Clinical Trial Protocol

Trial Title:	**Survival Improvement with Colecalciferol in Patients on Dialysis – The SIMPLIFIED Registry Trial**
Protocol Number:	SIM15
EudraCT Number:	2015-005003-88
ISRCTN Number:	15087616
Investigational Product:	Colecalciferol 60,000 IU fortnightly
Protocol Version:	6.0

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PROTOCOL SIGNATURES:

I give my approval for the attached protocol entitled **"*Survival Improvement with Colecalciferol in Patients on Dialysis – The SIMPLIFIED Registry Trial*"** dated 12 July 2017.

Chief Investigator

Name: Dr Thomas F Hiemstra

Signature:

Date:

Site Signatures

I have read the attached protocol entitled "***Survival Improvement with Colecalciferol in Patients on Dialysis – The SIMPLIFIED Registry Trial***" dated 12 July 2017 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 the GCP Directive 2005/28/EC.

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: _____

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Amendment History

Version No.	History	Date
V1.0	Final Protocol	28 January 2016
V2.0	Incorporated changes from MHRA and REC review	01 March 2016
V3.0	Corrected plasma vitamin D sample size from 300 to 230 in line with funding award Incorporated changes requested by NIHR ETSCC Updated Registration and Randomisation section in line with current process Updated the timelines for data downloads from NHS Digital in line with their processes Correction of typographical errors throughout	11 October 2016
V4.0	Addition of previously missed abbreviations and correction of typographical errors throughout. Clarification of protocol throughout, but mainly in inclusion/exclusion criteria and trial procedures / assessment sections Simplification of the baseline assessments	12 December 2016

V5.0	Update of the trial coordinator Addition of the previously missed abbreviations Clarifications in the trial synopsis, flow chart and background sections Addition of ergocalciferol to the exclusion criteria Removal of text messaging method in subject compliance monitoring Clarification of the frequency of blood results (as indirect assessments) for patients in the colecalciferol arm Clarification on the screening procedures and baseline assessments Clarification of the informed consent procure-consenting over the phone Correction of typographical errors throughout	22 March 2017
V6.0	Clarification on the exclusion criteria of persistent hypercalcaemia Clarification on the exclusion criteria of high dose colecalciferol and ergocalciferol Clarification on the use of other colecalciferol containing medications containing D3 Clarification on the assessment table Updating of the SAR reporting FAX number	12 July 2017

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1 ABBREVIATIONS

ACS	Acute Coronary Syndrome
AE	Adverse Event
ALP	Alkaline Phosphatase
CA	Competent Authority
Ca	Calcium
CI	Chief Investigator
CKD-MBD	Chronic Kidney Disease – Mineral Bone Disorder
CRF	Case Report Form
CV	Cardiovascular
DSUR	Development Safety Update Report
ERK	Extracellular signal-regulated kinase
ESA	Erythropoiesis Stimulating Agent
ESRD	End-Stage Renal Disease
GP	General Practitioner
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HRA	Health Research Authority
HSNI	Health and Social Care Services Northern Ireland
HTA	Health Technology Assessment
IDMEC	Independent Data Monitoring & Ethics Committee
IMP	Investigational Medicinal Product
ISD	Information Services Division Scotland
IU	International Units
MAPK	Mitogen-activated protein kinase
MED	Minimal Erythematous Dose
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR – HTA	National Institute of Health Research – Health Technology Assessment
NIMP	Non Investigational Medicinal Product
ONS	Office of National Statistics
OTC	Over the Counter
PEDW	Patient Episode Database for Wales
PI	Principal Investigator
PI3K	Phosphoinositide 3-kinase
PTH	Parathyroid Hormone

QoL	Quality of Life
R&D	Research and Development
RA	Regulatory Agency
RAAS	Renin-Angiotensin Aldosterone System
REC	Research Ethics Committee
RR	Relative Risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
STO	SIMPLIFIED Trial Office
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMG	Trial Management Group
TSC	Trial Steering Committee
UKIACR	United Kingdom and Ireland Association of Cancer Registries
UKRDC	United Kingdom Renal Data Collaboration
UKRR	United Kingdom Renal Registry
VDR	Vitamin D Receptor
VDRAs	Vitamin D Receptor Activators
VSMC	Vascular Smooth Muscle Cells

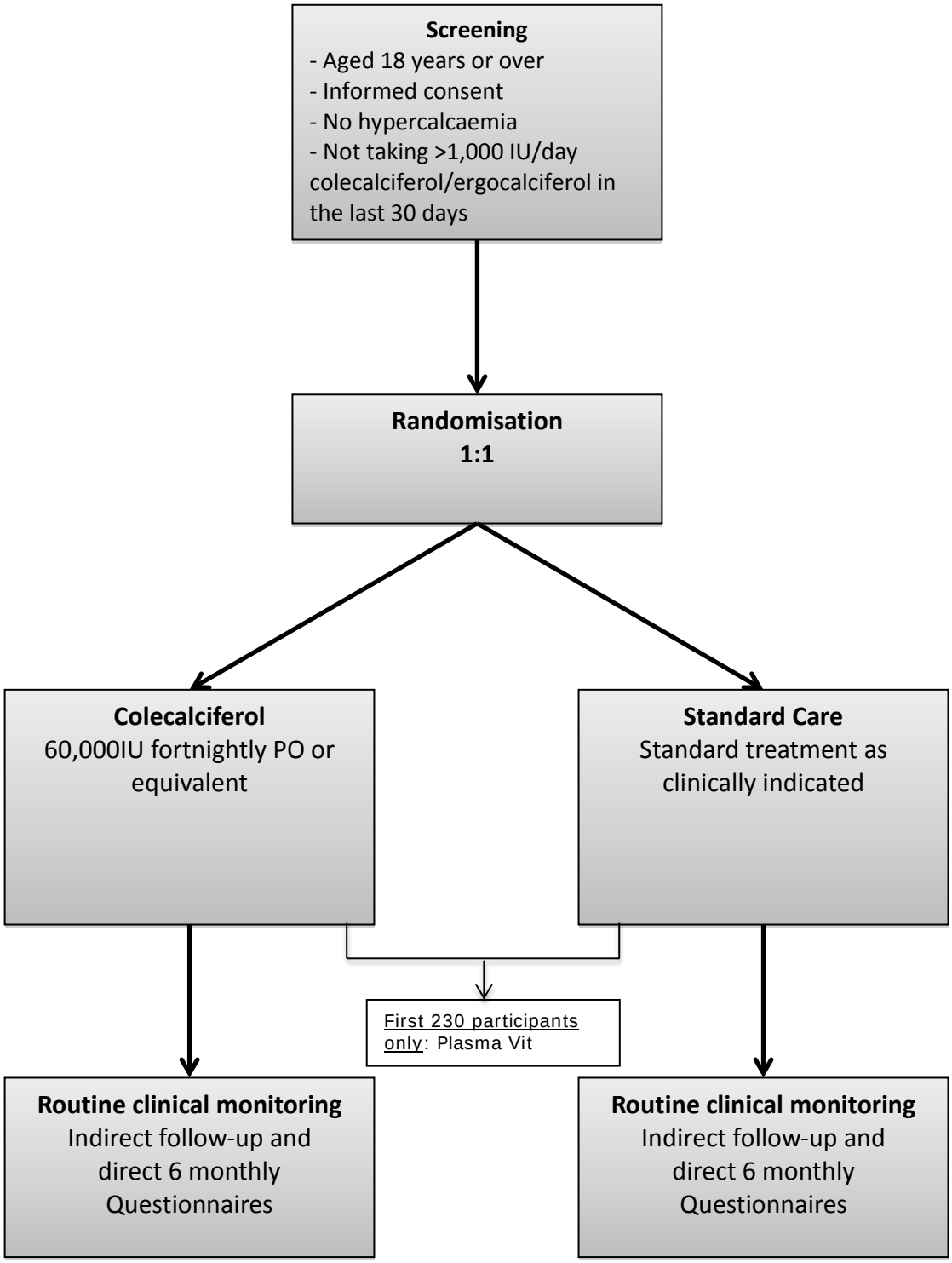
2 TRIAL SYNOPSIS

Title of clinical trial	**S**urvival **Imp**rovement with Co**l**ecalc**if**erol in Pat**ie**nts on **D**ialysis – the SIMPLIFIED registry trial
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge
EudraCT number	2015-005003-88
Medical condition or disease under investigation	Kidney Failure requiring dialysis
Purpose of clinical trial	To assess the effect of Colecalciferol supplementation on outcomes in patients with kidney failure receiving dialysis
Primary objective	To determine the effect of colecalciferol 60,000IU fortnightly on patient survival
Secondary objective (s)	To determine the effect of colecalciferol 60,000IU fortnightly on quality of life and secondary clinical outcomes
Trial Design	Phase 4, multicentre, open-label, blinded-endpoint, randomised, parallel-group trial
Trial Outcome Measures	**Primary:** • All-cause mortality **Secondary**: • Health Related Quality of Life (HRQoL / EQ5D) • Cardiovascular events requiring admission • Infections requiring admission • Cancer incidence • Fractures requiring admission
Sample Size	Approximately 4,200
Summary of eligibility criteria	**Inclusion Criteria** • Has given written informed consent to participate • Aged 18 years or over • UK Resident • Has End-Stage Renal Disease (ESRD) requiring dialysis **Exclusion Criteria** • Treatment on high dose (>1,000IU/day) colecalciferol or ergocalciferol in the last 30 days • Persistent hypercalcaemia (corrected calcium >2.62 mmol/l on three separate and sequential occasions without precipitating cause*)

	• Hypersensitivity to colecalciferol or any of the excipients • Life expectancy < 6 months • Women who are pregnant / planning to become pregnant or are breastfeeding • Opted out from contributing data to the UK Renal Registry (UKRR)
Investigational medicinal product and dosage	Colecalciferol 60,000IU fortnightly (equivalent to 1500 micrograms vitamin D_3)
Route(s) of administration	Oral
Maximum duration of treatment of a subject	Until the end of the trial (estimated median treatment duration 5.5 years)
Procedures	**Screening and enrolment** • Eligibility checks • Consent • Randomisation **Baseline** • Complete short CRF • EQ5D questionnaire
Treatment period procedures	• Plasma Vitamin D test for the first 230 participants • 6-monthly follow up questionnaire incorporating EQ5D • Medication check
End of Trial	Once 2,200 deaths have occurred
Procedures for safety monitoring during trial	The Trial Steering Committee (TSC) will provide overall supervision for the trial, to ensure that it is conducted in accordance with the protocol and principals of GCP, and to provide advice through its independent chairman. The Independent Data Monitoring and Ethics Committee (IDMEC) will assess safety through review of accumulating evidence throughout the conduct of the trial.
Criteria for withdrawal of patients	Patients may be withdrawn: 1. At the patient's request 2. If, in the view of the PI, further participation in the trial is deemed to pose an unacceptable risk to the patient, for example in the event of a SUSAR

** Patients in whom a precipitating cause for hypercalcaemia has been identified and addressed (for example, active vitamin D compounds reduced, calcium-based phosphate binders withdrawn, hyperparathyroidism treated, dialysate calcium adjusted) may be enrolled in the trial once the corrected calcium concentration has reduced below the upper threshold for exclusion from the trial.*
Historic hypercalcaemia is irrelevant providing the patient is not hypercalcaemic at the time of screening/randomisation.

