PBS-listed phosphate-lowering medications per annum increased by 126% and 149%, respectively. *If the same trend continues, the phosphate-lowering medications’ cost to the Australian government over the next 10 years will increase to more than A\$315 million, in today’s dollars.* In the USA, Medicare expenditures for phosphate-lowering medications for dialysis patients enrolled in Medicare Part D was US\$840.53 million (US\$ >1.5 billion for dialysis and non-dialysisKD combined) in 2014 alone.^{21, 22} Phosphate-lowering medications represented 37% of total Medicare Part D spending for dialysis patients in 2014.²¹ In addition, the annual out-of-pocket cost of aluminium hydroxide, a commonly prescribed phosphate-lowering medication in Australia, for an individual patient is A\$262.²⁰

Figure 3.2. Prescription numbers of (left panel) and spending on (right panel) phosphate-lowering medications in Australia (source: Medicare Statistics, Department of Human Services)



3.5 Summary and justification of the study

Although hyperphosphatemia is associated with increased mortality risk in ESKD patients, the KDIGO Guidelines suggestion of ‘lowering elevated phosphate levels towards the normal range’ is based on low quality evidence. Phosphate-lowering medications, the mainstay of phosphate-lowering treatment, are associated with

substantially increased pill burden and non-adherence, adverse gastrointestinal symptoms, poor quality of life; and are costly to individual patients and health systems. However, RCT evidence demonstrating that treatments that lower serum phosphate will improve patient-centred outcomes, such as survival and how patients feel or function, is insufficient to guide policy and drug prescribing. Currently available evidence demonstrates only *an association* and *not* a cause-effect relationship between phosphate and clinical outcomes in patients with ESKD.

An editorial justly asked “How can a medication class achieve 75% prevalence of use in a chronic disease population without evidence of clinical benefit”; and concluded that “Clinical trials of phosphate binders are the *only* way to determine the potential benefits and harms of these commonly used and expensive medications”.²³ Therefore, an adequately powered RCT is urgently required to evaluate whether reduction of serum phosphate concentration toward the normal level with phosphate-lowering medications reduces the risk of cardiovascular death or non-fatal major cardiovascular events; improves physical health, fatigue, and patient satisfaction in ESKD patients receiving dialysis; and is cost-effective.

Justification for designing a non-inferiority trial to evaluate the non-inferiority of the liberal phosphate target over the intensive phosphate control.

A non-inferiority trial requires that superior efficacy of the standard treatment over placebo has been convincingly established for a given indication in previous randomised trials²³. Although the strategy of intensive phosphate control has been suggested by the KDIGO Clinical Practice Guidelines for CKD-MBD, it has never been evaluated in a randomised trial. This level 2C suggestion is based entirely on low quality evidence from observational cohort studies and not randomised controlled trials. There is, therefore, currently insufficient evidence to design and justify a non-inferiority trial to evaluate the non-inferiority of the liberal phosphate target over the intensive phosphate control.

3.5.1 Preliminary work – Feasibility Trials

There have been two feasibility trials (led by Hutchison in the UK and Wald in Canada) comparing an intensive versus liberalised phosphate control strategies in ESKD patients (Table 3.3)²⁴⁻²⁶. These studies importantly demonstrated that it is feasible to enrol dialysis patients in phosphate target trials; and achieve and maintain separation of serum phosphate levels between the two trial arms.

Table 3.3. Summary of two phosphate target feasibility trials in ESKD patients

	TARGET ²⁴	SPIRIT ^{25, 26}
Setting	6 centres in Canada	2 centres in the UK
Total participants	104	104
Study population	Age>18 yrs, haemodialysis >3mo	Age>30 yrs, any dialysis > 6mo
Follow-up	26 weeks	13 months

Phosphate-lowering medications	Only calcium carbonate	Sevelamer, lanthanum
Intensive PO ₄ control/ achieved level	0.75 – 1.50 mmol/L Mean ± SD 1.46 ± 0.36	0.80 – 1.40 mmol/L Mean ± SD 1.64 ± 0.4
Liberalised PO ₄ control/ achieved level	2.00 – 2.50 mmol/L Mean ± SD 1.95 ± 0.45	1.80 – 2.40 mmol/L Mean ± SD 2.00 ± 0.4
Achieved difference in PO ₄	0.47 mmol/L (95%CI 0.36 to 0.56)	Mean difference >0.32 mmol/L

