United Kingdom Specific Appendix

The PHOSPHATE study will be conducted in the United Kingdom (UK) in accordance with the global PHOSPHATE protocol.

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

Region:	**United Kingdom**
Sponsor:	**The University of Cambridge and Cambridge University Hospitals NHS Foundation Trust** Research & Development Department (Box 277) Addenbrooke's Hospital, Hills Road Cambridge, CB2 0QQ Telephone: 01223 245151 e-mail: cuh.cctureguLatory@nhs.net
Chief Investigator:	Dr Rona Smith (University of Cambridge) Professor Patrick Mark (University of Glasgow) (Co-lead)
Regional Coordinating Centre:	Cambridge Clinical Trials Unit
UK Trial Personnel:	**Trial Statistician** Dr Simon Bond Cambridge Clinical Trials Unit (Box 111) Addenbrooke's Hospital, Hills Road Cambridge, CB2 0QQ Telephone: 01223 596471 E-mail: simon.bond7@nhs.net **Trial Coordinator** Maulik Patel Cambridge Trials Unit (Box 401) Addenbrooke's Hospital, Hills Road Cambridge, CB2 0QQ Tel: 01223 216809 Email: maulik.patel4@nhs.net

UK Appendix Amendment History

Version Number	History	Date
V1.0	• UK Appendix to Global Protocol	08 July 2021
V2.0	• Updates to the trial assessment timings	17 Nov 2021
V2.1	• Removal of references to EQ5D data sharing with SIMPLIFIED, removal of references to abbreviated PIS use. • The development of the joint SIMPLIFIED-PHOSPHATE PIS-ICF has been removed. • Updates to sponsor's and trial statistician's email address • Updates to trials coordinator's details • Addition of a feasibility section to the protocol as requested by the NIHR	05 Dec 2023

Protocol Signatures

I give my approval for the attached protocol entitled ***"Pragmatic randomised trial of High Or Standard PHosphAte Targets in End-stage kidney disease (PHOSPHATE)"*** Dated 4th April 2019 (v1.0) and the UK specific appendix dated 5th December 2023 (v2.1).

Chief Investigator

Name: Dr Rona Smith

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled ***"Pragmatic randomised trial of High Or Standard PHosphAte Targets in End-stage kidney disease (PHOSPHATE)"*** Dated 4th April 2019 (v1.0) and the UK specific appendix dated 5th December 2023 (v2.1) and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any subsequent amendments of the clinical trial regulations, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name: _____

Signature: _____

Date: _____

Abbreviations

AEs	Adverse events
CKD	Chronic Kidney Disease
CRF	Case Record Form
CTIMP	Clinical Trial of a Medicinal Product
CV	Cardiovascular
eDRIS	electronic Data Research and Innovation Service
ESKF	End Stage Kidney Failure
EPAC	Endpoint Adjudication Committee
EQ5D	EuroQol 5D
GTMC	Global Trial Management Committee
HES	Health Episode Statistics
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
KDIGO	Kidney Disease Improving Global Outcomes
NHS	National Health Service
NIHR	National Institute for Health Research
ONS	Office National Statistics
PEDW	Patient Episode Database for Wales
PI	Principle Investigator
PID	Patient Identifiable data
PTO	Phosphate Trial Office
Qol	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage
SIMPLIFIED	Survival Improvement with Colecalciferol in Patients on Dialysis
SMPC	Summary of Product Characteristics

SMR01	Scottish Morbidity Record
TIA	Transient Ischaemic attack
UKRR	UK Renal Registry
UKRDC	UK Renal Data Collaboration

Contents

1. Background and Rationale

Dialysis is associated with exceptionally high cardiovascular risk and poor quality of life

There are 28,876 patients with Kidney Failure (KF) receiving dialysis in the United Kingdom (UK). [1] Although dialysis is a life-sustaining therapy, the death rate among UK dialysis patients is very high, with one-year age-adjusted survival of only 88% (Figure 1).[2] The leading cause of death is cardiovascular (CV) disease,[3] with a relative risk of 10 to 100 times that of the general population (Figure 2). [4] This risk is not only driven by atherosclerotic deaths but by sudden cardiac death, heart failure and arrhythmias consequent upon increased arterial stiffening from vascular calcification with left ventricular remodelling, indistinguishable from that observed in healthy ageing. Dysregulation of bone mineral homeostasis is thought to be a key modulator of this CV risk burden. [5]