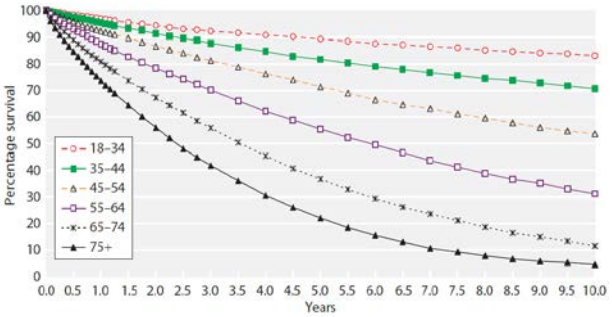
3 TRIAL FLOW CHART



4 INTRODUCTION

4.1 Background

Patients Receiving Dialysis are at Very High Risk of Death and have Reduced Quality of Life

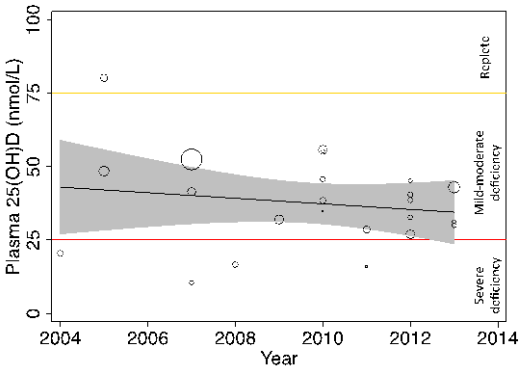


In the United Kingdom, nearly 30,000 people receive regular dialysis and 6,000 new patients start dialysis each year. Although this is a life-saving treatment, dialysis-requiring renal failure carries a worse prognosis than most malignancies,[1] with a mean 3-year survival of only 68%. The mean age of UK dialysis recipients is 65 years, and after 4 years on dialysis, fewer than 40% of those aged 65 and over remain alive. Those aged 60 – 69 years have 9 times the relative risk of death compared to the UK general population (2.5 for ≥ 85's to 26 for ≤ 29's). The three leading causes of death are cardiovascular disease, infections, and malignancy.[1]

Patients receiving maintenance dialysis experience significant physical, emotional, mental and psychological impairments which are reflected in Health Related Quality of Life (HRQoL) scores.[2] Dialysis patients value improved QoL more than they do improved survival.[3,4]

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 (erythropoesis stimulating agents,[5] lipid lowering,[6] calcimimetics[7]) or have not been adequately evaluated in randomised trials (phosphate lowering, active vitamin D sterols). There is an urgent unmet need for interventions that improve survival in patients receiving dialysis.

Vitamin D Deficiency is Highly Prevalent But Not Routinely Supplemented in Patients on Dialysis



Mean plasma 25(OH)D concentrations in patients receiving dialysis, from 23 reports between 2004 and 2013, weighted by sample size.

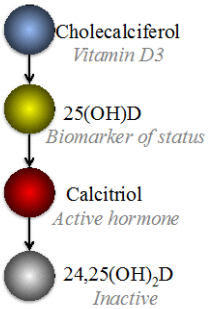
Severe vitamin D deficiency is defined as a plasma 25-hydroxyvitamin D (25(OH)D) concentration of ≤ 25nmol/L, mild-moderate deficiency as < 75nmol/L, and sufficiency ≥ 75nmol/L.[8] Plasma 25(OH)D begins to decline when the glomerular filtration rate falls below 45 ml/min/1.73m^2. Once patients reach dialysis, only a small minority are vitamin D sufficient. In a cohort of 6,518 German dialysis patients, 76% were vitamin D deficient.[9] Smaller studies report deficiency in 69 – 87%.[10-14] Despite the introduction of international and European guidelines to supplement vitamin D in this population, reports over the past decade consistently show vitamin D deficiency in dialysis patients (figure, left).[10,11,13-34] Since vitamin D is expensive to measure at approximately £30 per sample, and given that no randomised trials to date have assessed the effect of supplementation on outcomes, supplementation is not currently routinely undertaken in the NHS.

Current Treatment Paradigms do not Address Deficiency and Promote Vascular Calcification.

Dialysis patients are widely treated with the active vitamin D hormone, calcitriol, or its analogues. This practice arose decades ago, based on the false belief that the kidneys are the only site of activation. Although this view has been disproven and autocrine and paracrine activation occurs in every tissue, clinical practice has not changed. This treatment paradigm of active vitamin D compounds presents several serious concerns:

1. Systemic administration increases blood calcium and phosphate
2. Dose is limited by hypercalcaemia
3. It may potentiate vascular calcification
4. Potent induction of the vitamin D catabolic pathway, paradoxically potentiating vitamin D deficiency at the tissue level by catabolism of calcitriol and 25(OH)D at tissue level.

In contrast, the administration of colecalciferol would circumvent all of these limitations.



The term “vitamin D” refers to colecalciferol, synthesised in skin upon exposure to UV light. Colecalciferol is biologically inert, and is hepatically 25-hydroxylated in a substrate-dependent manner to yield 25-hydroxyvitamin D (25(OH)D). 25(OH)D is also largely biologically inactive, and its blood concentration is the most reliable marker of vitamin D status.[35] 25(OH)D is 1α-hydroxylated to the highly calcitropic active steroid hormone calcitriol (1,25-dihydroxyvitamin D). The false belief that calcitriol synthesis occurs only in the kidneys has led to the wide-spread use of calcitriol and its 1α-hydroxylated analogues (paricalcitol, alfacalcidol) in patients with kidney failure, primarily for the treatment of secondary hyperparathyroidism [these 1α-hydroxylated compounds are hereafter referred to as Vitamin D Receptor Activators (VDRAs)]. However, following the discovery of ubiquitous expression of the 1α-hydroxylase in extra-renal tissue,[36] it is now recognised that extrarenal synthesis of calcitriol occurs in most tissues and contributes to its circulating concentration.[37,38] Further, similar to other steroid hormone receptors, the vitamin D receptor (VDR) is ubiquitously expressed. Therefore, autocrine and paracrine synthesis of calcitriol occurs in target organs, and in health, the activation of the VDR in these tissues depends on adequate vitamin D concentrations.[39]

Consequences of Deficiency

Vitamin D is indispensible for skeletal health. Plasma concentrations below 20nmol/L result in rickets or osteomalacia.[40] However, the vitamin D endocrine system is involved in a wide range of cellular functions including cellular growth, proliferation, apoptosis, and inflammation.[39] A large body of evidence supports a role for vitamin D in reducing cardiovascular disease, malignancy and infections. In otherwise healthy persons, deficiency is strongly associated with cardiovascular, cancer and all-cause mortality, and key pathways in host defence are dependent upon vitamin D sufficiency;[41] each 25nmol/L reduction in 25(OH)D was associated with a 16% increase in all-cause mortality in a recent large meta-analysis including data from 849,412 subjects. The pooled relative risk (RR) was 1.35 (95% CI 1.13 to 1.61) for death from cardiovascular disease, 1.14 (1.01 to 1.29) for death from cancer, 1.30 (1.07 to 1.59) for non-vascular, non-cancer death, and 1.35 (1.22 to 1.49) for all-cause mortality.[42]

***Cardiovascular disease**:* The VDR is expressed in cardiac myocytes, vascular smooth muscle and endothelial cells. VDR knockout mice exhibit upregulation of the renin-angiotensin-aldosterone (RAAS) system, hypertension, left ventricular hypertrophy and heart failure.[43,44] In vitro, calcitriol directly suppresses renin expression, and regulates the proliferation of vascular smooth muscle cells (VSMC) and cardiac myocytes.[43,45] Vitamin D deficiency is associated with

increased arterial stiffness and endothelial dysfunction,[46] and predicts heart failure,[47] myocardial infarction, [48,49] stroke[50,51] and risk of cardiovascular death.[42,47]

Vascular calcification is highly prevalent in the ESRD population, where it is strongly associated with cardiovascular events and mortality.[52-54] Vitamin D deficiency is associated with increased arterial calcification across an array of studies,[55-58] including the development of coronary artery calcification,[59] and mice fed a vitamin D deficienct diet exhibit increased vascular calcification. In contrast, the systemic use of VDRAs (as is current practice in dialysis patients) may instead promote vascular calcification,[56] and indeed animal models of arterial calcification depend on the use of supraphysiological doses of calcitriol.[60]

This paradox is accounted for by virtue of increased intenstinal calcium and phosphate absorption, and increases in the plasma calcium phosphate product, with systemic VDRA use. Furthermore, administration of active vitamin D sterols result in a reduction of plasma vitamin D concentrations, due to potent induction of the vitamin D catabolic pathway.[56] These findings are consistent with evidence that polymorphisms in CYP24A1 associated with increased activity predict coronary artery calcification.[61]

Ensuring vitamin D repletion may therefore allow the autocrine and paracrine synthesis of calcitriol in cardiovascular tissues, activating VDR-dependent calcification inhibtory pathways. Calcitriol and its analogues, administered systemically, bypass the vitamin D auto-regulatory system and may paradoxically induce tissue calcitriol deficiency.