The PHOSPHATE Study builds on evidence from these two feasibility trials and has evolved into a large global collaborative trial with clinical endpoints. In addition, a feasibility survey in Australia across 33 renal units demonstrated strong support with 97% of sites were interested to participate in a multi-centre trial and to recruit a minimum of 20 participants. In New Zealand, eight renal units indicated support to recruit 100 participants. The PHOSPHATE trial will be conducted simultaneously in Australia, New Zealand, Canada and the UK.

4. STUDY HYPOTHESIS AND OBJECTIVES

4.1 Study hypothesis

Compared to a strategy of liberalised phosphate control, intensive phosphate lowering aimed at normalisation (≤ 1.50 mmol/L) reduces the risk of fatal or non-fatal major cardiovascular events in ESKD patients receiving dialysis.

4.2 Study objectives

4.2.1 Primary objectives

To test the hypothesis that, compared to a strategy of liberalised phosphate control, intensive phosphate-lowering aimed at reduction of serum phosphate concentration towards the normal level (≤ 1.50 mmol/L) reduces the risk of fatal or non-fatal major cardiovascular events in ESKD patients receiving dialysis. This hypothesis will be tested using a composite outcome including cardiovascular death, non-fatal myocardial infarction, coronary revascularisation, non-fatal stroke, and peripheral arterial event (revascularisation or amputation).

4.2.2 Secondary objectives

The trial will examine the effect of intensive reduction of serum phosphate level on all-cause mortality, individual components of the composite outcome, all-cause hospitalisation, and utility-based quality of life.

5. TRIAL DESIGN

5.1 Overall study design

The PHOSPHATE Study is an investigator-initiated, international, multi-centre, prospective, randomised, open-label, parallel-group, superiority, and pragmatic large simple trial (LST). A total of 3600 adult participants on phosphate-lowering

medications will be recruited from the participating renal units from Australia, New Zealand, Canada and the UK.

The participants will be randomised to either an intensive phosphate control - phosphate-lowering treatments aimed to intensively lower serum phosphate concentration towards normal level (≤ 1.50 mmol/L) or to a strategy of liberalised phosphate control - which will be achieved by discontinuation of all phosphate-lowering medications and commencing phosphate-lowering treatments only if serum phosphate concentration exceeds 2.50 mmol/L.

5.2 Study population

5.2.1 Inclusion Criteria

To be eligible to participate in this trial, participants need to satisfy ALL of these inclusion criteria:

1. Age ≥ 45 years, or Age ≥ 18 years with diabetes,
2. ESKD treated with haemodialysis or peritoneal dialysis, for at least 3 months,
3. Prescribed at least one phosphate-lowering medication at any dose.
4. Able to provide informed consent

5.2.2 Exclusion Criteria

Potential participants must have NONE of the following exclusion criteria:

1. Elective kidney transplantation scheduled within the next 6 months,
2. Concomitant major illness / comorbidity likely to result in death in the next 6 months in the view of the treating physician,
3. Participation in an interventional study that is likely to affect serum phosphate concentration.

5.2.3 Screening log

A screening log that lists all patients evaluated or considered for enrolment in the PHOSPHATE Study will be completed by trial study staff at each study site. The log will record all screened patients, whether or not they are enrolled into the study. For each patient considered for study entry the screening log will record if the patient was randomised, or the reason they were not enrolled. For example, the reasons for ineligibility (not meeting specific inclusion criteria; meeting one or more exclusion criteria) or the reasons for eligible patients not being enrolled in the study (e.g. patient refusal) will be recorded.

5.3 Comparators

5.3.1 Experimental intervention: Intensive phosphate control (≤ 1.50 mmol/L)

The intensive serum phosphate control (≤ 1.50 mmol/L) will be achieved by the treating physician by using phosphate-lowering treatments (including dietary phosphate restriction, phosphate-lowering medications, and optimisation of dialysis regimen) aimed to intensively lower serum phosphate concentration towards normal level (≤ 1.50 mmol/L).

