APPLICATION SUMMARY INFORMATION

Programme Name	HTA
Funding Opportunity	HTA Researcher-Led
Call	19/11 HTA Researcher-led call Primary Research
Host Organisation	University of Cambridge

Research Title
Pragmatic randomised trial of High Or Standard PHosphAte Targets in End-stage kidney disease - The PHOSPHATE trial

Research Type	Primary Research
Proposed start date, end date (duration)	From: 01/04/2020 to: 31/03/2027 (84 months)
Estimated research costs (not including NHS Support & Treatment Costs)	£1,868,258.00
Estimated NHS support & treatment costs	£194,800.00
Estimated Non-NHS intervention costs	£0.00

LEAD APPLICANT DETAILS & CV

Details of Lead Applicant	Dr Thomas Hiemstra
Job Position	University Lecturer in Trials
Department	School of Clinical Medicine
Email / Phone	thomas.hiemstra@me.com 01223336817
Organisation	The Chancellor, Masters and Scholars of the University of Cambridge

Lead Applicant Information – Qualifications

Degree / professional qualification - subject	Awarding body - date of award
BM BCh - Medicine	University of Stellenbosch - 15/12/1998
Other - MRCP	Royal College of Physicians (Edinburgh) - 01/06/2004
PhD - Medical Genetics	University of Cambridge - 01/02/2012
Other - CCT in Nephrology	GMC - 28/03/2012
Other - FRCP	Edinburgh Royal College of Physicians -

Degree / professional qualification - subject	Awarding body - date of award
	01/04/2015

Lead Applicant Information – Recent Relevant Publications

1. Jones RB, Hiemstra TF, Ballerin J et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA associated vasculitis: A randomised, non-inferiority trial. Ann Rheum Dis 2019, Mar;78(3):399-405.

2. Hiemstra TF, Walsh M, Mahr A et al. Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Controlled Trial. JAMA 2010 Dec 1;304(21):2381-8.

3. Odudu A, Hiemstra TF. Improving the External Validity of Clinical Trials in Dialysis Populations. Perit Dial Int. 2017 Sep-Oct;37(5):494-496

4. Hayer MK, Edwards NC, Slinn G et al. A randomized, multicenter, open-label, blinded end point trial comparing the effects of spironolactone to chlorthalidone on left ventricular mass in patients with early-stage chronic kidney disease: Rationale and design of the SPIRO-CKD trial. Am Heart J. 2017 Sep;191:37-46.

5. El-Damanawi R, Lee M, Harris T et al. A Randomised Controlled Trial of High versus Ad Libitum Water Intake in Patients with Autosomal Dominant Polycystic Kidney Disease: Rationale and Design of the DRINK Feasibility Trial. BMJ Open 2018, e022859.

6. Mader LB, Harris T, Klager S, Wilkinson I, Hiemstra TF. Inverting the Patient Involvement Paradigm: defining patient led research. Res Involv Engagem 2018 Jul 10;4:21

Lead Applicant Information – Research Grants Held

The Use of Rituximab In the treatment of Nephrotic Glomerulonephritis (TURING).
NIHR HTA 17/83/
£ 1,413,032
Start Date 1/6/2019
CO-APPLICANT

A UK multicentre randomised controlled trial to determine the efficacy of treatments for acute antibody mediated rejection in renal transplantation
NIHR HTA 16/167/120
£ 1,275,523
Start date 1/10/2018
CO-APPLICANT

A UK Multicentre trial to determine the efficacy of treatments for antibody mediated rejection.
Kidney Research UK
£ 750,000
Start date 08/2018
CO-APPLICANT

NURTuRE – changing the landscape of renal medicine to foster a unified approach to stratified medicine
Medical Research Council
£ 3,132,000
Start date 04/2018

CO-APPLICANT

PB-PG-0816-20027 PHOENIX-Feasibility: Picking up Hidden Osteoporosis Effectively during Normal CT Imaging without additional X-rays (Short Title: PHOENIX-F)
NIHR RfPB
£ 238,103
Start date 10/2017
CO-APPLICANT