Malignancy: Vitamin D deficiency is associated with an increased risk of a wide variety of cancers, and vitamin D supplementation may both reduce cancer incidence and improve survival. Evidence to support this notion emerged from epidemiological data indicating an association between latitude and cancer incidence, suggesting that decreased sunlight exposure was permissive to the development of malignancy.[62] Subjects who have high prediagnosis 25(OH)D concentrations consistently demonstrate a 30-40% reduction in the incidence of colorectal cancer compared to those with low circulating 25(OH)D.[63,64] Similar associations have been reported for prostate and breast cancer,[65] although these data are less robust. An association has also been reported for haematological malignancies.[66] This association of vitamin D deficiency with cancer is supported by data from genetic studies. A recent mendelian randomisation study confirmed an association with breast cancer of polymorphisms that relate to serum 25(OH)D concentrations,[67] and a meta-analysis of studies of the FokI VDR polymorphism demonstrated a significantly increased risk of cancer for the ff versus FF genotype (HR 1.08, 95% CI 1.01 – 1.16).[68]

At the cellular level, binding of calcitriol to the VDR exerts anti-cancer effects by a wide variety of mechanisms including induction of p21, stabilisation of p27, targeting of activated EGFR for lysosomal degradation, modulation of intracellular kinase pathways such as p38 mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinases (ERKs) and phosphoinositide 3-kinases (PI3Ks), suppression of the anti-apoptotic gene BCL2 and VEGF, and induction of the tumour suppression gene E-Cadherin, as reviewed by Dusso et al[39] and Feldman et al.[69] Some cancers exhibit abberantly high basal expression of CYP24A1, rendering them resistant to vitamin D.[69] This finding may be of relevance to dialysis, where the systemic administration of calcitriol and its analogues result in 1,000 – fold upregulation of tissue CYP24A1 expression, and may therefore paradoxically result in tissue calcitriol deficiency.

Infection: During the 19th century, the use of tuberculosis (TB) sanatoria in sunny climates was widely advocated and thought to result in clinical improvement in patients with Tuberculosis. The role of vitamin D in host defence was recently confirmed in a seminal paper by Liu et al, demonstrating that the production of the antimicrobial peptide cathelicidin in macrophages was vitamin D-dependent, and that vitamin D augmented antimicrobial killing in vitro.[41] Indeed, individuals who carry polymorphisms in the VDR gene, or in the gene encoding the vitamin D

binding protein (DBP), have increased susceptibility to tuberculosis.[70,71] Viral respiratory tract infections have long been understood to follow a seasonal course, with peak incidences during the winter months and a nadir during the summer months. Many studies have suggest an association between vitamin D deficiency and the incidence and duration of viral respiratory tract infections (reviewed by Bryson and colleagues[72]). Respiratory tract infections occur in 85% of hospitalised children with rickets, compared to 10% of controls.[73] Vitamin D deficiency is also associated with the severity of community acquired pneumonia,[74] bacterial infections in patients with chronic liver disease,[75] opportunistic viral infections after renal transplantation,[76] risk of Clostridium difficile infections,[77,78] and orthopaedic prosthetic infections.[79]

4.2 Clinical Data

4.2.1 Efficacy

Colecalciferol supplementation improves outcomes in those without kidney failure

Current evidence supports the notion that colecalciferol supplementation reduces mortality. In a recent large meta-analysis of randomised trials including 13,637 participants randomised to colecalciferol or placebo, Chowdhury et al reported that supplementation with colecalciferol in subjects without kidney failure reduced all-cause mortality (HR 0.89, 95% CI 0.8 – 0.99).[42] Second, a recent Cochrane Collaboration meta-analysis found a reduction in cancer mortality with colecalciferol supplementation (HR 0.88, 95%CI 0.78 to 0.98).[80] In patients with renal failure, one small trial of 126 patients randomised to high dose ergocalciferol or placebo demonstrated reduced cardiovascular events in the ergocalciferol arm (HR 0.37, 95% CI 0.14 – 1.0).[81] Colecalciferol may also improve musculo-skeletal symptoms, sleep, and QoL assessed by the SF36 RAND.[82]

Colecalciferol improves biomarkers associated with outcomes

Increases in PTH, plasma calcium, phosphate, and the calcium phosphate product have all been associated with reduced survival in the dialysis population. The current treatment paradigm of high dose VDRAs in patients receiving dialysis adversely affects these parameters, resulting in increases in calcium, phosphate and the calcium phosphate product (although PTH is reduced). Importantly, this treatment paradigm is not supported by current evidence,[83] and may potentiate extra-skeletal calcification and tissue deficiency of calcitriol due to induction of CYP24A1 expression. In contrast, the systemic administration of colecalciferol results in high tissue concentrations of calcitriol without the same risk of causing hypercalcaemia seen with 1α-hydroxylated VDRAs.[84,85] Furthermore, Colecalciferol use results in significant reductions in PTH, and either reduced or unchanged plasma calcium and phosphate concentrations.[13,16] Colecalciferol also results in reductions in bone alkaline phosphatase (ALP), and improves the achievement of treatment targets for calcium, phosphate and PTH concentrations.[13]

4.2.2 Safety

High dose colecalciferol supplementation with doses ranging from 1,333 to 7,142 IU per day has been reported in 13 studies including 1,381 patients.[13,16,20,26-29,86-92] Even those studies that utilised doses in excess of 4,000 IU per day did not report an increase in rates of hypercalcaemia with colecalciferol.[20,86-88,90] In fact, since colecalciferol reduces PTH, its use is predictably accompanied by reduced use of VDRAs and phosphate binders, and net reductions in plasma calcium.[16,29]

5 RATIONALE FOR THE SIMPLIFIED TRIAL

There has been little progress in reducing morbidity and mortality in patients with ESRD. Current interventions in wide use in the dialysis population in the UK include erythropoiesis

stimulating agents (ESA), intravenous iron, oral phosphate binders, lipid lowering, calcimimetics, and active vitamin D compounds. Despite their considerable cost to the NHS, evidence from adequately powered randomised trials to support their use does not currently exist.

ESA therapy to partially correct haemoglobin may improve quality of life,[93] but haemoglobin normalization is associated with increased risk of cardiovascular events.[5,94,95] Intravenous iron is currently the focus of the PIVOTAL UK randomised trial, funded by Kidney Research UK. No randomised trials have evaluated phosphate lowering in dialysis. Lipid lowering with simvastatin and ezetemibe was assessed in the Study of Heart and Renal Protection (SHARP) in 9,270 patients with chronic kidney disease.[6] Although overall the primary endpoint of atherosclerotic cardiovascular events was met, in the subgroup of patients on dialysis (n=3,023), lipid lowering did not improve outcomes. Calcimimetics for the treatment of secondary hyperparathyroidism was assessed in the 3,883 patient EVOLVE trial, which failed to meet the primary endpoint of reduced mortality and cardiovascular events.[7] The effect of VDRAs on clinically important outcomes has not been evaluated in randomised controlled trials.[83] There is an urgent unmet need for cost effective interventions that improve outcomes in this patient population.

Current national and international treatment guidelines recommend the measurement and supplementation of vitamin D in patients on dialysis, even when they are receiving treatment with VDRAs.[8,96] The Kidney Disease Improving Global Outcomes (KDIGO) initiative accept that current evidence is lacking, and indeed identifies vitamin D supplementation in dialysis as a key research objective, but nevertheless argues for its use on the basis that the intervention is safe and inexpensive. Caution is necessary, however, when extrapolating from epidemiological data, which are unable to completely mitigate against problems of confounding and reverse causality. Observational data similarly supported the use of anti-oxidant vitamins including vitamins C and E, which were found to be of no benefit or even harmful in adequately powered interventional trials.[97,98] Widespread supplementation with colecalciferol should therefore be rigorously tested in an adequately powered randomised trial.

The merits of population-wide colecalciferol supplementation are being assessed in the VITAL trial, which has randomised an unselected population of 26,000 North American participants to colecalciferol or placebo, and will assess the impact on cancer incidence and cardiovascular events.[99] This trial is expected to report in 2018. In contrast, despite the much higher prevalence of vitamin D deficiency in patients on dialysis, the effect of colecalciferol supplementation on survival and QoL is not being assessed in any current trials. Ongoing studies aim to address the effect of supplementation on surrogate outcomes such as plasma vitamin D concentration, cathelicidin concentrations (NCT01175798), mineral metabolism targets (EudraCT 2008-002387-33), and immune responses to vaccination (EudraCT 2011-004621-26).

Treatment of patients with ESRD is disproportionately costly, accounting for up to 2% of the NHS healthcare budget while representing only 0.05% of the population.[100] Despite this, nephrology lags behind most disciplines in testing interventions in randomised trials.[101] A key obstacle to trials in dialysis is the readiness with which treatment guidelines are accepted into clinical practice without adequate prior evaluation or introduction in a randomised manner. Examples include treatment targets for PTH, phosphate, calcium and haemoglobin. In a recent survey of UK renal units, most confirmed that vitamin D was neither routinely measured nor supplemented in the dialysis population (data on file). In contrast to other countries where supplementation is already more prevalent, this lag in implementing existing guidelines provides the opportunity to test the hypothesis that colecalciferol improves survival and quality of life in a population that is mostly treatment-naïve. There is an urgent need to address this question before guideline-driven colecalciferol supplementation becomes entrenched in clinical practice.

6 TRIAL DESIGN

6.1 Design

SIMPLIFIED is a prospective, randomised, open-label, pragmatic, multicentre registry-facilitated superiority trial of colecalciferol (also known as cholecalciferol) versus standard care in patients receiving dialysis.

6.2 Number of Centres

72 renal units across the UK contribute data to the UK renal registry (UKRR), and it is anticipated that SIMPLIFIED will be conducted in up to 65 of these units.

6.3 Number of Subjects

Approximately 4,200 subjects will be included in the trial.

6.4 Participants Trial duration

Assessment of the primary endpoint will require 2,200 events. It is estimated that this will require a median treatment period of 5.5 years, and an overall trial duration of approximately 7 years.

6.5 Trial objectives

6.5.1 Primary objective

To determine the effect of colecalciferol 60,000IU fortnightly on patient survival.

6.5.2 Secondary objectives

To determine the effectiveness of colecalciferol 60,000IU fortnightly in improving quality of life and secondary clinical outcome measures.

6.6 Trial Outcome Measures

6.6.1 Primary outcome measure

The primary outcome is all-cause mortality.

6.6.2 Secondary outcome measures

- Health-Related Quality of life by EQ5D
- Hospital admission-requiring composite cardiovascular events defined as CV death, acute coronary syndrome (ACS), heart failure or arrhythmia admissions, and stroke
- Infections requiring admission
- Cancer incidence
- Fractures requiring admission
- Cost-effectiveness of colecalciferol from the perspective of the NHS.