Since the phosphate concentration in this group is the same as that recommended by the KDIGO Guidelines (<1.50 mmol/L), this group represents the contemporary standard of care. Treating nephrologists or site investigators will be allowed to prescribe phosphate-lowering medications of their choice or local availability.

5.3.2 Control intervention: Strategy of liberalised phosphate control

All phosphate-lowering medications will be discontinued. Phosphate-lowering treatments (including dietary phosphate restriction, phosphate-lowering medications, and optimisation of dialysis regimen) will be commenced only if serum phosphate concentration exceeds 2.50 mmol/L. Treating physicians will be allowed to use phosphate-lowering medications of their choice and local availability to keep serum phosphate levels below 2.50 mmol/L and these medications will be discontinued if serum phosphate falls to 2.00 mmol/L or lower.

Justification for not mandating specific phosphate-lowering medications

The PHOSPHATE Study is testing two treatment strategies around phosphate lowering and is not testing specific phosphate-lowering medications. The choice of phosphate-lowering medication, if one is needed, will be at the discretion of clinicians.

This approach is similar to that of the Systolic Blood Pressure Intervention Trial (SPRINT), which compared the benefit of treatment of intensive blood pressure control (systolic blood pressure <120 mm Hg: experimental group) with less intensive blood pressure control (systolic blood pressure <140 mm Hg: control group)²⁷. The SPRINT was designed to compare strategies of intensive vs. less intensive systolic blood pressure control without mandating specific antihypertensive classes or agents to reach the treatment goal. Clinicians were allowed to use a wide array of drugs from multiple antihypertensive classes to achieve these blood pressure targets. Similar to the SPRINT, participants in the intensive phosphate control group are likely to receive phosphate-lowering medications as a single agent or in combinations. The network meta-analysis conducted by Palmer and colleagues showed that there were no statistical differences in all-cause or cardiovascular mortality risks between different phosphate-lowering medications. Therefore, treating nephrologists or site investigators will be allowed to prescribe phosphate-lowering medications of their choice or local availability instead of mandating specific phosphate-lowering medications.

5.3.3 Concurrent management

Dietary advice

All participants in the trial will receive dietary advice according to the usual standard of care and local practice. However, in the liberalised phosphate control group, advice specifically related to dietary phosphate restriction will be omitted unless the serum phosphate concentration exceeds 2.50 mmol/L.

Usual care

Other than the allocated trial intervention, all other aspects of care provided to participants will follow usual local practice. All participants will receive their usual

ESKD management as per local standard of care, including, but not limited to dialysis modality/regimen/access, dietary advice/intervention, transplant planning and management of target serum calcium and parathyroid hormone concentrations, malnutrition, hypertension, anaemia, oedema, and cardiovascular risk factors and disease. Patients can be dialysed in any setting (home, facility, community-house, home assisted, satellite).

5.3.4 Discontinuation/modification of trial phosphate strategy

The trial phosphate strategy may be temporarily or permanently discontinued in any of the following situations:

- serious adverse event thought likely due to the trial phosphate strategy ,
- pregnancy or condition where continuation of the trial phosphate strategy is not in the participant's best interests (e.g. adoption of palliative/conservative care),
- at participant's or treating physician's request.

Even if the trial phosphate control strategy to which the participant has been allocated has been modified or discontinued, the participant **should remain** in the trial and be followed until the end of study, (except where the participant withdraws consent to participate in the study) and analyses will be conducted using an intention-to-treat principle. More information on early withdrawal from the study is described in section 5.6.

5.3.5 Adherence to intervention

Monitoring of the serum phosphate concentration will be according to the usual standard of care at dialysis units. No additional serum phosphate monitoring will be required for trial conduct. Patients will be contacted via phone or in-person to change phosphate-lowering medication depending on the arm to which they are allocated

5.4 Randomisation

Participants will be randomised in a 1:1 ratio via a web-based randomisation system embedded within a trial database administered by the AKTN (Australian, New Zealand, and Canadian centres) or the Cambridge Clinical Trials Unit (UK centres). The systems will be accessible by centre staff via a password-protected encrypted website interface. Randomisation will be stratified by centre and use random permuted blocks to ensure similar numbers of participants in the two intervention groups at each centre.

