Statistical Analysis Plan

TRIAL FULL TITLE	Does oral sodium bicarbonate therapy improve function and quality of life in older patients with chronic kidney disease and low-grade acidosis?
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TRIAL STATISTICIAN	Peter T. Donnan
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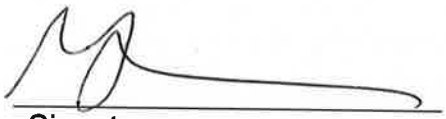
SAP AUTHOR	Peter T. Donnan

Signatures

By signing this document I am confirming that I have read and approve the Statistical Analysis Plan (SAP) for the trial.

Miles Witham

Chief Investigator



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Peter T. Donnan

Trial Statistician

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List of Abbreviations

AE	Adverse event
AR	Adverse reaction
BNF	British National Formulary
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
eGFR	Estimated Glomerular Filtration Rate
EMEA	European Medicines Agency
EuroQoL/ED-5D	Standardised instrument to measure health outcomes
GCP	Good Clinical Practice
HbA1c	Glycated Haemoglobin
HIC	Health Informatics Centre
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Products
ISF	Investigator Site File
ITT	Intention To Treat
KDQoL	Kidney Disease Quality of Life
MCID	Minimum Clinically Important Difference
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
PSF	Pharmacy Site File
PI	Principal Investigator
PIS	Participant/Patient Information Sheet
PIN	Participant/Patient Identification Number
PTH	Parathyroid hormone
QC	Quality Control
R&D	NHS Board/Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
RN	Research Nurse
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPPB	Short Physical Performance Battery
SUSAR	Suspected Unexpected Serious Adverse Reactions
TASC	Tayside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
WPD	Working Practice Document

1 Introduction

Current practice varies with regard to the use of bicarbonate therapy in patients with chronic kidney disease (CKD) and mild acidosis. Measurement and correction of acidosis is part of standard care for patients managed under renal services, but is far less common for patients managed by primary care or Medicine for the Elderly services.

Older people with CKD invariably have a wide range of comorbid diseases. A narrow focus on kidney disease indices alone is therefore unlikely to reflect what is important to the patient. Conversely, CKD, especially with acidosis, exacerbates a number of other disease states that are common and important for older people, including muscle weakness, osteoporosis and cardiovascular disease.

For these reasons, an approach examining function and quality of life is essential to test whether bicarbonate intervention in older people is worthwhile. Physical function and quality of life are the outcomes that older people themselves consider to be the most important as evidenced by a Delphi consensus exercise involving both older patients and clinicians caring for older people, not the postponement of death as the primary goal of therapy.

Our approach in designing this study was therefore to focus first and foremost on indices of physical and psychosocial function and quality of life, underpinned by measures of muscle function that correlate with daily activities and which predict future dependence. Added to these are a series of outcomes examining the effect of the intervention on the major associated disease states – renal function, bone health and cardiovascular health.

2 Study Objectives and Outcomes

2.1 Study Objectives

2.1.1 Primary Objective

To determine whether oral bicarbonate therapy improves physical function compared to placebo in older people with CKD and mild acidosis.

2.1.2 Secondary Objectives

To determine whether oral bicarbonate therapy improves health-related quality of life compared to placebo in older people with CKD and mild acidosis.
To compare the impact of oral bicarbonate therapy against placebo on biochemical markers of chronic kidney disease in older people with CKD and mild acidosis.
To assess whether use of oral bicarbonate therapy is associated with an excess of adverse events compared with placebo in older people with CKD and mild acidosis.
To estimate the cost-effectiveness of using oral bicarbonate therapy compared with placebo in older people with CKD and mild acidosis.

3 Study Methods

3.1 General Study Design and Plan

The design is a randomised, multicentre, double-blind, parallel group, placebo controlled trial. The treatment and follow up will last a maximum of 2 years for each participant. Outcomes are measured at 0, 3, 6, 12, 24 months. The original target for recruitment was 380 participants (190 allocated to sodium bicarbonate and 190 allocated to placebo)

3.2 Inclusion-Exclusion Criteria

3.2.1 INCLUSION CRITERIA

1. Participant is willing and able to give informed consent for participation in the study
2. Male or female aged 60 yrs or above
3. Last known estimated Glomerular Filtration Rate (eGFR) <30 ml/min (i.e. CKD stages 4 and 5)
4. Serum Bicarbonate/CO2 <22 mmol/L
5. Able (in the Investigators opinion) and willing to comply with all study requirements.