Patients receiving maintenance dialysis experience significant physical, emotional, mental and psychological impairments which are reflected in poor Health Related Quality of Life (HRQoL) scores.[6] Dialysis patients value improved QoL more than they do improved survival.[7,8]

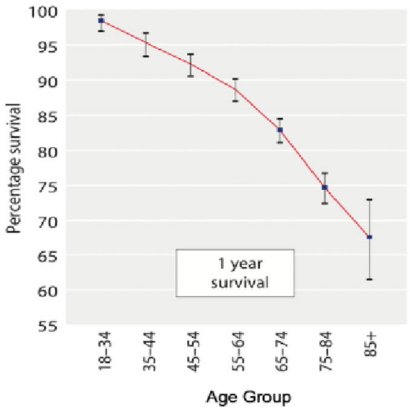

***Figure 1**. One-year survival by age group for incident dialysis patients. Data from the UK Renal Registry.1*

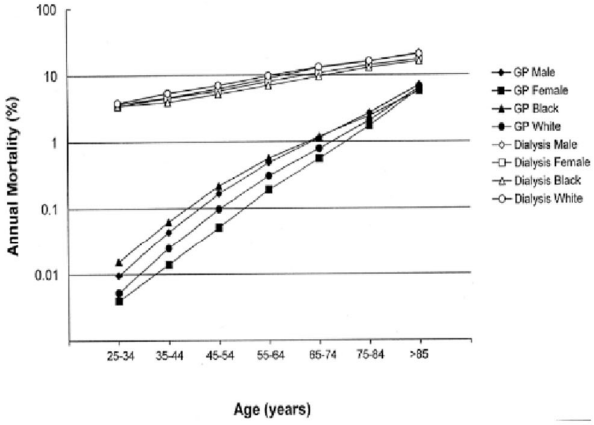

***Figure 2**. Cardiovascular mortality in patients on dialysis compared to non-CKD controls.*

A wide range of interventions currently employed in this population in the NHS, at considerable cost, are aimed at improving survival and quality of life, but have either failed to show any benefit (erythropoiesis stimulating agents,[9] lipid lowering,[10] calcimimetics[11]) or have not been adequately evaluated in randomised trials.

Phosphate lowering is an entrenched therapeutic target

Binding of intestinal phosphate in patients with KF has been practiced for more than half a century. [12] Today, 88% of UK dialysis patients require binders [13] to achieve treatment targets. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend lowering phosphate 'towards the normal range', [14] while UK treatment guidelines recommend a phosphate 'between 0.9 and 1.5 mmol/L', at or just above the normal range.[15] Other guidelines in wide use set similar targets, and such guidelines are ubiquitously and rigorously applied. Indeed, management of phosphate is a key driver of monthly blood sampling mandated by treatment guidelines.

Despite the cost and resultant demands on staff time resulting from the application of phosphate lowering guidelines, data from the UK Renal Registry (UKRR) show that only 55.6% of dialysis patients achieved a serum phosphate below 1.7 mmol/L. The low rate of target achievement may be attributed to the difficulty in maintaining sufficient dietary phosphate restriction, the side effect burden of binders, and clinician and patient attitudes, given the well documented lack of trial data and the associated pill and side effect burden. Binders are expensive, costing up to £5,000 per year per patient;[16] their use contributes to one of the highest pill burdens of any chronic disease (up to 15 binders per day)[14],

resulting in both high non-adherence and reduced quality of life.[17,18] Despite this, there is no existing evidence from adequately powered randomised trials that phosphate lowering with any binder improves clinical or patient reported outcomes or is cost-effective, as has even been reported in the popular press.[19]

Existing treatment guidelines base recommendations for phosphate lowering entirely on low quality evidence from observational and pre-clinical studies.[13,20,21] It is difficult to understand how a class of drug can achieve >85% uptake in a disease population without any randomised trial evidence of benefit, and at considerable cost to the NHS.

2. UK Trial Specifics

2.1 Sites

72 renal units across the UK contribute data to the UK renal registry (UKRR), and it is anticipated that PHOSPHATE will be conducted in up to 60 of these units recruiting approximately 2000 UK participants.