5.5 Blinding

5.5.1 Who will be blinded after assignment to interventions

Due to the nature of the trial interventions, participants, treating nephrologists and investigators will not be blinded. Outcome assessors, including trial statisticians and principal investigators will remain blinded.

5.6 Duration of follow up and early withdrawal from the study

All participants enrolled in the study will be followed until a total of 1,190 study endpoints have occurred. The planned follow-up for the study is unlikely to exceed 5 years from recruitment of the first participant. A participant may be withdrawn from the study earlier in any of the following situations:

- withdrawal of consent to remain in the trial,
- transfer to another renal unit which is not an active study site,
- loss to follow up

Permanent cessation of trial phosphate target does not constitute participant withdrawal. If the trial phosphate strategy is stopped permanently for any reason, the participant is to continue participating and data collection will continue until the final study follow-up time point. If a participant expresses a wish not to complete questionnaires, they should remain in the study and other trial-related data will be obtained from medical records review, and/or other treating physicians. Every effort will be made to determine each participant's status on the components of the primary outcome. Consent forms at study entry will also include consent to data linkage and all other legal means to determine survival status. The integrity and validity of the study relies on following up randomised participants until the target number of primary outcome events has occurred.

5.7 Outcome measures

5.7.1 Primary outcome measure

Time to a composite endpoint of the following events:

1. Cardiovascular death
2. Non-fatal myocardial infarction
3. Coronary revascularisation
4. Stroke
5. Peripheral arterial event

5.7.2 Secondary outcome measures

1. Individual components of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, coronary revascularisation, non-fatal stroke and peripheral arterial event)
2. Time to all-cause death
3. All-cause hospitalisation
4. Quality of life measured using EQ-5D-5L

6. TRIAL PROCEDURES

6.1 Recruitment of participants

Participants will be recruited from renal units that provide a comprehensive nephrology service in Australia, New Zealand, Canada and the UK. Participants must meet the study inclusion criteria and not meet any exclusion criteria.

6.2 Patient consent

Patient consent forms will be approved by the responsible Independent Ethics Committee (IEC) for each participating site prior to the beginning of the trial at the site. A copy of the final approved version will also be filed with the regional coordinating centre, following approval from the IEC and governance office.

If the participant is unable to read the PICF, an impartial witness will be present during the entire discussion and will also be responsible for signing and dating the form on the participants' behalf if he or she is unable to write in English or in the same language used in the consent form. In doing so, the witness attests that the information that was explained to the participant was accurately represented on the consent form and that it was apparently understood by the participant, and that informed consent was freely given by the participant.

After discussing the trial, ample time will be given to the participant, accompanying person or legal representative to enquire about the trial and decide whether to participate. No person involved with the trial will coerce or unduly influence the decision to participate in a trial.

A copy of the signed consent form and the patient information sheet will be supplied to the participant. The original signed consent forms will be filed in the Site Trial Master File, and a copy placed in the patient's hospital medical record as required.

Patient consent must be obtained prior to the randomisation or initiation of any trial procedures, including screening tests to confirm eligibility. Patients will not be randomised until a signed consent form is filed at site.

The Global Trial Management Committee will continue to review the medical literature, and any other relevant information impacting on the continuation of the trial. Consent forms and patient information sheets will be revised should any relevant and important new information become available, and resubmitted for site IEC approval.

6.3 Screening and randomisation

Screening of the potential participants will occur during their usual visit to their treating physician or through the study site's integrated patient database. The potential participant will have an initial consultation with a renal physician to discuss study participation. This will include a preliminary eligibility check.

Randomisation must occur only after obtaining informed consent. Randomisation must occur within one month of obtaining informed consent. This will include a check to ensure that the patient is still eligible.

6.4 Study visits schedule

There will be no designated study visits. All participants will be assessed by their treating nephrologists at 1-3 monthly intervals based on the local standard practice.

6.4.1 Trial-specific investigations

There will be no trial-specific laboratory or radiological investigations. Any investigations will be performed per usual clinical indication. All trial-related titration of phosphate-lowering medications will be based on blood tests that are part of standard dialysis care.