Survival Improvement with Cholecalciferol in Patients on Dialysis – the SIMPLIFIED registry trial (14/49/127)
NIHR HTA
£ 1,472,221
Start date 03/2017
LEAD APPLICANT

High water intake versus standard care in APDKD - a randomised feasibility trial
British Renal Society
£ 29,580
Start date 04/2016
LEAD APPLICANT

Development of a hand-held potassium sensor: a pilot feasibility study
Kidney Research UK
£61,256
Start date 01/10/2016
CO-APPLICANT

PREVIOUS APPLICATION HISTORY

Relevant NETS Programmes previous application information (within the last 3 years)

Other funders previous application information

Application Type: Outline Application

Funding Body: NIHR Funding Scheme: HTA

Project Title: NIHR127873 - Pragmatic randomised trial of High Or Standard PHosphAte Targets in End-stage kidney disease - The PHOSPHATE trial

Outcome: Not Funded Date of Outcome: 16/11/2018

Please indicate how your current research proposal differs from this previous application:

The present resubmission has considered the implications of conducting a UK only trial. We remain of the view that an adequately powered UK only trial will not easily be possible. We present some modelling of different scenarios in the attached cover letter to substantiate this position. Further, our previous submission coincided with consortium submissions to NHMRC and CIHR for 17% and 28% respectively of the overall cohort. We propose that at least 55% of the cohort is recruited in the NHS and thus expect the UK to lead a global trial.

The primary outcome is unchanged from the previous submission. We have sought to make clear that the association of high phosphate with CV events is derived only from observational data, and that meta-analyses of trials have shown no conclusive evidence of benefit with phosphate lowering. We consider the choice of primary outcome to be the correct one.

We have changed the proposal such that the delivery of the intervention is embedded in clinical practice as recommended by the board.

We have provided evidence from the NIHR-funded and Canadian pilot trials that separation between arms in phosphate is achievable, and have additionally incorporated interim assessment of separation.

Proposed PPI involvement is more extensively described.

The RfPB trial has now been published and is provided as supplementary material.

If unsuccessful, please indicate why:

The feedback received fro the Board was summarised as below:

The Committee concluded this was an important question but had a number of concerns which need to be addressed.

• The applicants should change the study to be a UK only trial as it was unclear of the need for an international collaboration. The numbers of eligible patients available in the UK should be sufficient and allow for rapid recruitment.

• The Committee was unconvinced of the choice of primary outcome as it favoured one arm of the trial over the other.

• The applicants should ensure the intervention is delivered through standard NHS practice, rather than through research staff.

• The applicants should provide reassurance that the phosphate levels between arms will show separation.

Other funders previous application information
• Patient and Public Involvement needs further detail and clarity on involvement throughout the study. • The Committee would like to see the results of the RfPB trial included in the proposal.

RESEARCH TEAM

Lead Applicant

Specify Lead Applicants role in research
Responsibility for all aspects of trial management and oversight, chairing trial management group meetings, initiating site set up, liaising with the TSC and DMEC, and providing study reports.