Inclusion criteria for patients already on bicarbonate therapy

1. Participant is willing and able to give informed consent for participation in the study, including washout period
2. Male or female aged 60 yrs or above
3. Last known estimated Glomerular Filtration Rate (eGFR) <30 ml/min (i.e. CKD stages 4 and 5)
4. Able (in the Investigators opinion) and willing to comply with all study requirements.

3.2.2 EXCLUSION CRITERIA

1. Severe cognitive impairment precluding written informed consent
2. Already taking bicarbonate therapy
3. Documented renal tubular acidosis (such patients are likely to require bicarbonate, often in very large doses)
4. On renal replacement therapy (haemodialysis or peritoneal dialysis)
5. Anticipated to start renal replacement therapy within 3 months
6. Participant who is terminally ill, as defined as less than 3 months expected survival
7. Decompensated chronic heart failure (to ensure that fluid overload is not exacerbated by the additional sodium load from the intervention)
8. Bisphosphonate therapy (to avoid obscuring bone turnover effects; patients with CKD stages 4/5 should not usually be taking bisphosphonates as this is a listed contraindication)
9. Uncontrolled hypertension at screening visit (BP>150/90 despite use of four agents, unless in the opinion of the local PI there is evidence of adequate BP control from 24 hour BP monitoring, home BP monitoring or primary care BP records).

10. Subject participated in another clinical trial (other than observational trials and registries) concurrently or within 30 days prior to screening for entry into this study
11. Participant has a known allergies to sodium bicarbonate or lactose

3.2.3 Exclusion criteria for patients already on bicarbonate therapy

1. Severe cognitive impairment precluding written informed consent
2. Documented renal tubular acidosis (such patients are likely to require bicarbonate, often in very large doses)
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10. Participant has a known allergies to sodium bicarbonate or lactose

3.3 Randomisation and Blinding

Randomisation was performed via a centrally controlled web-based GCP compliant randomisation system, run by Tayside Clinical Trials Unit (TCTU). Randomisation was stratified by site. To ensure balanced assignment across critical variables, a minimisation algorithm was employed, using baseline age (<75 years vs >=75 yrs), sex (male vs female) and CKD stage (4 vs 5).

3.3.1 Treatment Allocation

Participants are allowed to continue all their usual medication throughout with the exception of participants undergoing the washout phase, who will cease taking oral bicarbonate.

Participants commence therapy at a dose of 500mg of oral sodium bicarbonate or placebo three times per day. At 3 months, if serum bicarbonate is found to be <22 mmol/L, the dose is increased to 1g three times per day or placebo. The study medication is administered as oral tablets. Placebo and active tablets are identical in appearance.

If study drug needs to be stopped or the patient wishes to stop they remain in the study and attend outcome visits in order to perform an intention to treat analysis.

4 Sample Size

The trial originally planned to randomize a total of 380 participants; 190 to bicarbonate and 190 to placebo.

The Minimum Clinically Important Difference (MCID) for the SPPB is a 1 point difference. Assuming a SD of 2.6 as found in our previous work, we would require 143 patients per group if two-sided alpha = 0.05 and power = 90%

For the EQ-5D the MCID is 0.074. To detect this with two-sided alpha = 0.05 and power of 90%, assuming a SD of change of 0.2 as found in our previous studies, requires 154 patients per group.

Progression to dialysis in a previous trial of bicarbonate therapy was lower in patients allocated to bicarbonate (7%) than in the control arm (33%). The proposed sample size will have 90% power to successfully detect a more conservative difference of 7% in the bicarbonate arm and 18% in the control arm at 2 years.

Assuming a 10% loss to follow up every 6 months (a pessimistic estimate, based on previous medication trials in frail older people in our centre), we estimated that we would require 380 patients to ensure adequate power for the primary outcome and the EQ-5D at 12 months. This rate of attrition would leave 250 evaluable patients at 2 years.