6.5 *Data Collection schedule*

Data collection will be kept to a minimum and focus on baseline data, data for endpoint ascertainment and monitoring separation of serum phosphate levels (Table 6.1). Individual countries may collect additional data (refer to Country Specific Appendices for further details)

Table 6.1 Global Study Data Collection Schedule

Data Collection Timing	Screening	Baseline	3 Monthly	6 Monthly	End of Study
Inclusion/ exclusion criteria	X				
Informed Consent	X				
Randomisation		X			
Demographics		X			
Medical history		X			
Key concomitant medications		X			
Serum phosphate level*		X	X		X
Primary endpoints			X		X
All-cause death			X		X
All-cause hospitalisation			X		X
EQ-5D-5L		X		X	

*A maximum of 3 phosphate results will be entered, at least 4 weeks apart

6.6 Clinical assessment

6.6.1 Baseline demographic characteristics

Date of birth

Sex

Height and weight

Race/Ethnicity

Medical history (diabetes mellitus, myocardial infarction, coronary artery disease, heart failure, stroke, peripheral arterial disease, cancer, parathyroidectomy, calciphylaxis)

Primary cause of kidney disease

Smoking history

Key concomitant medication – phosphate-lowering medication, calcium, nutritional vitamin D, active vitamin D (calcitriol), cinacalcet.

6.6.2 Laboratory procedures and investigations

Local laboratory

The frequency of monitoring of serum phosphate concentration will be according to the usual local standard of care. All dialysis centres monitor serum phosphate concentrations every 1-3 monthly as standard practice. No additional serum phosphate monitoring is required.

Quality of Life

Information on quality of life will be collected using the generic health status instrument, the EQ-5D-5L, at baseline and 6 monthly for at least 2 years.

6.7 Assessment of safety

6.7.1 Definitions

Serious Adverse Event (SAE)

An adverse event (any untoward medical event, see below) is classified as SERIOUS (SAE) if it meets any one of the following criteria:

- Death
- Life-Threatening: The subject/participant was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the subject's/participant's death.
- Hospitalisation (initial or prolonged): Requires admission to the hospital (for 24 hours or more) or prolongation of a hospital stay.
- Disability: Resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the subject's/participant's body function/structure, physical activities or quality of life.
- Congenital Anomaly/Birth Defect
- Important medical events: Other medically important events that, in the opinion of the investigator, may jeopardise the subject/participant or may require intervention to prevent one of the other outcomes listed above.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an adverse event related to an investigational medicinal product that results in death of subject/participant or is life-threatening/disabling AND is unexpected or unanticipated.

6.7.2 Study specific reportable adverse events

Adverse events will be managed as per usual local clinical care practice.

Events that are already being collected as part of the study primary or secondary outcomes will be reported as study endpoints and not as Serious Adverse Events.

Events that are not study endpoints and meet the criteria for an SAE will be reported if judged, in the opinion of the site investigator, possibly or probably related to the randomised phosphate target. SAEs judged not or unlikely related to the randomised phosphate strategy will not be reported because these events are not informative in determining the safety of the study intervention. All events related to adverse pregnancy outcomes, and any congenital anomaly or birth defects will be reported, whether related to randomised phosphate target or not.

Since side effects of all available phosphate-lowering medications that are approved and used widely in clinical practice are well known, ADRs of individual phosphate-lowering medications will not be recorded.

6.7.3 Period of Observation

For the purposes of this study, the period of observation for collection of treatment-related serious adverse events will be from the time of randomisation until the participant's end-of-study visit.

7. STATISTICAL CONSIDERATIONS

7.1 Sample size calculation

A sample size of 3,564 participants was calculated on the basis of the following assumptions: an annual rate of the primary outcome of 13% in the liberalised phosphate control group, a three year recruitment period, a five year total study duration, and 1% loss to follow-up. A two-sided log-rank test with an overall sample size of 3,564 participants has 80% power at the 5% significance level to detect a hazard ratio (HR) of 0.85 (a 15% intervention effect). The overall number of primary outcome events required is 1,190. A sample size of 3,564 participants has more than 90% power to detect a larger 20% intervention effect (HR 0.80). Therefore, the trial aims to enrol 3,600 participants.