6.6.3 Exploratory outcome measure

Exploratory analyses will attempt to model the joint evolution of VDRA use and secondary endpoints.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

To be included in the trial the patient must:

- Has given written informed consent to participate
- Aged 18 years or over
- UK Resident
- Has ESRD requiring dialysis

7.2 Exclusion Criteria

The presence of any of the following will preclude patient inclusion:

- Treatment with high dose (>1,000IU/day) colecalciferol or ergocalciferol in the last 30 days
- Persistent hypercalcaemia (corrected calcium >2.62 mmol/l on three separate and sequential occasions without precipitating cause†)
- Hypersensitivity to colecalciferol or any of the excipients of the product
- Life expectancy < 6 months
- Women who are pregnant / planning to become pregnant or are breastfeeding
- Opted out from contributing data to the UKRR

7.3 Treatment Assignment and Randomisation Number

Patients will be randomised to the treatment group or control group in a 1:1 ratio using a central computerised randomisation system.

7.4 Subject withdrawal criteria

- Patients will be withdrawn at the discretion of the PI/CI if continuation in the trial is deemed to be against the patient's best interest, for example in the event of a SUSAR.
- Patients may withdraw consent for continuation in the trial at any point. Patients may either withdraw only from trial participation (allowing ongoing capture and use of their data until the end of the trial), or may withdraw both from the trial and all further data capture.
- Patients with persistent hypercalcaemia may be withdrawn from the trial if, in the opinion of the treating clinician, colecalciferol is contributing to hypercalcaemia. Prior application of the hypercalcaemia and vitamin D toxicity algorithms (Appendix 4 and 5 respectively) is a prerequisite to withdrawal for hypercalcaemia.

Reasons for patient withdrawal will be recorded in the Case Report Form (CRF).

Patients in the colecalciferol arm who become pregnant during the trial will be withdrawn from treatment, but will remain in the trial.

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† Patients in whom a precipitating cause for hypercalcaemia has been identified and addressed (for example, active vitamin D compounds reduced, calcium-based phosphate binders withdrawn, hyperparathyroidism treated, dialysate calcium adjusted) may be enrolled in the trial once the corrected calcium concentration has reduced below the upper threshold for exclusion from the trial.
Historic hypercalcaemia is irrelevant providing the patient is not hypercalcaemic at the time of screening/randomisation.

8 TRIAL TREATMENTS

8.1 Colecalciferol group

Patients randomised to receive colecalciferol will be prescribed colecalciferol 60,000 IU fortnightly by their nephrologist from local sources, in addition to standard care.

For the majority of patients, standard care at entry will include VDRAs, and their continued use based on local treatment guidelines will be permitted. It is anticipated that, in the colecalciferol arm, the use of these agents will become greatly reduced.

8.2 Control Group

Participants randomised to the control group will receive standard care based on local treatment guidelines, but will not be permitted to receive colecalciferol or ergocalciferol > 1000IU per day for the duration of the study, unless vitamin D deficiency-related osteomalacia is diagnosed.

Patients in the control group will be permitted to continue treatment with any active (1α-hydroxylated) compounds, including alfacalcidol, calcitriol, paricalcitol and 22-oxacalcitriol. The control group will also be permitted to take low dose (≤ 1000IU) of colecalciferol or ergocalciferol.

8.3 Colecalciferol dosage schedule

8.3.1 Route of Administration

Colecalciferol 60,000IU by mouth, administered fortnightly (for subjects receiving haemodialysis, this is likely to coincide with their dialysis treatment).

8.3.2 Maximum duration of treatment of a subject

Treatment will continue until the primary endpoint has been reached (2200 events). It is anticipated that this will be between 5.5 and 7 years.

8.3.3 Procedures for monitoring subject compliance

1. For patients receiving in-centre haemodialysis, colecalciferol will normally be administered as part of the dialysis prescription where possible, and hence will be supervised.
2. Patients receiving home therapies (peritoneal or home haemodialysis) will receive reminders by smartphone app or email as per patient preference.
3. Patients will complete a questionnaire every 6 months whilst in the trial. This will include self-reporting of compliance.
4. Plasma vitamin D will be measured during the first year of the trial. Samples will be taken 4 months after the baseline visit for the first 230 patients enrolled into the trial.

8.4 Presentation of the drug

Patients may be prescribed any UK licenced oral preparation of colecalciferol that would permit the oral administration of a 60,000IU dose once per fortnight, or equivalent (e.g. 30,000IU weekly).

8.5 Known drug reactions & interaction with other therapies

Interactions with other medicinal products and other forms of interaction:

All known interactions are listed in the latest version of the SmPC for prescribed colecalciferol. As the trial permits the use of all UK licensed oral preparations of colecalciferol, the relevant SmPC for the brand used must be referred to as per standard clinical practice when determining interactions.

Contra-indicated medications:

1. Other colecalciferol containing medications (e.g. calcichew D3: patients taking calcichew D3 doses that equate to > 1,000IU colecalciferol in the last 30 days are not eligible for the trial. Such patients may become eligible once colecalciferol has been discontinued for 30 days. Calcichew D3 should be converted to calcichew without D3 for participants randomised to the colecalciferol arm. Participants in the control arm may continue to use calcichew D3 providing that the total colecalciferol dose does not exceed 1,000 IU per day). Any decision to withdraw colecalciferol >1,000 IU should be made on clinical grounds.
2. Ergocalciferol-containing medications

8.6 Dosage modifications

The treatment dose may be reduced in the presence of persistent hypercalcaemia and evidence of vitamin D toxicity. In the event that vitamin toxicity is suspected, the hypervitaminosis D algorithm provided in Appendix 5 should be followed.

8.7 Legal status of the drug

Colecalciferol is licenced in the UK for the treatment of vitamin D deficiency.

8.8 Drug storage and supply

Colecalciferol will be supplied as per local practice. Colecalciferol will not require trial-specific dispensing, labelling or accountability records. The storage conditions will be as stipulated for the brand used at each site.

8.9 Concomitant therapy

With the exception of colecalciferol or ergocalciferol (as described under heading 8.5), there is no contra-indicated concomitant therapy.

8.9.1 Active Vitamin-D Compounds

Active vitamin D compounds are 1α-hydroxylated vitamin D sterols and include:

- Alfacalcidol
- Calcitriol
- Paricalcitol
- 22-Oxacalcitriol

8.9.1.1 Colecalciferol group

Participants in the colecalciferol group may continue to receive active (1α-hydroxyated) compounds as clinically indicated, either for the treatment of secondary hyperparathyroidism, or hypocalcaemia.

It is anticipated that colecalciferol 60,000IU fortnightly will reduce or remove the requirement for active vitamin D. Prescriptions for active vitamin D preparations should be assessed regularly along with routine dialysis reviews as per local policy.

8.9.1.2 Control group

Patients in the control group will continue to receive standard care. For many participants, this will include an active vitamin D preparation.

9 PROCEDURES AND ASSESSMENTS

9.1 Screening

Screening may take place on the dialysis unit, in dialysis clinics, or in the patient's home for those receiving home therapies, and should be carried out by delegated members of the trial team.

The screening and baseline visits may be readily combined in those patients who agree to participation in the trial.

9.1.1 Screening Assessments

Screening will be restricted to an assessment of inclusion and exclusion criteria and obtaining informed consent.

The screening table is shown below. In order to be eligible, responses must be as indicated. Eligibility must be confirmed by a medically qualified person.

Criteria	Yes	No
Provide informed consent	✓	
Aged 18 years or over	✓	
UK resident	✓	
Renal failure requiring dialysis	✓	
Treatment with high dose colecalciferol or ergocalciferol (> 1,000IU per day) in the last 30 days‡		✓
Persistent hypercalcaemia (corrected calcium >2.62 mmol/l on three separate and sequential occasions without precipitating cause).		✓
Hypersensitivity to colecalciferol or any of the excipients		✓
Life expectancy ≤ 6 months		✓
Women who are pregnant / planning to become pregnant or are breastfeeding		✓
Opted out from contributing data to the UKRR		✓

‡ Patients prescribed colecalciferol or ergocalciferol > 1,000 IU/day may be included after a 30 day run-in if clinically appropriate to discontinue colecalciferol.

9.1.2 Informed consent

The patient will be provided with the approved Patient Information Sheet 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 trial 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. Consent interviews may be conducted by telephone.

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 on to the study.

9.1.3 Subject Registration and Randomisation

The PI or suitably qualified and delegated member of the study team will register the patient by entering their screening data into the Simplified web portal. Once the full screening details have been entered and eligibility confirmed, the patient will be randomised by the system. Please refer to the Simplified Trial Manual for details on how to complete the screening and randomisation process via the Simplified web portal.

9.2 Baseline assessment (Entry)

Patient demographics and full medical history will be taken at baseline. The following will be recorded in the CRF:

a) Date of birth
b) Ethnicity
c) Dry-weight in Kg
d) Gender
e) Significant past medical history
f) Comorbidity, specifically but not exclusively:
    i. Heart Failure
    ii. Ischemic Heart Disease
    iii. Cardiovascular Disease
    iv. Diabetes
    v. Neoplastic disease
g) Dialysis modality
h) Vascular Access if relevant
    i. Fistula
    ii. Tunnelled dialysis catheter
    iii. Other
i) Biochemical parameters§
    i. Corrected Calcium
j) Current Medication

§ 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.

i. Active vitamin D
ii. Other vitamin containing preparations
iii. Cinacalcet
iv. Phosphate binders
v. Statin
vi. ACE inhibitor
vii. Angiotensin Receptor Blocker
viii. Other

k) Health-Related Quality of Life (EQ5D)**
l) Confirmation of contraception use (where appropriate)

9.3 Follow-up, trial assessments (6-monthly)

SIMPLIFIED is a pragmatic trial. Many variables often captured face to face or during trial visits will be captured indirectly using a variety of data sources including ONS, Hospital Episode Statistics (HES) or equivalent, UK and Ireland Association of Cancer Registries (UKIACR) and the UKRR.

9.3.1 Indirect Assessments

a) Data on the primary endpoint (death) will be captured via regular data tranches from ONS.

b) Data on relevant secondary endpoints will be captured using HES data downloads (or equivalent in Scotland, Wales or Northern Ireland), obtained regularly for the trial population. Given the low risk nature of the intervention, the high complication rate in the trial population, and the intensiveness of routine clinical monitoring, SIMPLIFIED will only register serious adverse events of special interest, including hospitalisation resulting from acute coronary syndrome, infection or fracture).

c) Data on the development of cancer will be obtained via regular data downloads from UKIACR

d) Laboratory data will be obtained from the results of routinely collected blood tests via the UKRR on an on-going basis. Calcium and 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 SIMPLIFIED secure data hosting area on all participants in the trial. Monitoring for hypercalcaemia will be driven by routine clinical practice and management based on local hypercalcaemia guidelines and practices.