2.2 UK dialysis Trials Platform

The PHOSPHATE trial will be embedded in a dialysis trial platform based on the NIHR HTA funded SIMPLIFIED trial of colecalciferol versus standard care (IRAS ID: 192416, HTA Project: 14/49/127, EudraCT: 2015-005003-88 https://simplified.medschl.cam.ac.uk/). SIMPLIFIED aims to enrol 4,200 UK dialysis patients (current recruitment ~ 2400) from up to 50 UK dialysis centres. The trial is a collaboration with the UK Renal Registry (UKRR) and links all participant records with the UKRR and NHS Digital/SAIL/eDRIS. After enrolment, all outcomes are captured via linkage with the UKRR and routinely collected datasets. PHOSPHATE will harness all SIMPLIFIED systems.

SIMPLIFIED participants will be eligible for co-enrolment in PHOSPHATE and vice versa. We do not consider it likely that there will be interaction between colecalciferol (SIMPLIFIED) and phosphate lowering (PHOSPHATE). Both interventions are prevalent in the target population. Colecalciferol does not influence phosphate concentrations. As both trials will share a unified platform, we will be able to assess any interaction.

2.3 Trial Duration

Assessment of the primary endpoint will require 1,190 events. It is estimated that this will require a recruitment period of 3 years; median treatment period of 4.5 years, and an overall trial duration of approximately 7 years in the UK.

2.4 Trial Feasibility

As part of the NIHR HTA funding application, early reviews of participant recruitment and phosphate level separation will be conducted at 6, 12 and 18 months to ensure that the trial is viable to complete. Figures in the green zone indicate that the trial should continue unchanged; the amber zone indicate that mitigating actions may need to be implemented, and the red zone requires discussion whether it is feasible for the trial to continue with the TSC and funder. However, these targets must be considered in the global context of trial progress in terms of recruitment and phosphate separation.

	6 Months	12 Months	18 Months
Recruitment	>150	>449	>883
	≤150	≤449	300 – 883
		<150	<300
PO4 separation	≥0.32	≥0.32	≥0.32
	0.2-0.32	0.2-0.32	<0.32

2.5 Exploratory Outcome

NHS costs and cost-effectiveness of phosphate lowering.

2.6 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 (usually known as phosphate binders, specific drug choice is left to local site investigator discretion), and optimisation of dialysis regimen) aimed to intensively lower serum phosphate concentration towards normal level (≤1.50 mmol/L). See Figure 3 for a flow diagram of phosphate level management for the intensive phosphate control arm