Lead Applicants % FTE Commitment	20%

Joint Lead & Co-Applicants

Name	Position Held	Role / % FTE	Department	Organisation
Professor Ian Wilkinson (Co-Applicant)	Professor of Therapeutics	Co-investigator FTE - 2.5%	Experimental Medicine	The Chancellor, Masters and Scholars of the University of Cambridge
Dr Afzal Chaudhry (Co-Applicant)	Director of Clinical Informatics and National Lead for PatientView	Co-applicant FTE - 2.5%	Medicine	Cambridge University Hospitals NHS Foundation Trust
Professor Dorothea Nitsch (Co-Applicant)	Professor of Clinical Epidemiology	Co-applicant FTE - 2.5%	Epidemiology	London School of Hygiene & Tropical Medicine
Professor Patrick Mark (Co-Applicant)	Professor of Nephrology	Co-applicant FTE - 2.5%	Institute of Cardiovascular and Medical Sciences	The University Court of the University of Glasgow
Dr Simon Bond (Co-Applicant)	Lead Statistician	Statistician FTE - 10%	Cambridge Clinical Trials Unit	Cambridge University Hospitals NHS Foundation Trust
Dr Edward Wilson (Co-Applicant)	Senior Health Economist	Health Economist FTE - 5%	Public Health	The Chancellor, Masters and Scholars of the University of Cambridge
Associate Professor Ron Wald (Co-Applicant)	Associate Professor	International co-investigator (Canada) FTE - 2.5%	Department of Medicine	University of Toronto

Name	Position Held	Role / % FTE	Department	Organisation
Dr Sunil Badve (Co-Applicant)	Research Fellow and Nephrologist	International co-investigator (Australia) FTE - 2.5%	Nephrology	The George Institute for Global Health
Ms Tess Harris (Co-Applicant)	Patient and CEO of the PKD Charity	Co-applicant FTE - 2.5%	Private	Patient co-applicant
Professor Alastair Hutchison (Co-Applicant)	Medical Director	Co-investigator FTE - 2.5%	Medicine	Dorset County Hospital NHS Foundation Trust

Joint Lead Applicant

Justification for Lead Applicant

Relevant expertise and experience of Joint Lead Applicant

Please declare any conflicts or potential conflicts of interest that you or your research team may have in undertaking this research, including any relevant, non-personal & commercial interests that could be perceived as a conflict of interest.
The applicants declare that there are no existing or potential conflicts of interest.

SUMMARY OF RESEARCH

Plain English Summary of Research

THE PROBLEM

The kidneys maintain normal phosphate levels in the blood by excreting it into the urine. When kidneys fail, phosphate levels in the blood rise, and doctors believe this may be harmful to blood vessels and the heart. Consequently, most dialysis patients take medicines (up to 15 tablets per day) to lower phosphate. These are known as 'BINDERS' because they work by binding phosphate in the intestine before it is absorbed from the diet. Binders have many side effects, and patients struggle to take them. Binders are expensive, costing the NHS up to £5000 per patient per year.

Despite this, there have NEVER been any trials to test whether lowering blood phosphate with binders makes any difference in improving the health of dialysis patients by keeping the heart and blood vessels healthy, helping them feel better, or improving quality of life.

THE QUESTION

Does lowering blood phosphate with binders reduce angina, heart attack, stroke, circulation problems to the legs including amputation, or death from any of these causes?

HOW WILL WE DO THE STUDY?

Patients needing dialysis will be asked to participate in a randomised trial.

Patients will be assigned to one of two groups: A) Intensive phosphate lowering (towards normal or a blood level less than 1.5) or B) Liberal phosphate (blood level 2 to 2.5). The intensive group will receive binders to reach a low phosphate; the liberal group will only receive binders if their blood phosphate goes very high (more than 2.5).

HOW WILL WE LIMIT THE BURDEN ON PATIENTS?

Patients taking part in the study will have ONLY ONE STUDY VISIT at the start of the trial. This is possible because information about the health of dialysis patients is routinely collected by the NHS.

Dialysis patients can register on PatientView (https://patientview.org) to allow them to view their own blood test results. PatientView is active in all kidney units in the United Kingdom. Hospital laboratories send blood test results on all registered patients to the UK Renal Registry (UKRR). The UKRR provides patients with access to their own results via the PatientView website. We will use the PatientView data to monitor phosphate and will recommend changes to binder doses based on these results. The UKRR also collects other information about dialysis patients which will also be sent to the trial team.

The NHS collects information on anyone admitted to hospital (through NHS Digital). From this information we can establish whether patients have had serious illnesses. Using these existing data sources means that we do not need to call patients in for extra study visits. It also means the study will

Plain English Summary of Research

cost less than it might otherwise have done.