9.3.2 Direct Assessments

9.3.2.1 Vitamin D concentrations – 4 Months

During the first year of the trial, the first 230 participants will have a 25-hydroxyvitamin D concentration measured after 4 months. Sampling will require approximately 1ml of blood, and is described in the trial manual. Samples will be sent to the core biochemistry facility for central analysis. No other assessments are required at this time point.

*** EQ5D may be completed using the paper form included in the baseline CRF, or may be entered directly using the trial-specific smartphone/tablet application. If the EQ5D is completed electronically, this must be confirmed on the baseline CRF.*

9.3.2.2 *Trial assessments – 6 monthly +/-6 weeks*

For all participants, trial assessments will be carried out every 6 months ± 6 weeks. Assessments 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 dialysis units or home address for those on home therapies), telephone interview (which may coincide with dialysis), secure web-portal, or smartphone/tablet application.

Assessments will include the following:

a) Dialysis Status
b) HRQoL using the EQ5D questionnaire
c) Self-reported drug adherence
d) Current medications
e) Hospital admissions and indication

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

9.4 End of Trial Participation

SIMPLIFIED is an event driven trial and will continue until 2,200 events have accrued. 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 colecalciferol unless ongoing treatment is indicated as per local or national treatment guidelines. If colecalciferol is discontinued after the end of the trial, patients should return any unused study drug to their dialysis centre.

9.5 Schedule of Assessments

Assessment Schedule	Pregnancy testing	Plasma vitamin D	Treatment Supplied	Comorbidity	SAR reporting	Blood results	Medication review	Adherence reporting	EQ5D
Baseline	✓			✓		✓	✓		✓
Month 4 (only in first 230 subjects)		✓							
6-Monthly for trial duration (indirectly completed by participants)				✓			✓	✓	✓
Routinely and as required			✓		✓				
Captured via data linkage						✓			

9.6 Trial restrictions

Pregnancy in patients receiving dialysis is highly unusual. Female patients actively seeking to conceive should not be included in the trial. Trial participants in the colecalciferol arm who become pregnant should discontinue colecalciferol.

Women of childbearing potential randomised to colecalciferol must use one of the following, reliable forms of contraception for the entire duration of treatment and for 4 weeks after last colecalciferol treatment:

- Oral contraceptive (either combined or progesterone alone)
- Contraceptive implant, injections or patches
- Vaginal ring
- Intrauterine device (IUD, coil or intrauterine system)
- Condom **and** cap or diaphragm **plus** spermicide (chemical that kills sperm)
- True abstinence where this reflects your usual and preferred lifestyle

Women of childbearing potential do not need to use contraception if they:

- Have been randomised to the control group
- Have only one partner, and the man has had an operation to cut the tubes that carry sperm (vasectomy)
- Cannot become pregnant
- Practice true abstinence as part of their usual and preferred lifestyle (no sexual activity from the first dose until 28 days after the last dose of colecalciferol). If they become sexually active, they must use one of the methods listed above.

10 ASSESSMENT OF SAFETY

10.1 Routine Safety Monitoring in Dialysis Patients

Dialysis is a life-saving treatment. Non-adherence to dialysis results in a rapid deterioration in patient health, and ultimately in death. Dialysis patients are therefore intensively monitored. Dialysis sessions involve continuous haemodynamic monitoring, and comprehensive

biochemical and haematological tests are performed at least monthly. All dialysis data for each patient are reviewed by renal unit staff, typically in “sit down ward round” meetings, where clinical parameters and test results are reviewed and treatments adjusted.

In-centre haemodialysis
The majority of patients (85% of the target population) receive in-centre haemodialysis 3 times per week. Sessions are scheduled in advance. In-centre dialysis is overseen by nursing staff and clinicians, or with named clinical cover. Changes in a patient’s health are usually identified by dialysis unit staff, or reported to dialysis unit staff by patients. Given the nature of dialysis treatment schedules (a fixed, named slot is allocated to every patient), it is immediately apparent when patients fail to attend. This is usually the result of an intercurrent illness (or more rarely non-adherence). Given the grave implications of a failure to dialyse, patients or their relatives are immediately contacted to identify the reasons for non-attendance.

Home Therapies
Patients who are well may receive dialysis at home, in the form of home haemodialysis or peritoneal dialysis. For such patients, the same imperative for regular monitoring of biochemistry and dialysis parameters exists, and contact with their treating centre therefore occurs at least 3 monthly. Given the complexity of the intervention, all home therapies patients have direct access to a specialist on call service provided by their dialysis unit. Clinical teams are made aware of problems via this route, during scheduled patient contact, or in the course of delivering equipment and consumables. Units also increasingly employ remote monitoring.

Hospital admissions
Patients admitted to hospital will require dialysis within 24 to 48 hours of admission. Clinical teams are therefore obligated to contact renal teams in the event of an emergency admission. In the case of elective admissions, dialysis treatment during the course of the admission is planned in advance.

10.2 Safety of Colecalciferol

Colecalciferol is a very safe treatment. It is biologically inert, and requires 1,25-hydroxylation for activation. Patients randomised to colecalciferol in SIMPLIFIED will receive the equivalent of 4,285IU colecalciferol per day. This dose should be viewed against the physiological cutaneous synthesis of 10,000IU – 25,000IU of colecalciferol upon exposure to 1 minimal erythematous dose (MED) of sunlight.[102]

Colecalciferol is used to fortify foodstuffs in the United Kingdom, and is available over the counter (OTC). Consistent with this very favourable safety profile, listed adverse reactions are limited to hypercalcaemia, rash, itch and hives.

It should also be noted that most participants in the trial will receive active vitamin D compounds such as alfacalcidol, calcitriol or paricalcitol, and this will remain the case in the control group. The use of colecalciferol in SIMPLIFIED is therefore likely to be much safer than the standard of care.

10.2.1 Reference Safety Information (RSI)

The reference safety information to be used in this trial for assessing whether an adverse reaction is expected is in section 4.8 of the SmPC for colecalciferol 20,000IU capsules (Fultium-D3, Internis Pharma Ltd.).

10.3 Definitions

Term	Definition
Adverse event	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily caused by or related to this treatment.
Adverse Reaction	All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Unexpected Adverse Reaction	An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI). When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any untoward medical occurrence that at any dose: - results in **death**, - is **life-threatening** - requires **hospitalisation** or **prolongation** of existing inpatients´ hospitalisation, - results in persistent or significant **disability or incapacity**, - is a congenital anomaly or birth defect. - Is another important medical event Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

10.4 Safety Monitoring in the SIMPLIFIED trial

Trial participants will consent to the use of data captured by the UK Renal Registry (UKRR), Office of National Statistics (ONS), United Kingdom and Ireland Association of Cancer Registries (UKIACR), Hospital Episode Statistics (HES), Information Services Division Scotland (ISD), Patient Episode Database for Wales (PEDW) and Health and Social Care Services Northern Ireland (HSNI) data at the start of the trial. The STO will collect all events associated with hospital admissions from HES, ISD, PEDW or HSNI data as appropriate, and deaths from ONS on a continuous basis. All hospitalisation-requiring and hospitalisation-associated events, and all deaths, will therefore be captured continuously directly by the STO.

Given 1) the intensive monitoring of dialysis patients in routine clinical care described above, 2) the comprehensive data on clinical events recorded directly by the STO, and 3) the favourable safety profile of colecalciferol, the SIMPIFIED 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. Reactions that are either serious (SARs) or serious and unexpected (SUSARs) will require reporting (see Appendix 1 & 2). Principal Investigators (PIs) will be required to record and report SARs and SUSARs to the STO as described under 10.9 and 10.10 below. *
3. All Adverse Events (AEs) will be captured using the routine data sources described above. These data will be filtered to identify all SAEs
4. The resulting line listing of SAEs will be reviewed by the CI and reported to the Sponsor every 6 months.
5. Line listings of SAEs and reported SARs & SUSARs will form the basis of the Development Safety Update Report (DSUR) to be submitted annually to the MHRA and REC.

***Recording and Reporting by Principal Investigators**
Principal Investigators are not required to record or report to the STO any AEs or ARs unless these fulfil the criteria for a SAR (see 10.9):

1. Serious
2. Directly attributable to colecalciferol

10.5 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the latest version of the RSI. This must be used when making a determination as to the expectedness of the adverse reaction.

10.6 Expected Adverse Events/Serious Adverse Events (AE/SAE)

The principal investigator or delegated members of staff do not need to record or report any expected adverse events (AEs) or Serious Adverse Events (SAEs). All adverse events are captured directly by the STO as described in 10.4.

10.7 Evaluation of SAEs

The Trial Office will identify from continuously collected HES, ISD, PEDW, HSNI and ONS data any SAE/SARs.

10.8 Reporting SAEs

SAEs will be identified as described in 10.4, and will be reviewed by the CI. SAE/SARs will be reported to the Sponsor as a line listing at least 6 monthly throughout the duration of the trial. This listing will form the basis of the annual DSUR submission.

10.9 Reporting Serious Adverse Reactions (SARs)

All SARs (serious adverse events that are judged to be related to colecalciferol) must be reported by the PI to the Chief Investigator and Sponsor within 24 hours of awareness using the SAR reporting form. Further review of expectedness will be undertaken by the Chief Investigator.

10.10 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected serious adverse reactions related to colecalciferol that occur in the trial and are also unexpected (SUSARs) are subject to expedited reporting. Principal investigators that become aware of a SUSAR should contact the trial office immediately to be guided through the reporting process.

The Sponsor has delegated the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor
- MHRA
- Ethics Committee

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

10.10.1 Timelines for reporting SUSARs

10.10.1.1 Fatal or life-threatening SUSARs

All parties listed in 10.10 must be notified as soon as possible but no later than **7 calendar days** after the STO and Sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

10.10.1.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 10.10 as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

10.10.2 How to report a SUSAR

10.10.2.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the following criteria are met:

a) a suspected Investigational Medicinal Product (IMP) (colecalciferol)

b) trial subject code number

c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship

d) an identified reporting source

e) An unique trial identifier (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)

f) an unique case identification (i.e. sponsor's case identification number).

10.10.2.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other

available sources. Further available relevant information should be reported as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

10.10.2.3 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

10.11 Pregnancy Reporting

Pregnancy reporting is required within 7 days of notification for any female patient receiving active treatment with colecalciferol.

All pregnancies within the trial should be reported to the Chief Investigator and the Sponsor using the pregnancy reporting form.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

11 TOXICITY – EMERGENCY PROCEDURES

The risk of vitamin D toxicity at the specified dose is extremely low.