Changes to the sample size during the conduct of the trial

On the advice of the independent Trial Steering Committee, recruitment was stopped once 300 participants had been randomised, due to slowing recruitment rates. The last participant was randomised in February 2017. On a further recommendation from the Trial Steering Committee, the funder mandated that follow up be stopped once the last participant had reached the 12 month follow up point. The result of this action is that follow up for a small number of participants will be truncated and will not proceed to 24 months.

The last visit of the last participant is scheduled for February 2018.

5 Proposed Analyses

General considerations

The final analysis will be performed after all data have been entered and the database has been locked.
All analyses will be performed on intention to treat population (i.e. by group randomised to) unless otherwise specified.
A two-sided p value of <0.05 will be taken as significant for all analyses unless otherwise specified
No adjustments for multiple testing are planned
All analyses will be performed using SAS v9.4

Baseline details

Descriptive statistics will be generated for baseline characteristics, by treatment group.

For each continuous variable, mean, standard deviation, median, 25th and 75th percentiles, maximum and minimum will be generated.

For each categorical variable, percentage, numerator and denominator will be generated

The list of baseline variables to be analysed is given in Appendix A.

Concomitant medications in use at the baseline visit will be presented by medication category but not by dose or frequency

Changes to concomitant medications during the trial will not be presented

5.1 Analysis of the primary outcome

The primary outcome is the between-group difference in change in the Short Physical Performance Battery (SPPB) at 12 months. For each treatment group, the mean and standard deviation at baseline and at 12 months will be generated.

Analysis will use a mixed model, adjusted for baseline measurement and hence estimating difference in change between trial arms. In addition, fixed factors for trial arm (Sodium Bicarbonate, placebo) minimisation variables (age, sex, and stage of CKD), as well as a random effect variable for recruitment site will be added to the regression model.

Prespecified subgroup analyses for the primary outcome will be performed using the following factors, by fitting a treatment by factor interaction for each in the analysis:

- Participants with a SPPB score of <10 (denoting a frailer subgroup) vs >=10
- Participants with a baseline serum bicarbonate level of >18 mmol/L vs those with serum bicarbonate ≤18 mmol/L
- CKD stage (4 vs 5)
- Gender (male vs female)
- Age (>75 vs <=75 years)

Prespecified sensitivity analyses for the primary outcome:

We will perform the following sensitivity analyses for the primary outcome:

a) excluding participants undergoing washout prior to randomisation will be performed.
b) Comparing participants with >80% adherence vs <=80% adherence

Missing data in the analyses of the primary outcome:
The pattern of missing data will be examined and if necessary missing data will be analysed by multiple imputation, assuming that the assumption of Missing at Random is reasonable.

5.2 Analysis of secondary outcomes

Analysis of secondary outcomes will be performed using mixed model repeated measures analysis adjusted for baseline values and minimisation variables age, sex and CKD stage, and site as a random effect variable.

Models will incorporate data from all timepoints available for the outcome under test

Secondary outcome analyses will be performed for the following outcomes:

1. Six minute walk distance
2. Handgrip strength
3. Weight
4. Mid-arm muscle circumference
5. Triceps skinfold thickness
6. Mid-thigh circumference
7. EQ5D-3L score – results will first be mapped to preference weights before analysis
8. EQ5D thermometer
9. KDQoL questionnaire total score
10. Creatinine
11. Cystatin C
12. Estimated glomerular filtration rate (calculated using MDRD4 equation)
13. Estimated glomerular filtration rate (calculated using CKD-EPI cystatin C equation)
14. Urinary protein/creatinine ratio
15. Urinary albumin-creatinine ratio
16. TRACP-5b
17. Bone-specific alkaline phosphatase
18. PTH
19. 25-hydroxyvitamin D
20. 1,25-hydroxyvitamin D
21. B-type natriuretic peptide
22. Haemoglobin
23. Total cholesterol
24. HDL cholesterol
25. Serum albumin
26. TSH
27. Serum Potassium
28. Serum Calcium
29. Serum Phosphate
30. HbA1c
31. Serum bicarbonate
32. Systolic blood pressure
33. Diastolic blood pressure

For each measure, descriptive data (mean, standard deviation, median, 25th/75th percentiles, minimum and maximum) will also be generated for each time point.

For blood pressure, the mean of the second and third readings at each visit will be used as the value to include in analyses.