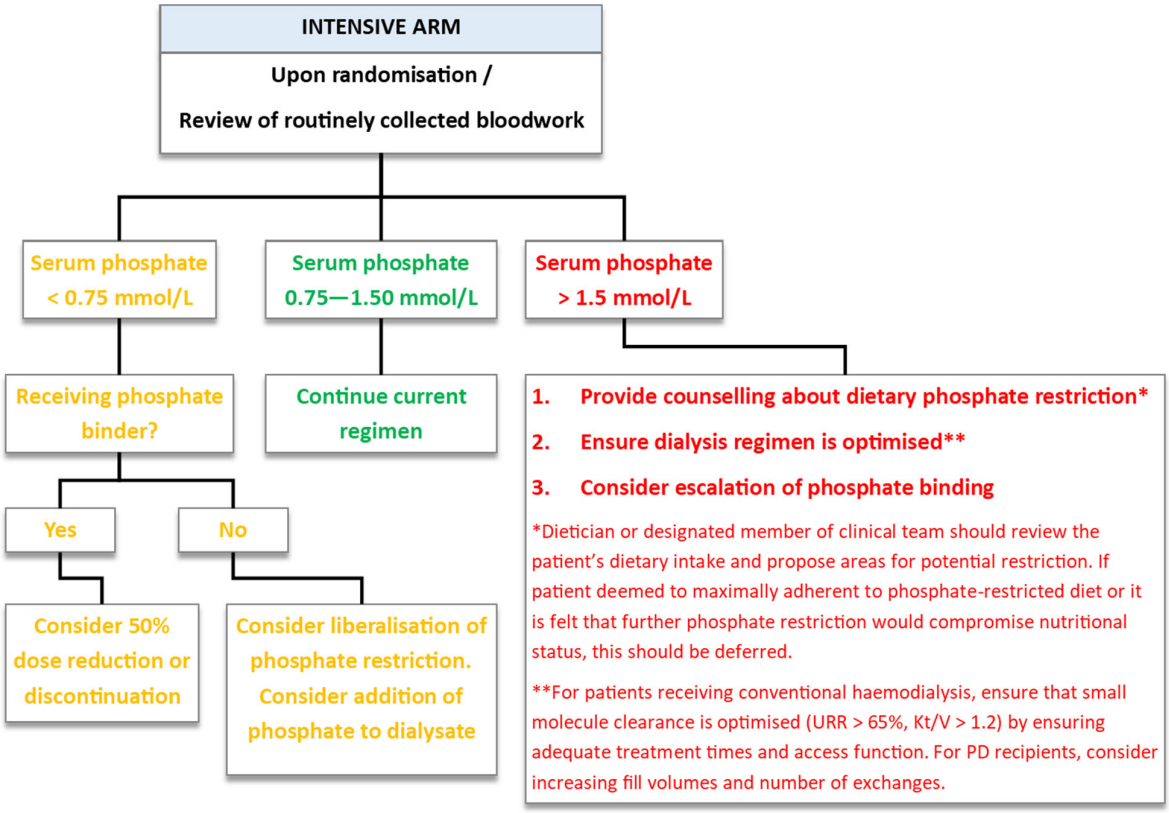

Figure 3. Phosphate level management flow diagram for the Intensive phosphate control arm.

2.7 Control intervention: Strategy of liberalised phosphate control

At enrolment, all phosphate-lowering medications will be discontinued, unless phosphate > 2.5, when continuation is permitted. During the trial, phosphate-lowering treatments (including dietary phosphate restriction, phosphate-lowering medications (binders), 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. See Figure 4 for a flow diagram of phosphate level management for the liberalised phosphate control arm