HOW MANY PATIENTS DO WE NEED?

3600 patients would need to participate. Since it may not be possible to enrol so many patients from the UK alone, we have joined forces with colleagues in Australia and Canada. Patients from all three countries may be enrolled in the study. We expect more than half to come from the UK.

HOW LONG WILL THE TRIAL LAST?

6 Years.

DO WE HAVE THE RIGHT TEAM?

We have assembled a group of researchers with exceptional experience and expertise in doing trials in dialysis in the UK and across the world. We will also have a patient team member.

MAKING RESULTS KNOWN

We will publish results of the study in journals, online (including social networks) and at kidney meetings across the world.

Research Plan

1. THE PROBLEM

RESEARCH QUESTION

Does lowering serum phosphate in patients on dialysis reduce a cardiovascular (CV) events and CV death?

BACKGROUND

There are 28876 patients with End Stage Kidney Disease (ESKD) receiving dialysis in the United Kingdom.[1] Phosphate retention leading to hyperphosphataemia is a hallmark of ESKD and, given that observational data suggest that higher plasma concentrations of phosphate are associated with worse outcomes including cardiovascular events and mortality,[2-4] most patients with ESKD receive medications that bind phosphate in the gut, thus limiting phosphate absorption and lowering phosphate concentration. These medications are commonly referred to as ‘binders’.

Binders are expensive, costing up to £5000 per year per patient;[5] their use contributes to one of the highest pill burdens of any chronic disease (up to 15 binders per day)[6], resulting in both high non-adherence and reduced quality of life.[7,8] Despite this, there is no existing evidence from randomised trials that phosphate lowering with any binder improves clinical or patient reported outcomes or is cost-effective, as lamented in a recent article in The Guardian.[9]

Research Plan

- Hyperphosphataemia Is Associated With Mortality

Although dialysis is a life-sustaining therapy, the death rate among UK dialysis patients in very high, with one-year age-adjusted survival of only 88%.[10]

Hyperphosphataemia is considered a 'non-traditional' risk factor for the excess mortality in ESKD.[11] Observational data suggest a U-shaped association with mortality,[12] and a meta-analysis of observational studies reported that all-cause and cardiovascular mortality increased by 18% and 10% respectively for every 0.3 mmol/L increase in serum phosphate.[13] Pre-clinical and clinical studies have shown that hyperphosphataemia is associated with atherosclerotic coronary artery disease, heart failure, left ventricular hypertrophy, arterial medial calcification, cardiac valvular and other soft tissue calcification and secondary hyperparathyroidism.[14]

Despite these associations, data from interventional trials to support phosphate lowering are lacking. In a meta-analysis of interventional trial data, there was no convincing evidence of survival benefit with any phosphate binder except sevelamer,[15] and the benefit of sevelamer was dependent on the inclusion of one small trial (n=466)[16] with a high risk of bias, which conflicted with findings from the largest trial of sevelamer to date (n=2101).[17] Uncertainty therefore exists as to whether hyperphosphatemia is causal and phosphate lowering with binders is beneficial, while binders confer a considerable side effect burden.[15,18]

- An Entrenched Therapeutic Target

Binding of intestinal phosphate in patients with ESKD has been practiced for more than half a century.[19] Today 88% of UK dialysis patients require binders[20] to achieve treatment targets. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend lowering phosphate 'towards the normal range',[6] while UK treatment guidelines recommend a phosphate 'between 1.1 and 1.7 mmol/L', at or just above the normal range.[21] Data from the UK Renal Registry (UKRR) show that only 55.6% of dialysis patients achieved a serum phosphate below 1.7 mmol/L. This may be attributed to clinician and patient attitudes, given the well documented lack of trial data and the associated pill and side effect burden.