7.2 Statistical analysis

The intervention effect for the primary composite outcome will be illustrated by Kaplan–Meier product-limit estimates of the event-free survival time and analysed using a two-sided log-rank test stratified by country (Australia, Canada, New Zealand, and UK). Hazard ratios and corresponding 95% confidence intervals for the intervention effect adjusted for country will be calculated from a Cox proportional-hazards regression model. Intervention group differences according to major subgroups at randomisation (age, gender, country, race, diabetes, cardiovascular disease, time on dialysis) will be examined in Cox regression models incorporating an intervention group by subgroup variable interaction. The intervention effect for time-to-event secondary outcomes will be analysed using the same methods. Intervention groups will be compared on quality of life (EQ-5D-5L) scores using a linear mixed model. If there is substantial censoring due to transplantation and/or death, a joint modelling approach will be used accommodate the informative dropout.

Interim analyses on the primary outcome will be conducted using O'Brien-Fleming boundaries. There will be three interims and a final analysis. The interim analyses will be done when approximately 25%, 50% and 75% of the required events have occurred.

8. DATA MANAGEMENT

PHOSPHATE study data will be captured electronically as outlined in the Country Specific Operations manual. Original consent forms are to be stored locally. Investigators are required to maintain all study documentation, including copies of case report forms, Informed Consent documents, ethics committee approvals and correspondence, participant questionnaires, for a period of fifteen years after the

closure of the trial. Supporting documents for study endpoints and serious adverse events should be filed in the participant source document folder and a copy sent to the coordinating centre.

8.1 Data Sharing

Data sets will be made available to researchers within the PHOSPHATE Study for analysis of sub-studies and country specific outcomes after the primary manuscript has been accepted for publication.

For researchers outside the PHOSPHATE study, individual participant data will be made available upon request to a Data Access Committee, a review board set up to assess proposals based on sound science, benefit-risk balancing and research team expertise. Appropriate data will be made available to approved proposals. This process will be in effect for a period of 2 to 5 years following publication of the main study results. After 5 years, the data will be available in the Sponsor's data warehouse but without investigator support other than deposited metadata.

9. QUALITY ASSURANCE

9.1 Training

Each investigator participating in this study will meet the following criteria:

- Be accessible, interested, and be supported by well organised staff and systems for care management and research requirements.
- Availability of diagnostic facilities to support study data requirements.
- Availability of physician emergency response at all times.
- Adequate time to conduct study.
- Adequate training and experience of personnel to conduct study.
- Adequate training in definition of important end-points of the study
- Ability to recruit enough subjects to conduct study
- Provide evidence of proficiency in the tenets of Good Clinical Practice.

9.2 Site monitoring

This study will be monitored by the regional coordinating centres or their designee in accordance with ICH Good Clinical Practices (GCP), 21CFR Part 312. Study sites may be visited when the progress of the study will be discussed with the principal investigator and the data will be checked for completeness and accuracy. Source documents from which the data are obtained will be made available at the time of review. Progress may be made remotely or by telephone when deemed appropriate.

9.3 Auditing

For the purpose of data validation, the principal investigators will permit a member of the central coordinating centre or its designee to inspect the source data and compare them with the study data. Pre-study audits, interim audits and post study audits may be performed. Notification of these audits will be sent to all investigators in advance.

9.4 Data monitoring

An independent Data and Safety Monitoring Board (DSMB) with a minimum of four and no more than six members will be constituted by the Central Coordinating Centre and operate in accordance with the PHOSPHATE DSMB Charter. Members will have no financial or scientific conflicts of interest with the PHOSPHATE trial. The DSMB Chairperson will be a clinician with extensive clinical trials and DSMB experience. The statistician will be an experienced clinical trials statistician with extensive DSMB experience. Two members, one of whom may be the Chairperson, will be nephrologists with clinical trials and DSMB experience. If the Chairperson is not a cardiovascular expert, an additional clinician with expertise in this medical specialty may be included.

The DSMB remit is to protect the safety of trial participants and the scientific integrity of the trial by monitoring accumulating safety and operational data. The DSMB will also review results from accumulating outcome data with a remit to recommend stopping the trial early for efficacy if in the opinion of members this is warranted by the totality of evidence. The DSMB will make their recommendations to the GMC Chairperson regarding trial continuation and modifications to trial design and procedures while maintaining confidentiality of the accumulating data. The GMC will retain sole decision-making responsibility for modifications to or early stopping of the trial.