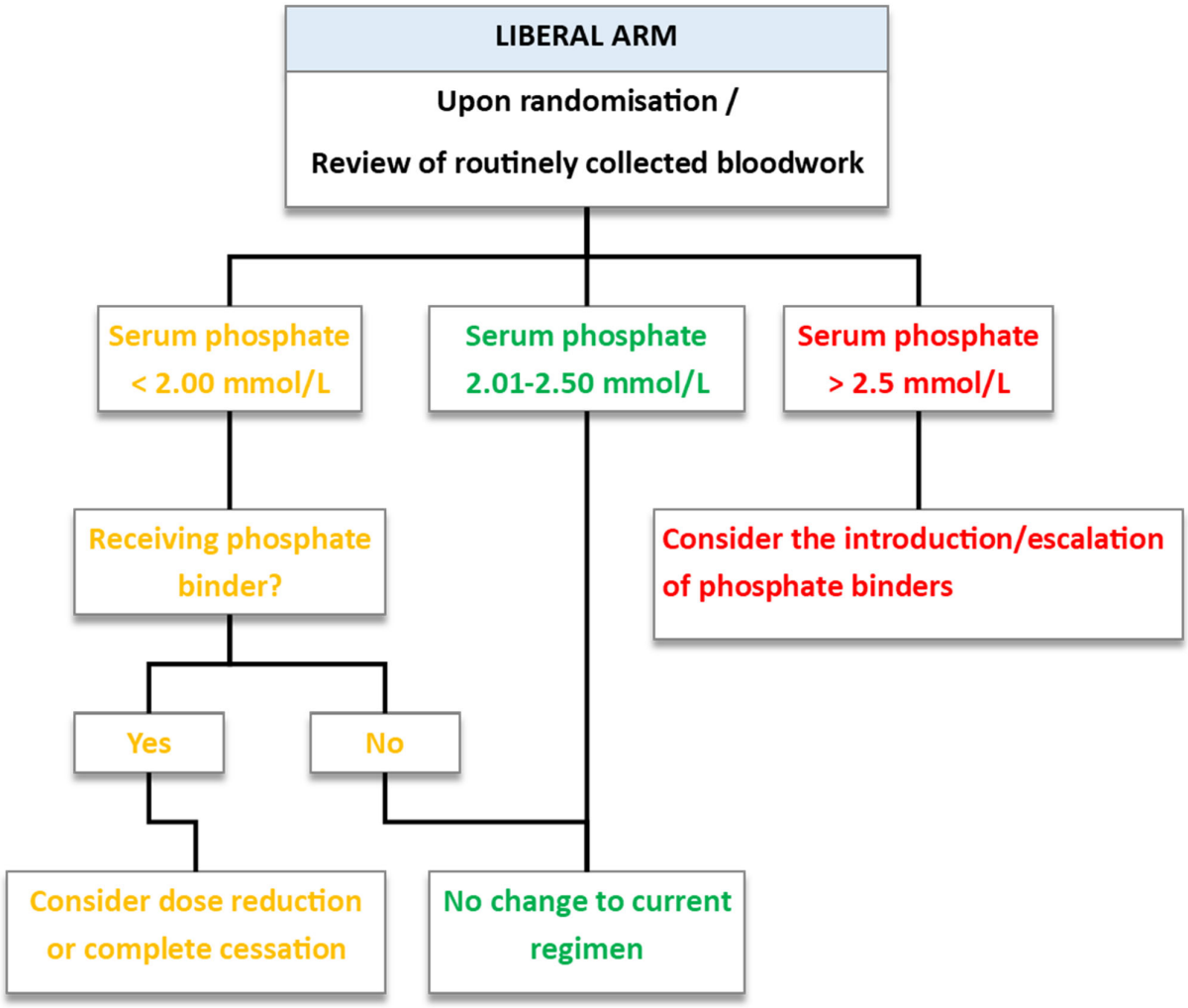

Figure 4. Phosphate level management flow diagram for the liberalised phosphate control arm.

3. UK Trial Participants

3.1 Participant Consent

Patients will be provided with the approved Patient Information Sheet by post, or at a routine dialysis appointment and advised to take it away with them to review the information in more detail. If the patient is interested in the study, a member of the study team will discuss the study with them and answer any questions they may have, usually at a subsequent dialysis appointment but consent discussions could also take place by telephone. The investigator or designee will obtain written, informed consent from each patient before any study procedures are undertaken. This does not need to be in person (telephone or videoconferencing calls are permitted, but a real-time two-way discussion must take place),

but the consent form must be countersigned by the same member of the study team who discussed the trial with the patient.

Should a patient require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators. Patients who do not fully understand the information provided will not be enrolled onto the study.

3.2 Monitoring adherence to phosphate target:

Separation of phosphate levels between both study arms will be monitored. Phosphate levels will either be entered into the database by daily feeds from UKRR (UK Renal Registry) for sites with Renal Patient View (or equivalent), from regular automated data feeds from local sites electronic medical records, or recorded on CRFs and manually entered into the database. Reports on separation of phosphate levels between both arms will be generated. Feedback and reminders will be provided if phosphate targets are not achieved. It is the responsibility of local site staff to feed this information back to individual trial participants.

3.3 Discontinuation/modification of trial phosphate strategy

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

- Kidney transplant,
- 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.

3.4 End of Trial Participation:

PHOSPHATE is an event driven trial and will continue until 1,190 events have accrued globally. When the trial ends, all patients will be notified via their preferred method of notification, as indicated at the last trial review. Participating centres will be notified that the trial has ended, and asked to discontinue the allocated phosphate management strategy unless ongoing treatment is indicated as per local or national treatment guidelines.

4. Trial Assessments

For all participants, trial assessments will be carried out every 6 months ± 6 weeks. Assessments at time point 0 (Baseline) and time point 2 (12 months) will be administered by the local site team.

These two assessments will include the following:

a) HRQoL using the EQ5D questionnaire
b) Adherence to assigned phosphate target
c) Any permanent changes to renal replacement therapy
d) Concomitant medications
e) Details of phosphate binders

The remaining time points (1 and 3+) will be administered centrally and will not require a face-to-face interview. Participants will be given the option of conducting assessments by mail (via return in a self-addressed, stamped envelope sent to the patient) or telephone interview (which may coincide with dialysis)

These assessments will include the following:

a) HRQoL using the EQ5D questionnaire

At each assessment, patients will also be asked to indicate their preferred method for the subsequent assessment and to provide any updated contact details.