2. IMPORTANCE TO PATIENTS AND THE NHS

- No RCT Evidence To Support Phosphate Lowering

Previous trials of binders have focused on licensing requirements for achieving reductions in phosphate. None of the 77 randomised trials of binders to date have assessed the effect of phosphate lowering on clinically meaningful or patient-centered outcomes such as cardiovascular (CV) events or quality of life.[15] Instead, most trials compared sub-classes of phosphate binders in achieving existing phosphate targets. The median sample size was only 40, the median follow-up duration 6 months, and most trials had a high risk of bias and other methodological shortcomings. Further, the median all-cause and cardiovascular mortality rates ranged between 3.0 and 0.1 per 100 person-years, indicating that these trials included a relatively low-risk population.

Therefore, current treatment guidelines base recommendations for phosphate lowering entirely on low quality evidence from observational and pre-clinical studies.[15,18,20] 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.

Research Plan

- Pill Burden, Non-Adherence and Poor Quality of Life

Dialysis patients have one of the highest pill burdens (median 19) of any chronic disease, and remarkably, binders account for 50% of this.[6] In a large study, 64%, 37%, 20% and 10% of patients were taking ≥6, ≥9, ≥12 and ≥15 binders per day respectively.[22] Given this burden, it is unsurprising that self-reported adherence to phosphate binders varies between only 38% and 55%.[7,8]

A variety of binders are in common use in the UK including Aluminium hydroxide (Al), Calcium carbonate or -acetate (Ca), Sevelamer (Sr), Lanthanum (La) and Sucroferric oxyhydroxide (Fe). All of these are associated with side effects including dementia risk, anaemia, osteomalacia and the need to measure serum levels (Al), gastro-intestinal side effects (Al, Ca, Sr, La, Fe – 8-38%), possible vascular and soft tissue calcification (Ca), metabolic acidosis (Sr - 34%), peripheral oedema (La – 24%), myalgia (La – 21%) and change in bowel habit (Fe – 24%).

- Phosphate Is of Little Relevance to Patients

Several studies have shown that biochemical markers such as phosphate matter little to dialysis patients. In a study using the nominal group technique in 82 Canadian and Australian dialysis patients, biochemical outcomes including phosphate ranked very low on their priorities for outcomes.[23] A recent Delphi survey involving 1181 participants showed that biochemical parameters ranked joint lowest among dialysis patients of 20 key clinical outcomes.[24]

3. A TRIAL OF TWO PHOSPHATE TARGETS IS FEASIBLE

Against this background, NIHR HTA advertised a commissioned call (12/31) during 2012 for feasibility studies to establish whether 'phosphate binders reduce mortality and improve quality of life in patients with advanced kidney disease'. Three bids were submitted by members of the UK nephrology research community. However, none were funded since this coincided with a successful investigator-led bid by co-applicant Hutchison to NIHR RfPB (PB-PG-0711-25112) for the SPIRIT feasibility trial (ISRCTN24741445) of two phosphate targets in patients on dialysis.[25,26]

SPIRIT randomised 104 dialysis patients aged ≥30 years to a liberal (1.8 – 2.4 mmol/L) or a low phosphate target (0.8 – 1.4 mmol/L), followed for 1 year. The objectives of SPIRIT were to 1) assess the proportion of patients achieving and maintaining phosphate targets, and to assess 2) the proportion of patients willing to be randomised, 3) dropout rate, 4) pill burden and 5) to carry out an exploratory evaluation of the major vascular event rate. SPIRIT demonstrated a sustained mean separation between trial arms in phosphate of 0.34 mmol/L. Of the target population, 39% were considered eligible after exclusions for age, dialysis vintage, planned transplantation, phosphate < 1.4 mmol/L, and uncontrolled secondary hyperparathyroidism. Of those approached, 53% consented (equivalent to 21% of the target population enrolling into the trial). SPIRIT used only calcium-free phosphate binders (sevelamer, lanthanum), and showed an annual dropout rate of 27%.