Hypercalcaemia is common in dialysis patients even in the presence of vitamin D deficiency, and it is a poor indicator of toxicity in this setting. Furthermore, active vitamin D preparations in common use in dialysis patients are highly calcaemic and require frequent dose adjustment.

National and international treatment guidelines define targets for corrected calcium concentrations (as well as PTH and phosphate). Most renal units either follow these guidelines or employ local guidelines that define biochemical target ranges for Chronic Kidney Disease Mineral Bone Disorder (CKD-MBD). This would include monthly review of biochemistry results and the adjustment of treatments in response to hypercalcaemia.

The commonest causes of hypercalcaemia are iatrogenic (secondary to 1α-hydroxylated vitamin D preparations), and hyperparathyroidism. Current interventions in response to hypercalcaemia include reduction or discontinuation of 1α-hydroxylated vitamin D preparations, reduction or discontinuation of calcium-containing phosphate binders, reduction in dialysate calcium, and the introduction of calcimimetics.

11.1 Response to hypercalcaemia

Where local guidelines for the management of hypercalcaemia are operational, these may be applied. Where local guidelines are not in use, where ambiguity exists, or where principal investigators favour the use of SIMPLIFIED guidelines, the hypercalcaemia algorithm provided in Appendix 4 may be used.

If all appropriate actions have been taken and patients remain hypercalcaemic in the absence of an identifiable cause, and if vitamin D toxicity is suspected, the toxicity algorithm provided in Appendix 5 should be followed.

If vitamin D toxicity is confirmed, colecalciferol should be temporarily discontinued until hypercalcaemia resolves. Colecalciferol should be reintroduced as described in Appendix 5.

The STO must be notified of any change in colecalciferol dose using the Simplified secure web portal.

12 EVALUATION OF RESULTS

12.1 Response criteria

12.1.1 Primary efficacy

The primary efficacy endpoint is time to all-cause death. Deaths will be identified from Office of National Statistics (ONS) data on a running basis with regular downloads for the duration of the trial. All deaths occurring from the date of randomisation will be included. The cause of death will be captured from the cause listed on the death certificate.

Prior to the primary analysis, survival status will be confirmed by cross-referencing UKRR and ONS data. For participants where no death has been recorded by either ONS or the UKRR at the end of the trial (once 2,200 deaths have been recorded), follow-up time will be censored at the point of last known follow-up. Last known follow-up will be defined as whichever is most recent of either the date of last recorded UKRR-submitted dialysis results or last 6-monthly questionnaire follow-up.

The primary endpoint will be analysed by intention to treat.

12.1.2 Secondary Efficacy

Secondary efficacy parameters include:

- Health-Related Quality of life by EQ5D
- Hospital admission-requiring composite cardiovascular events defined as CV death, acute coronary syndrome (ACS), heart failure or arrhythmia admissions, and stroke
- Incidence of infections requiring admission
- Incidence of Malignancy
- Incidence of fractures requiring admission
- Cost-effectiveness of colecalciferol from the perspective of the NHS.

13 STORAGE AND ANALYSIS OF SAMPLES

Samples for the measurement of plasma vitamin D concentration will be collected after 4 months and sent to a central storage facility at the University of Cambridge. All samples will be stored securely in a -80°C freezer prior to analysis by a central laboratory as described in the trial manual.

14 STATISTICS

14.1 Statistical methods

14.1.1 Primary assessment of colecalciferol efficacy at scheduled study end

The primary efficacy analysis will be by “intention-to-treat” adjusted for baseline characteristics including age, gender, diabetic status and dialysis vintage. The primary analysis will be carried out after the occurrence of 2,200 events, using Cox proportional hazards regression modeling to test the effects of randomisation to colecalciferol on all-cause mortality. The survival times will be summarised using Kaplan-Meier curves. All estimates of hazard ratios associated with treatment and baseline covariates will be provided with 95% confidence intervals and p-values.

14.1.2 Secondary assessments

Secondary assessments will evaluate

- The effect of randomisation to colecalciferol on QoL using EQ5D data
- Intention to treat analyses on the effect of randomisation to colecalciferol on:
  - Hospitalisation with cardiovascular events including atherosclerotic events, arrhythmias, heart failure, and stroke
  - Infection requiring admission
  - Incidence of malignancy
  - Fracture requiring admission
- Intention-to-treat analysis of time to first non-atherosclerotic cardiovascular event (any cardiovascular death, admission-requiring heart failure, arrhythmia)

Secondary endpoints will be assessed using time to event analysis (Cox proportional hazards regression modeling). Time to event data will be summarised using Kaplan-Meier curves. The treatment effect for secondary endpoints will be reported using point estimates, with nominal 95% confidence intervals and p-values.

However the overall conclusions of the study in terms of formal inference to reject or retain the null hypotheses associated with each endpoint will explicitly account for multiple testing to restrict the family-wise error rate (the overall chance of one or more type I errors) to below 5%. A gate-keeper approach will be adopted to assess the primary endpoint of all-cause mortality, whereby only if the hypothesis of no effect on all-cause mortality is rejected will any other formal inference take place. The detailed approach to be taken with the remainder of the endpoints will be specified in full in the statistical analysis plan before any examination of endpoints broken down by treatment arm occurs. The endpoints considered, will include:

- HRQoL
- Hospitalisation with cardiovascular events including atherosclerotic events, arrhythmias, heart failure, and stroke
- Infection requiring admission
- Incidence of malignancy
- Fracture requiring admission

Events that may occur multiple times (acute coronary syndrome, fracture) will be analysed using repeated events analysis. The procedure for repeated event failure-time analysis will be described in the statistical analysis plan.

14.1.3 Exploratory analysis: VDRA use

VDRA use will be captured and summarised, broken down by treatment arm. Exploratory analyses that attempt to model the joint evolution of VDRA and efficacy endpoints will be performed.

All continuous variables will be summarised using the following descriptive statistics: n (number of non-missing observations), mean, standard deviation, median, maximum and minimum. The frequency and percentages (calculated using the number of non-missing observations as the denominator) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Control, Colecalciferol) and will be annotated with the total population size relevant to that table/treatment, including any missing observations. Exploratory figures will also be provided such as histograms and boxplots and may lead to the transformation of endpoints as judged appropriate to aid the interpretation of summary statistics.

14.2 Interim analyses

A feasibility assessment will be carried out between months 12 and 15 of the trial. Feasibility will be predicated on recruitment rate (target 887 patients recruited after 12 months), and separation between arms by plasma vitamin D concentration after 4 months of treatment of 20nmol/l.

14.3 Number of Subjects to be enrolled

The study will recruit 4200 patients over 3 years. We estimate that the control arm has a 3-year survival of 68%. Using Cox proportional hazards regression (two-sided 5% significance) will enable a hazard ratio of 0.87 to be detected with 90% power assuming that 2200 events occur during the trial (estimated to require a duration of 7 years).

14.4 Criteria for the premature termination of the trial

The trial may be terminated prematurely on the recommendation of the Independent Data Monitoring and Ethics Committee (IDMEC) and the Trial Steering Committee if in their view, in the light of analyses of safety and any other information considered relevant, the randomized comparisons in the study have provided **both** (i) "proof beyond reasonable doubt"[††] that for all, or some specific types of, patients prolonged use of colecalciferol is clearly indicated or clearly contraindicated; **and** (ii) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the results of other trials.

14.5 Statistical analysis plan

A statistical analysis plan will be finalised before any analysis is undertaken. Any additions or changes to the analyses between the first version and when the data is initially examined, or from the protocol, will be fully documented.

14.6 Procedure to account for missing or spurious data

We do not anticipate a substantial rate of missing data, and hence will generally perform complete case analysis, and report the amount of missing data. If the rate exceeds 10% then a set of sensitivity analyses will be added to the statistical analysis plan.

14.7 Definition of the end of the trial

The trial will end once 2,200 deaths have been recorded.

15 DATA HANDLING AND RECORD KEEPING

15.1 CRF

Screening and baseline data will be captured using a paper CRF, and entered into the trial database using the secure Simplified web portal. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers, the investigators, clinical trial monitors, Auditors and Inspectors as required.

†† Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of at least three standard deviations in major morbidity or mortality in an interim analysis would be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance.

All CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used.

Please refer to the Simplified Trial Manual for further details on completion and retention of the CRF.

15.2 Source Data

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

Source documents include:

1. Patient medical records
2. Screening / Baseline paper CRF
3. Original signed consent forms
4. UKRDC-held blood test results
5. HES datasets or equivalent (e.g. ISD)
6. ONS data
7. Follow-up questionnaires (in paper or electronic format as per patient preference).

15.3 Data Protection & Patient Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Trial participants will provide explicit consent to the use of patient identifiable data for the purposes of the conduct of the trial. The STO will hold patient identifiable data on all trial participants including name, date of birth, gender, NHS number or equivalent, home address and postcode, telephone number and email address where applicable. Patient identifiable data will be stored separately from anonymised trial data on a secure server hosted within University of Cambridge School of Clinical Medicine Secure Data Hosting Service‡‡. Patient identifiable data will be accessible to the STO within the Cambridge Clinical Trials Unit, clinical trial monitors, auditors and inspectors as required. It is necessary to 1) perform validation of NHS numbers and linkage to routinely collected datasets (UKRR, 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 trial.

15.3.1 NHS Digital (Hospital Episode Statistics), Office of National Statistics, UKRR (Patient/View) and UK and Ireland Association of Cancer Registries (UKIACR)

Applications will be made to the relevant bodies to access outcome data routinely collected by them. This may include Hospital Episode Statistics and mortality information. The applications and resulting data will be managed by the STO, Coordinating Centre at the Cambridge Clinical Trials Unit and the University of Cambridge.

‡‡ http://cscs.medschl.cam.ac.uk/about-us/policies/patient-identifiable-data-2/

15.3.2 Identifiable Data Transfer from Local Site to STO and Coordinating Centre

All identifiable data will be securely sent to the STO and/or the Coordinating Centre by recorded delivery or via secure data transfer and stored in a separate, password-encrypted database in compliance with the Data Protection Act, with permission for access restricted to delegated trial staff. Consent will be sought for the transfer of identifiable information.

16 TRIAL STEERING COMMITTEE

The Trial Steering Committee (TSC) is responsible for the review of the trial and related activities at regular intervals. The TSC also provides overall supervision for the trial, to ensure that it is conducted in accordance with the protocol and GCP and to provide advice through its independent chairman. The committee will aim to convene at regular intervals to review the data and discuss if the trial is on course to meet the sample size requirements. The details of the TSC are set out in the Simplified Trial Steering Committee Charter.