5. UK Data Specifications

5.1 Data Management

All data will be collected in a bespoke database developed and managed by Cambridge Clinical Trials Unit and stored in the Secure Data Hosting Service (SDHS) which is provided by the University of Cambridge Clinical School as an ISO:27001 certified Safe Haven for members of the School to store sensitive data, including Personally Identifiable Data.

5.2 Data Linkage

PHOSPHATE is a pragmatic trial. Many variables often captured face to face or during trial visits will be captured indirectly via regular data tranches using a variety of data sources including ONS or equivalent, Hospital Episode Statistics (HES) or equivalent

and the UKRR. Laboratory data will be obtained from the results of routinely collected blood tests via the UKRR on an on-going basis when possible. Phosphate concentrations are measured regularly in all UK dialysis patients as part of standard care, and these data are submitted to the UKRR. These (and other relevant biochemistry and haematology) results will be linked daily from the UKRR to the PHOSPHATE secure database for participants in the trial. All other biochemical and haematological parameters that will be extracted via the UKRR UKRDC, are not relevant to inclusion in the trial, and will not be captured at entry.

5.3 Endpoint Confirmation

Primary and secondary outcomes will be ascertained by data linkage from ONS and HES data sets (or equivalent in Scotland and Wales). Investigators will be encouraged to upload supporting documentation to the trial database in order to facilitate endpoint verification. This supporting information will be reviewed by the central data manager for completeness and consistency.

Endpoint adjudication will be performed on all deaths occurring after randomisation and classify the cause of death according to the following schema:

1. Non-cardiovascular - A definite non-cardiovascular cause of death must be identified. The local investigator will be requested to assess the cause of death. Where the local principal investigator confirms a clear non-cardiovascular cause of death, this will be accepted. The endpoint reviewer(s) will look at all Case Record Forms and source documents where available.

2. Cardiovascular (CV) – A definite CV cause of death must be identified. The local principal investigator will be requested to assess whether the death was definitely:

a. Death due to acute myocardial infarction

b. Sudden cardiac death

c. Death due to heart failure

d. Death due to stroke

e. Other CV death (e.g. pulmonary embolism, cardiovascular procedure-related)

The endpoint reviewer(s) will look at CRFs and source docs where available.

3. Undetermined cause of death (i.e. cause of death unknown) – the local investigator cannot identify a cause of death. The endpoint reviewer(s) will look at all CRFs and source docs where available.

The endpoint reviewer(s) will also review and adjudicate the following reported non-fatal cardiovascular events:

- Acute myocardial infarction
- Coronary revascularisation
- Peripheral arterial events
- Hospitalisation for unstable angina*
- Hospitalisation for other angina*/chest pain*
- Stroke/TIA**/other cerebrovascular events (i.e. subdural/extradural haemorrhage) **
- Hospitalisation for heart failure

** Hospitalization for unstable angina, other angina or for other chest pain are not study endpoints but such events will be reviewed by the EPAC to ensure that acute myocardial infarction events have not been missed.

**TIAs and other cerebrovascular events (subdural haemorrhage, extradural haemorrhage) are not study endpoints but will be reviewed by the endpoint reviewer(s) to ensure that stroke events have not been missed.

If further review is required, the endpoint will be forwarded to the UK Endpoint adjudication Committee for discussion.

6. Safety Reporting

Trial participants will consent to the use of data captured by the UK Renal Registry (UKRR), Office of National Statistics (ONS), and Hospital Episode Statistics (HES) data at the start of the trial. Scottish and Welsh participants will consent to the use of equivalent data from relevant sources, for example the General/Acute Inpatient and Day Case dataset (SMR01) and the Patient Episode Database for Wales (PEDW) respectively. The PTO will collect all events associated with hospital admissions from HES, SMR01, PEDW data (or equivalent) as appropriate, and deaths from ONS (or equivalent) on a continuous basis. All

hospitalisation-requiring and hospitalisation-associated events, and all deaths, will therefore be captured in regular intervals and directly by the PTO.