Simultaneously, a Canadian feasibility trial (TARGET) by Wald (co-applicant) and colleagues was conducted in 104 dialysis patients from 6 Canadian centres, randomised to either a liberal (2.0 – 2.5 mmol/L) or low (0.75 – 1.5 mmol/L) phosphate target.[27] Key differences with SPIRIT were 1) a higher upper phosphate target of >2.0 mmol/L, 2) shorter follow-up time, 3) no lower age limit and 4) exclusive use of calcium-based binders. TARGET achieved wider separation between trial arms of 0.47 mmol/L, and notably had no dropouts during follow-up, consistent with the lower side effect burden of calcium-based binders.

Research Plan

Together, these two trials demonstrate that it is possible to achieve separation in serum phosphate between trial arms of 0.3 mmol/L or greater. Both SPIRIT and TARGET have informed the design of the present proposal.

4. RESEARCH QUESTION

Is lowering serum phosphate in patients on dialysis effective and cost-effective in reducing a composite of fatal and non-fatal CV events?

5. RESEARCH PLAN

We will conduct an efficient, pragmatic open-label blinded endpoint (PROBE) parallel-group randomised controlled superiority trial of liberal (2.0-2.5 mmol/L) versus intensive (<1.5 mmol/L) serum phosphate targets to determine the effectiveness and cost effectiveness of phosphate lowering in patients receiving dialysis.

SETTING

Dialysis centres in the United Kingdom.

POPULATION

Inclusion criteria
- Age ≥ 45 years, or age ≥ 18 years with diabetes
- Dialysis requiring kidney failure for at least 3 months (90 days)
- Prescribed at least one phosphate binder at any dose

Exclusion criteria
- Elective kidney transplantation scheduled
- Life expectancy < 6 months

INTERVENTION

Participants assigned to the intervention arm will receive binders to achieve a phosphate target ≤ 1.5 mmol/L (towards the normal range).

CONTROL

Participants assigned to the control group will receive binders only if serum phosphate > 2.5 mmol/L, with cessation of phosphate binders if phosphate ≤ 2.0 mmol/L.

Both groups will receive dietary advice according to standard care for local practice at the start of the trial. Patients in the control arm will not receive any further dietary phosphate restriction advice unless serum phosphate exceeds 2.5 mmol/L.

Research Plan

OUTCOMES

The primary outcome is the time to the composite of CV mortality or non-fatal CV events including acute coronary syndrome, hospitalisation for unstable angina, coronary revascularisation, stroke, peripheral arterial event or peripheral arterial revascularisation. Heart failure events will NOT be an outcome of interest due to the challenge in distinguishing symptoms related to fluid overload in ESKD patients from those due to primary myocardial dysfunction.

Secondary outcomes will include

- Cost-effectiveness of phosphate lowering from the perspective of the NHS
- Time to CV mortality
- Time to nonfatal CV event
- Time to all-cause mortality
- Differences in bone mineral parameters including calcium, phosphate, PTH
- Phosphate binder use (pill-burden, medication usage, self-reported adherence)
- Fractures
- Calciphylaxis
- Health-Related Quality of Life (EQ5D, SF36)
- Gastro-intestinal Symptom Rating Scale
- Itch/Pruritus visual analogue scale

SAMPLE SIZE CALCULATION

Assuming an event rate of 12% per year for the primary outcome in the control arm,[28] a 1% loss to follow-up and a competing event rate of 5% from transplantation or non-cardiovascular death, we estimate that 3,600 participants recruited over 3 years and followed for an additional 3 years would accrue 1,302 first primary outcome events and yield 83% power to detect a hazard ratio of 0.85 in the intensive phosphate arm.