17 INDEPENDENT DATA MONITORING & ETHICS COMMITTEE

The Independent Data Monitoring & Ethics Committee (IDMEC) will assess the accumulating evidence for safety and efficacy throughout the conduct of the trial.

During the trial, details of all serious adverse events (SAEs) and other safety data will be provided regularly in strict confidence to the chairman of the independent IDMEC. In the light of this information and any other information considered relevant, the IDMEC will advise the Steering Committee if, in their view, the randomised comparisons in the study have provided **both** (i) "proof beyond reasonable doubt"[§§] that for all, or some specific types of, patients prolonged use of colecalciferol is clearly indicated or clearly contraindicated; **and** (ii) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the results of other trials.

The Steering Committee can then decide whether to modify the study, or to seek additional data. Unless this happens, the Steering Committee, collaborators, study participants and all study staff (except those who provide the confidential information to the IDMEC) will remain blind to the interim results on mortality and morbidity until the end of the study.

The details of the IDMEC are set out in the SIMPLIFIED Independent Data Monitoring and Ethics Committee charter.

18 ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator must ensure that

[§§] *Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of at least three standard deviations in major morbidity or mortality in an interim analysis would be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance.*

each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator will obtain written informed consent from each patient before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each patients signed informed consent form and provide a copy to 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.

Any new information which becomes available, which might affect the patient's willingness to continue participating in the trial will be communicated to the patient as soon as possible via their preferred method of communication.

18.2 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.

18.3 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

18.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA/REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to HRA/REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the patients (Urgent Safety Measures). In this case, accrual of new patients will be halted until the HRA/REC and/or MHRA approval has been obtained.

In the event of an Urgent Safety Measure, principal investigators will be notified by telephone, information will be posted on the trial-specific website, and the participants will be notified directly using their expressed preferred mode of communication.

18.5 Peer Review

The SIMPLIFIED was funded by the NIHR HTA (14/49/127) following a 3-stage submission process with extensive peer review.

18.6 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.

18.7 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 your Trust's policy.

19 SPONSORSHIP, FINANCE AND INSURANCE

The trial is jointly sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The trial is funded by the UK National Institute of Healthcare Research (NIHR) Health Technology Assessment agency (HTA), award number 14/49/127.

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.

20 MONITORING, AUDIT AND INSPECTION

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. 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 patient 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.

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.

21 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 and Sponsor immediately.

Deviations from the protocol which are found to recur 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 to the Sponsor without any delay.

22 PUBLICATIONS POLICY

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Study Report prepared.

The NIHR Health Technology Assessment (HTA) requires notification of all outputs arising from the trial 28 days before publication.

All surviving participants in the trial will be notified of the trial results using their preferred method of communication. A synopsis of trial results will be provided on the trial-specific website.

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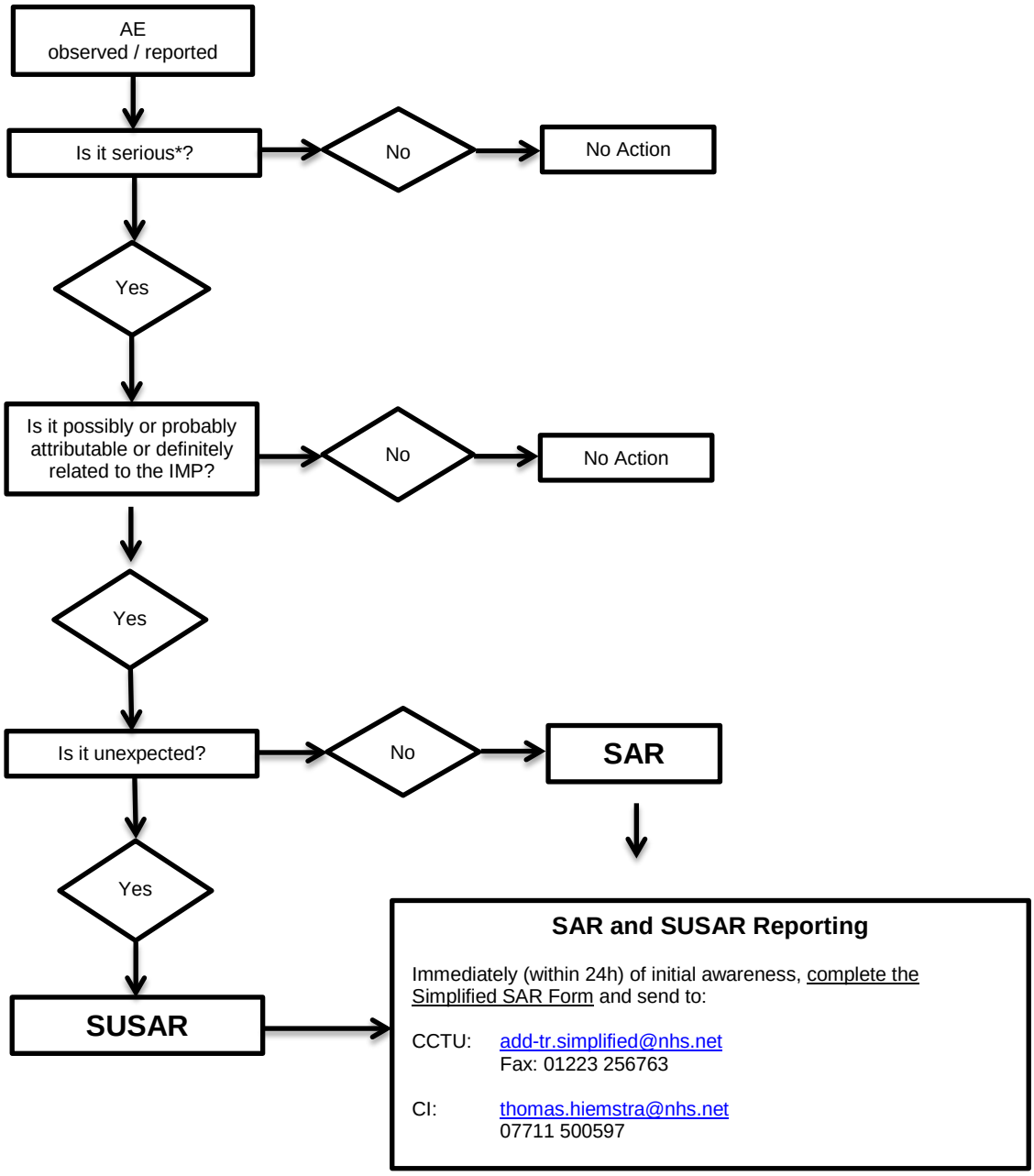
24 APPENDICES

24.1 Appendix 1 - Safety Reporting Flow Chart

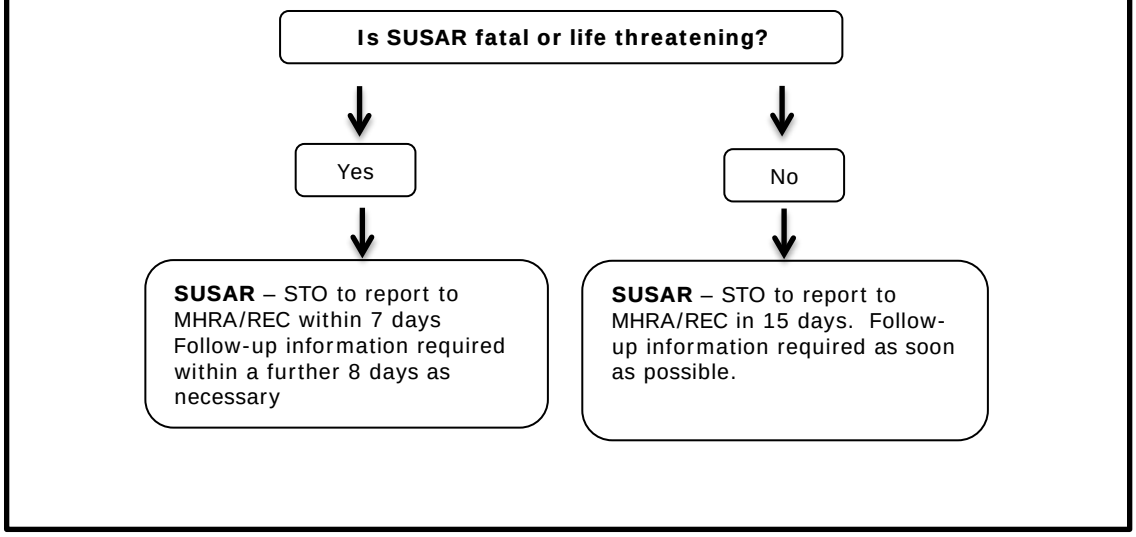


* Criteria for Seriousness categorisation
The event:

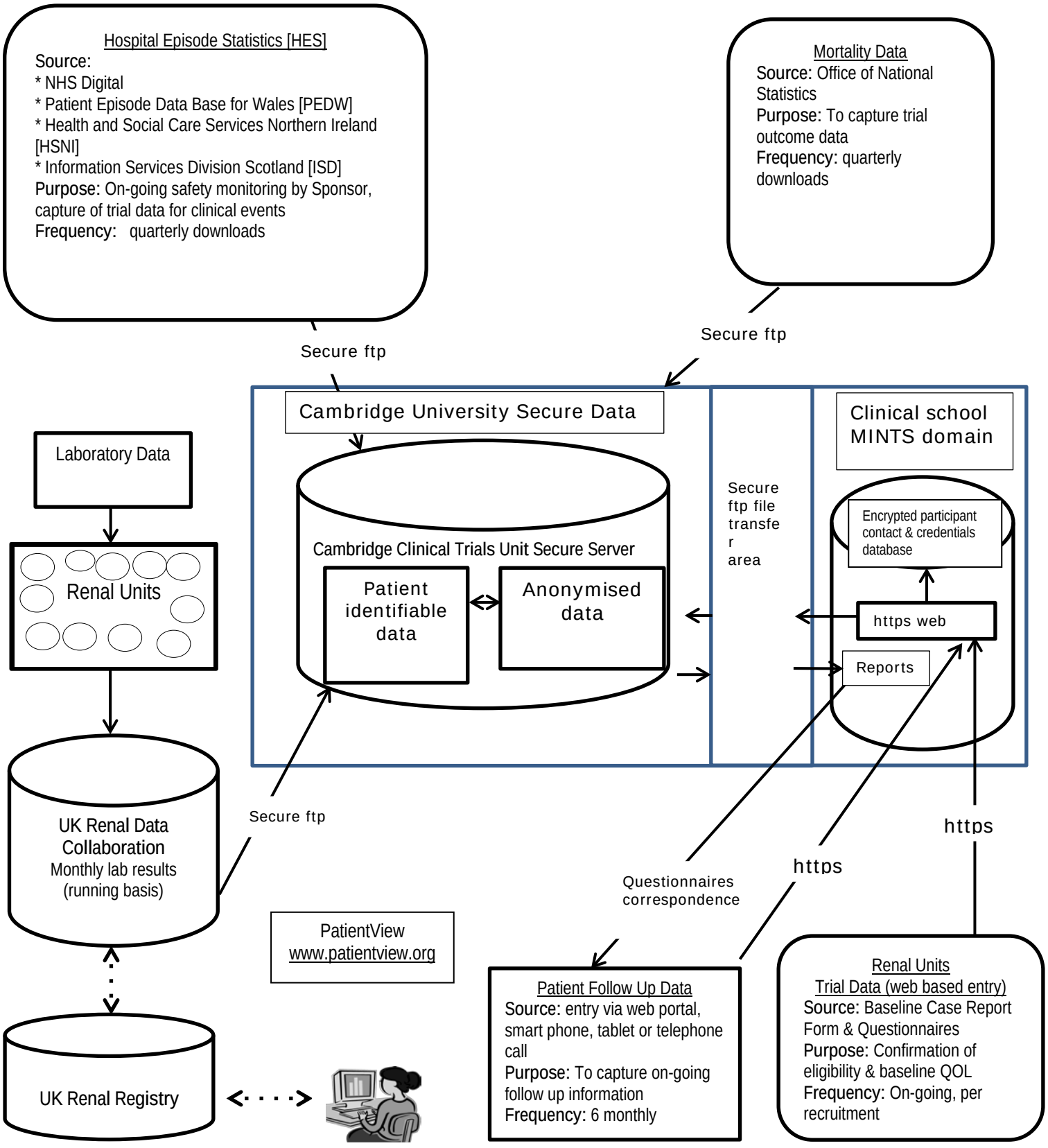
- Results in death
- Is life threatening
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another important medical event

24.2 Appendix 2 – Sponsor SUSAR Reporting Procedure

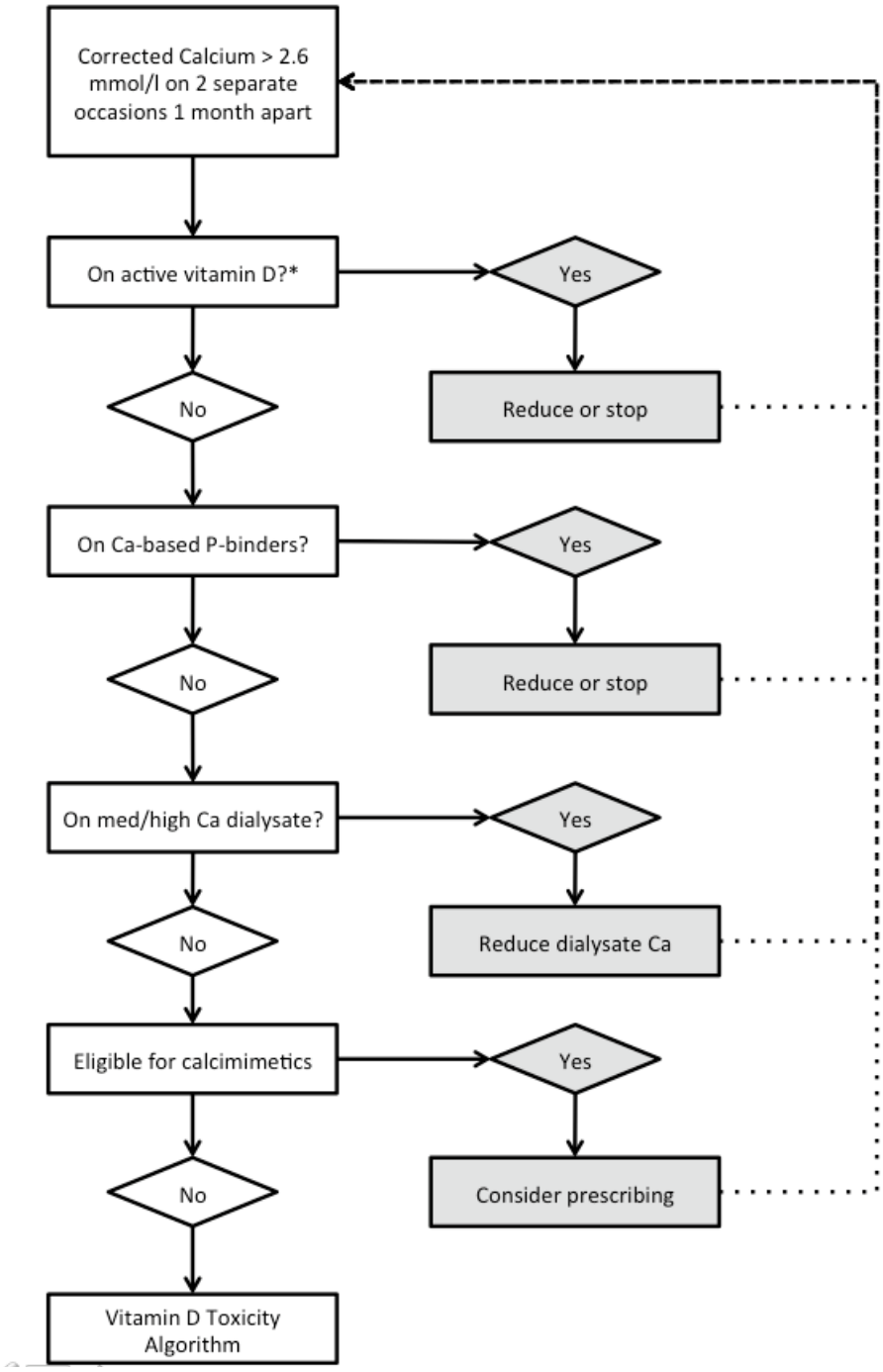
SUSARs – Following initial SAR report the STO will submit an electronic SUSAR report to the MHRA, the SAR report/cover letter to the REC and notify all participating investigators of the event



24.3 Appendix 3 – Data process diagram



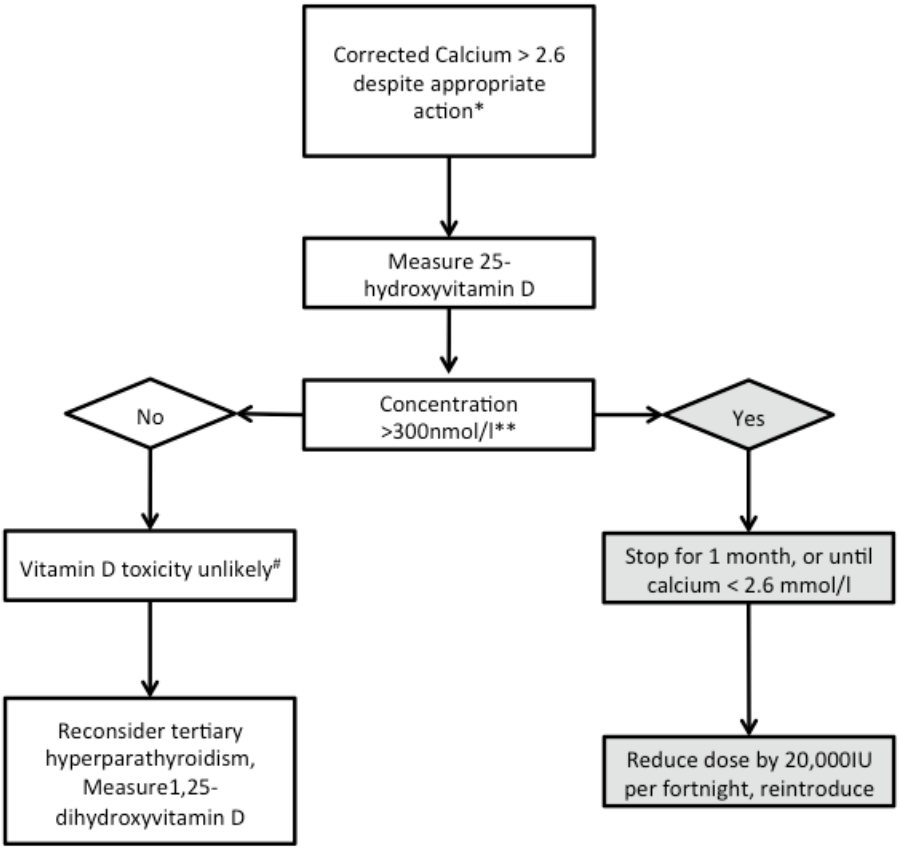
24.4 Appendix 4 – Hypercalcaemia Algorithm



Appendix 4: Hypercalcaemia algorithm. Where local guidelines are operational, these may take precedent. In the absence of local guidelines or based on site preference, the above algorithm may be used to make the requisite changes to concomitant therapy.

Given that colecalciferol treatment should at least partially restore endogenous calcitriol synthesis, the reduction or withdrawal of active vitamin D compounds should be prioritised.
**Active vitamin D: All 1α-hydroxylated vitamin D compounds including (but not limited to) alfacalcidol, paricalcitol, calcitriol and 22-oxacalcitriol.*

24.5 Appendix 5 – "Suspected Vitamin D Toxicity" algorithm.



Appendix 5 – Suspected vitamin D toxicity. In the event that all identifiable causes of hypercalcaemia (Appendix 3) have been excluded or addressed, vitamin D toxicity should be considered in patients receiving colecaciferol. This includes discontinuation of *1α-hydroxylated vitamin D compounds, since toxicity results from increased circulating calcitriol concentrations. Therefore, vitamin D toxicity cannot be attributed to colecalciferol in the presence of concomitant treatment with 1α-hydroxylated compounds.*
25-hydroxyvitamin D3 concentrations (25(OH)D3) should be measured. Toxicity is possible if 25(OH)D3 exceeds 300nmol/l (25(OH)D2, if measured concomitantly, should not be considered. Once toxicity is diagnosed, colecalciferol should be withdrawn until calcium returns to ≤ 2.6mmol/l. Colecalciferol should then be reintroduced after reducing the dose by 20,000IU per fortnight.

*Hypercalcaemia algorithm, Appendix 4
** Vitamin D toxicity typically occurs with doses approaching 50,000IU per day, resulting in concentrations of 354nmol/l or greater. Up to 10,000IU per day is not associated with toxicity.[104] The trial protocol administers 4,825IU per day.