Missing Data within multicomponent outcome measures

For the EQ5D, missing domains are not imputable (as per the EQ5D manual). Therefore any questionnaire with a missing response for one or more of the five health status domains will be treated as a missing questionnaire. Responses from the EQ5D thermometer will be treated separately (i.e. missing data from the thermometer will not preclude use of the 5 domain score and vice versa)

For the KDQoL, the score is derived from the mean of responses, as per the KDQoL manual. Missing responses are not included in the score; the mean is derived only from those components with responses. Missing responses do not therefore obviate use of the questionnaire for a given participant.

6 Safety Analyses

An all patient group analysis will be performed for safety variables

6.1 Adverse Events

Adverse events (AE) will be coded with MedDRA 16.1. Where more than one diagnosis is present in the AE description, the AE will be split with all the descriptors kept the same for all diagnosis. Adverse events will be reported by primary System Organ Class (SOC) and Preferred Term (PT).

Subjects will be counted only once when calculating the incidence of AEs. An overview table will be created counting the number of adverse events by system organ class and preferred term.

Descriptors for Adverse events will be tabulated separately as described for categorical variables in section 8. The total number of AEs will be used as basis for tabulation.

Adverse events will be presented in two ways:

1) Including all participants during their period of follow up (intention to treat)
2) Including only those events taking place when taking study medication (i.e. a per-protocol analysis). AEs occurring more than 3 days after cessation of study medication will be censored in this analysis.

6.2 Deaths, Serious Adverse Events and other Significant Adverse Events

Serious Adverse Events (SAE) will be reported with all other AEs as described in section 6.1. However, they will be reviewed for the trial report on a case by case basis by the PI.

Adverse events of particular interest will be reported separately in tabular form.

These events are:
- All-cause death
- Deaths due to cardiovascular events (myocardial infarction, stroke, peripheral vascular disease, sudden cardiac death including arrhythmic cardiac death)
- Deaths due to end-stage renal failure
- Commencement of dialysis
- Numbers with at least one fragility fracture (fracture of wrist, neck of femur, pubic ramus, neck of humerus, vertebra)
- Numbers with at least one fall
- Falls rate (falls per year)

7 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

8 Technical Details

All analysis will be performed using SAS 9.4. All data, analysis programs and output will be kept on the Mackenzie Server and backed up according to the internal IT SOPs.

Analysis programs will be required to run without errors or warnings. The analysis programs for outcomes will be reviewed by a second statistician, and any irregularities within the programs will be investigated and fixed and date of finalised analysis programs will be signed and recorded.

9 Statistical Report

A statistical report will be created with all analyses presented according to the analyses outlined in the SAP. Thiswill form the basis of any future paper or report and will be assessed for consistency.

Appendix A. List of descriptor variables for Baseline characteristics

Mean age (years) (SD)	
Age 60-69 (%)	
Age 70-79 (%)	
Age 80 and over (%)	
Female sex (%)	
Ethnicity	White
	East Asian
	Black
	South Asian
	Hispanic
	Other
Cause of renal dysfunction	Hypertension
	Diabetes mellitus
	Glomerulonephritis
	Polycystic kidney disease
	Vascular disease
	Other
	Not known
Cardiovascular comorbidity	Ischaemic heart disease
	Stroke
	Heart failure
	Peripheral vascular disease
Previous fragility fracture (%)	
Median number of medications (IQR)	
Medication use:	ACEi/ARB
	Phosphate binder
	EPO
	Iron
Mean eGFR (ml/min/1.73m^2) (SD)	
CKD stage 5 (%)	
Mean serum bicarbonate (mmol/L) (SD)	
Mean haemoglobin (g/L) (SD)	
Mean serum potassium (mmol/L)(SD)	
Mean SPPB (SD)	
Mean six-minute walk distance (m) (SD)	
Mean handgrip strength (kg) (SD)	Males
	Females
Mean BMI (kg/m^2) (SD)	
Mean MAMC (cm) (SD)	
Mean TSF (mm) (SD)	
Mean MTC (cm) (SD)	
Mean EQ-5D (SD)	
Mean KDQOL (SD)	
Mean office systolic blood pressure (mmHg) (SD)	
Mean office diastolic blood pressure (mmHg) (SD)	