A 15% reduction in HR is considered realistic given 1) the association from observational data of a 10% increase in CV death for every 0.3 mmol/L increment in phosphate, 2) a separation of between 0.34 and and 0.47 mmol/L is reasonable to expect (from SPIRIT and TARGET) and 3) non-fatal CV events are included in the primary outcome.[13,26,27]

TRIAL METHODS

- A Global Phosphate Trial Consortium

PHOSPHATE forms part of a global consortium led by the lead applicant (TFH). The consortium was formed in 2017, driven by our view that it would be challenging to enrol a sufficient sample size in the UK alone in a timely manner. This view is informed by the applicants' experience of enrolling to dialysis trials (SIMPLIFIED, H4RT, BISTRO, PIVOTAL). SIMPLIFIED has to date enrolled approximately 1450 patients over 26 months. The PIVOTAL trial[29] enrolled 2141 patients over 32 months, but with considerable dedicated research nurse funding. Against this background we planned to enrol 2000 participants in the UK over 3 years. We submitted simultaneous applications to NIHR HTA, NHMRC (APP1162410, n=600) and CIHR (n=1000). Both the CIHR (CAD $1,526,175.00) and NHMRC (AUS $1,748,533.55) have funded the respective proposals, with TFH as global lead and a co-applicant on both grants.

Research Plan

A global trial management committee (chaired by the lead applicant) has been established, agreeing a core protocol to address the primary outcome but allowing for country-specific variation in conduct and secondary design.

In response to the Board's recommendation for a UK only trial, our projections indicate that we would need to recruit for approximately 4.5 years to reach 3600 participants in the UK only, thus significantly extending overall trial duration in order to observe the requisite number of events. We provide further detailed estimates in the accompanying cover letter.

We therefore continue to propose a UK-led international trial in partnership with our Canadian and Australian colleagues, aiming to enrol at least 55% of the trial cohort (n=2000) from the UK.

- A UK Dialysis Trial 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 (14/49/127, https://simplified.medschl.cam.ac.uk/). Briefly, SIMPLIFIED aims to enrol 4,200 UK dialysis patients (current recruitment ~ 1500) from up to 50 UK dialysis centres. The trial is a collaboration with the UK Renal Registry (UKRR) and links all participant records with UKRR and NHS Digital or equivalent datasets. After enrolment, all outcomes are captured via linkage with the UKRR and routinely collected datasets.

PHOSPHATE will harness all SIMPLIFIED systems. Participants will consent to the SIMPLIFIED platform (data linkage, follow-up questionnaires) and will consent separately to PHOSPHATE randomisation. SIMPLIFIED participants will be eligible for co-enrolment in PHOSPHATE and vice versa which will lead to considerable efficiencies:

1. More rapid site set-up
2. More rapid recruitment to PHOSPHATE
3. Use of an existing trial network
4. Single HRQoL data capture shared between trials
5. Shared database infrastructure
6. Single cohort submission to NHS Digital for all platform participants (shared costs)

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.

- Enrolment

Participants will be approached by dialysis unit staff during dialysis sessions or follow-up clinics. Sites will be notified of all potentially eligible patients from review of administrative data sources. Eligible participants may also be identified by local research staff from dialysis unit records. All patients who are prescribed a binder will be eligible for enrolment and randomisation.

- Randomisation

Participants will be randomised 1:1 by a web-based randomisation tool embedded within the trial database, administered by the Cambridge Clinical Trials Unit. Randomisation will trigger an automated query of submitted patient identifiers with the UK Renal Registry to verify that linkage can be

Research Plan

established. Randomisation will be stratified by centre.

- Blinding

Participants and research staff will not be blinded to the intervention.

- Schedule of Visits and Follow-Up

Participants will have a screening visit to assess eligibility and to obtain consent. Eligible participants will undergo a baseline assessment and randomisation.

Once patients are enrolled, there will be no further face to face trial visits. Laboratory data for phosphate concentration will be obtained from the PatientView (PV) dataset (https://www.patientview.org/). PV is supported by all UK renal units and administered by the UKRR. Clinical laboratories feed data on registered patients directly to the UK Renal Data Collaboration (UKRDC) every 24 hours. This allows PV to display patients' own laboratory data to them via the PV web portal or smartphone application. Registration with PV will be a prerequisite for participation in PHOSPHATE (many prospective patients will already be enrolled with PV).