10. ETHICS AND DISSEMINATION

10.1 Adherence to regulations and guidelines

The study will be performed in accordance with the 2000 Edinburgh, Scotland Revision of the Declaration of Helsinki, the NHMRC Statement on Human Experimentation, Joint NHMRC/AVCC Statement and Guidelines on Research Practice, applicable ICH guidelines.

10.2 Ethics committee approvals

This protocol and the template informed consent forms contained in Appendices will be reviewed and approved by the coordinating centre and the applicable Independent Ethics Committee [IEC] with respect to scientific content and compliance with applicable research and human subjects' regulations. The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents as well as any subsequent modifications, will also be reviewed and approved by the applicable IEC.

10.3 Modification of the protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by Global Trial Management Committee, and

approved by the IEC prior to implementation and notified to the health authorities in accordance with local regulations.

10.4 Informed consent

Trained Research Staff will introduce the trial to patients. Using the Patient Information and Consent Form (PICF), Research Staff will discuss the trial with the patient in detail. Patients will then be able to have an informed discussion with the participating consultant, and will be encouraged to discuss their potential participation in the trial with family members and close friends. Research staff will obtain written informed consent from patients willing to participate in the trial.

10.5 Protection of patient confidentiality

Patients' records and the data generated by the study will be confidential in line with the recommendations of the competent authority and the relevant privacy legislation(s). Any information that may identify a patient will be excluded from data presented in the public arena. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded identification (ID) number only. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

10.6 Insurance

To be provided through the sponsor in each country.

10.7 Dissemination of results

At the conclusion of the study results will be communicated to participants, Principal Investigators and other study staff via a variety of media including a newsletter, publication in a peer reviewed journal, conference presentation and the Sponsors' websites.

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12. APPENDICES

Appendix 12.1. Summary of Protocol Changes

Version	Affected Section	Changes Made	Rationale

Appendix 12.2. Example of EQ-5D-5L (Australian English)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems with walking around
- I have slight problems with walking around
- I have moderate problems with walking around
- I have severe problems with walking around
- I am unable to walk around

PERSONAL CARE

- I have no problems with washing or dressing myself
- I have slight problems with washing or dressing myself
- I have moderate problems with washing or dressing myself
- I have severe problems with washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

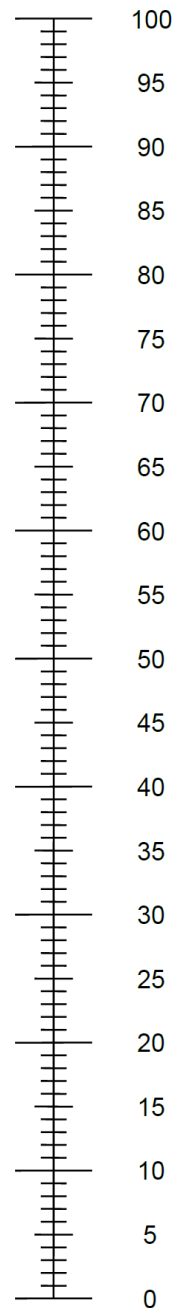
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

Appendix 12.3. Country Specific Appendix

The PHOSPHATE study will be conducted in XXX in accordance with the global PHOSPHATE protocol.

This appendix outlines the specific aspects of implementation of the PHOSPHATE protocol in XXX. For all aspects of the PHOSPHATE study not mentioned in this appendix, the main PHOSPHATE protocol will prevail.

Region:	
Sponsor:	
Trial Management Committee Chair:	
Trial Director:	
Regional Coordinating Centre:	
Exploratory Outcomes: (include country specific visit schedule with all study assessments)	
Country sub-studies:	
Data Management: (Outline methods of data collection to be used in the country)	
Monitoring adherence to phosphate target:	
Data Linkage:	
Endpoint Confirmation:	
Other: Country specific appendices	

Table 12.3 Country Specific Study Data Collection Schedule

Appendix 12.4. Country Specific Master Participant Information and Consent Form