Given:
1) the intensive monitoring of dialysis patients in routine clinical care
2) the comprehensive data on clinical events recorded directly by the PTO
3) this is a non-CTIMP study
the PHOSPHATE trial will utilise the following risk-adapted safety reporting approach:

1. Serious Adverse Events (SAEs) will not be recorded and reported (using the standard reporting form) to the sponsor within the usual 24h time frame.
2. All Adverse Events (AEs) will be captured using the routine data sources described above. These data will be filtered to identify all SAEs
3. The resulting line listing of SAEs will be regularly reviewed by the CI
4. Only events related to the study intervention which are **serious AND unexpected** need to be reported to the central PHOSPHATE team at the Cambridge Clinical Trials Unit. The chief investigator should email the REC using the 'Non-CTIMP safety report to REC' form within 15 days of becoming aware of the event. For the PHOSPHATE trial, the study intervention comprises dietary measures, dialysis adjustments and the prescription of phosphate binder medications. Expected adverse events deemed related to phosphate binders are unexpected if not listed in the relevant smpc.

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

7. Data Handling and Record Keeping

All data will be transferred into an electronic Case Report Form (eCRF), which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The eCRFs must be completed in a timely manner. Completeness and accuracy of the eCRF are the responsibility of the investigator. The eCRF will be accessible to trial coordinators, data managers, the Investigators, Clinical Trial Monitors, Auditors and Inspectors, as required.

A trial specific data management plan will describe in detail the data management processes using the eCRF and the trial database.

A copy of the data associated with a trial participant will be provided to the local PI at the end of the trial. All data entries will be made in the eCRF. It will not be possible to edit any data fields already marked as complete. Requests for corrections or additions will need to be made using the data change request form or logging a data change request in the eCRF.

Study participants will provide explicit consent to the use of identifiable data for the purposes of the conduct of the study. Personal identifiable data (PID) will be stored separately from anonymised study data on a secure server hosted within University of Cambridge School of Clinical Medicine Secure Data Hosting Service.[1] PID will be accessible to the PHOSPHATE trial team within the Cambridge Clinical Trials Unit, monitors, auditors and inspectors as required. It is necessary to 1) perform validation of NHS numbers and linkage to routinely collected datasets (NHS Digital, ONS), and 2) to generate datasets with participant details for mail merge creation of questionnaires, and is therefore imperative to the conduct of the study.

7.1 Source Data

To enable peer review, monitoring, audit and/or inspection, the investigator must agree to keep records of all participants (sufficient information to link records e.g. CRFs, hospital records), all original signed informed consent forms and copies of the CRF pages.

Source data may include but are not limited to:

- Informed Consent Form
- Relevant sections of the Case Report Form (written or electronic), as defined by the TPM
- Medical Records (written or electronic)
- On-line laboratory test results systems
- Participant Questionnaires (written or electronic)

[1] https://www.medschl.cam.ac.uk/research/information-governance/sdhs-security-policy/

7.2 Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

8. Ethical and Regulatory Considerations

The consent information and consenting procedure are described under section 3, and will be approved by the REC.

8.1 Ethical committee review

Before the start of the trial or implementation of any amendment, we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports, as required.

8.2 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC. The only circumstance in which an amendment may be initiated prior to REC approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the REC approval has been obtained.

8.3 Peer Review

The PHOSPHATE trial has been peer-reviewed as part of the 19/11 HTA Researcher-led call Primary Research by the National Institute of Health Research (NIHR).

8.4 Trial Steering Committee

A UK Trial Steering Committee (TSC) with an independent chair will be appointed as per NIHR guidelines. The TSC will oversee the UK arm of the trial, making recommendations on trial conduct and reporting on progress to the NIHR. TSC reports will also be submitted to the GTMC. The trial steering committee (TSC) will meet in person or by teleconference at least every 6 months for the first 2 years of the study, and annually thereafter, and more frequently as the need arises. The details of the TSC are set out in the Simplified Trial Steering Committee Charter.

8.5 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of good clinical practice, the protocol and applicable local regulatory requirements and laws.

8.6 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with local Trust policies.

9. Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The study will be funded by the NIHR HTA award127873.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently. The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

9.1 Monitoring, Audit and Inspection

Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

On-site or remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

9.2 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator immediately. Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach. Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

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