Site teams will receive regular automated updates on their trial participants, indicating whether they are at or outside the target range for their trial arm. Reports will be provided at least monthly, and more frequently if required. Site teams will be required to review phosphate values against trial targets during routine review (typically 6-weekly).

PHOSPHATE-UK is a trial of phosphate targets, not of individual binders. The majority of UK dialysis centres use a variety of binders depending on tolerance and patient preference. These include Ca, Sr, La, Al and Fe. Participants may take any binder in order to achieve phosphate targets. Site teams will be required to record binder prescriptions every 3 months.

Trial outcomes data will be captured via NHS Digital (or SAIL/eDRIS). Patients will be asked to complete a questionnaire every 6 months via paper mail, email, phone or smartphone application which will include an assessment of HRQoL (as in operation for SIMPLIFIED).

- Study-Specific Procedures

There will be no trial-specific procedures or blood samples. Phosphate binder management will be based on blood tests that are part of routine clinical practice.

- Trial Duration

The overall trial duration will be 6 years (36 months recruitment).

- Internal Feasibility Assessment

An internal feasibility assessment will be undertaken 12 months after enrolment of the first patient. Feasibility endpoints will include recruitment rate and separation between trial arms in serum phosphate. The event rate will be assessed after the 500th UK participant reaches 12 months follow-up.

- Patient Involvement

Research Plan

The Manchester Kidney Patients Advisory Group proposed a trial of phosphate lowering prior to the onset of the SPIRIT trial and have remained enthusiastically supportive of the follow-on trial. A trial of phosphate lowering in dialysis was proposed by the Addenbrooke's Kidney Patient Association to the Patient Led Research Hub (www.plrh.org). The proposal is supported by patient members of the UK Renal Trials Network.

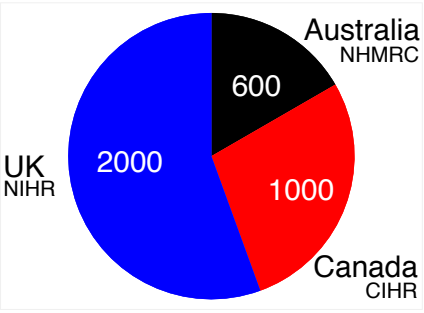
The PHOSPHATE TSC will include a patient member. PHOSPHATE will be supported by the SIMPLIFIED patient panel, a group of 15 patients and carers who will meet at least annually during trial conduct to provide advice and feedback to the trial team, and 4-monthly during the first year. During the design and set-up stage, the patient panel will be invited to contribute to the design of study materials. Given the use of PatientView at the UKRR, the UKRR patient panel will also provide input and PPI oversight.

Patient experience and feedback will be published in the trial participant newsletter, which will invite patients to provide comments and suggestions direct to the trial team via email.

UPLOADS

The following pages contain the following uploads:

Upload Name
Flowchart
References



UK Dialysis Patients
N=3600

Randomisation
1:1

Internal Feasibility
12 months

Recruitment
36 months

Intensive
Phosphate < 1.5

Liberal
Phosphate 2 – 2.5

PatientView
Phosphate measurements

CCTU
Cambridge Clinical Trials Unit

Trial Sites

NHS Digital

Linkage

Follow-up
36 months

1302 Primary Outcome Events

References

1. MacNeill SJ, Ford D, Evans K, Medcalf JF. UK Renal Registry 20th Annual Report: Chapter 2 UK Renal Replacement Therapy Adult Prevalence in 2016: National and Centre-specific Analyses. Nephron Clin Prac. Karger Publishers; 2018;139 Suppl 1:47–74.

2. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. American Journal of Kidney Diseases. W.B. Saunders; 1998;31:607–17.

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