Supplemental Information ALTERED STUDY

Contents

ALTERED STUDY STATISTICAL ANALYSIS PLAN

Trial Full Title – Does Allopurinol Regress Left Ventricular Hypertrophy in End Stage Renal Disease?

EudraCT Number - 2013-001436-22

SAP Version 2.0
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Agreed by:

Study CI Prof Allan Struthers _____ Date 28/9/17

Study PI Dr Elaine Rutherford _____ Date 27/9/17

1 Professional Summary

This study will establish whether allopurinol reduces LV mass and improves endothelial/vascular function in patients undergoing haemodialysis. The primary outcome measure is change in left ventricular mass indexed to body surface area following a year of therapy with allopurinol or placebo. Allopurinol has been shown to regress left ventricular mass indices in patients with ischaemic heart disease, mild chronic kidney disease and diabetes. If allopurinol also regressed LV mass in the end stage renal population then this could fully justify a large mega trial to see if allopurinol reduces the extremely high rate of CV events and deaths in such patients. Such a large mega trial in End Stage Renal Disease (ESRD) could be relatively good value overall since cardiovascular events/deaths are so high in ESRD.

The study will also consider if allopurinol will improve endothelial function which will be measured using FMD and PWA. The chance of positive results on LV mass

reduction and endothelial function is very high since we found allopurinol to have such positive effects in mild renal disease. Additionally we will get preliminary data on the safety and tolerability of allopurinol in dialysis patients.

2 Study Objectives

This SAP applies only to the second (main) part of the ALTERED study and does not consider the dose finding study.

2.1 Primary Objective

The primary objective will be to see if Allopurinol can reduce left ventricular mass (as measured by MRI) in patients with ESRD.

2.2 Secondary Objectives

- To decide on optimum dosing regimen of allopurinol in ESRD from pilot study (covered by pilot study).
- To assess effect of allopurinol on endothelial function as measured by FMD and PWA.
- To assess safety of allopurinol in ESRD.

3 Study End Points

3.1 Primary Outcomes

The primary outcome is to determine if allopurinol, induces a change in Left ventricular Mass Index in patients with ESRD when compared to placebo.

3.2 Secondary Outcomes

Secondary outcomes are:

- To determine if there is a change in LV end systolic volume, LV end diastolic volume or LV ejection factor with allopurinol in ESRD patients compared with placebo.
- To determine if there is a difference in endothelial function with allopurinol compared with placebo, measured by FMD and PWA
- To determine if there are changes in inflammatory blood markers, in ESRD with allopurinol compared with placebo.
- To assess, if there are changes in BP control as measured by clinic BP and 24hr BP monitoring with allopurinol compared with placebo

4.0 General Study Design and Plan

The ALTERED trial is a randomised, double blinded, placebo controlled multi-centre study conducted in NHS Tayside, NHS Ayrshire & Arran & NHS Greater Glasgow & Clyde to compare allopurinol 300mg to placebo.

Patients will be enrolled in this trial for a period of between 12 to 13 months.

At screening visit an initial history and clinical examination will be performed. Participants will then undergo an echocardiogram to ensure no significant heart failure (unless they have had an ECHO in the previous 4 years). Should the participant be eligible for the study they will have a Cardiac Magnetic Resonance Imaging (MRI) scan prior to their baseline (Randomisation) visit. They will also have bloods taken for safety analysis, have a 12 lead ECG done, vital signs recorded and if they agree have 24 hour BP monitoring.

Once the patient is known to be eligible they will return - for the first randomisation, dosing visit at any time up to four weeks after screening. At this randomisation visit post dialysis session, eligible participants will be randomly assigned to either placebo or allopurinol 100mg.

They will continue on allopurinol/placebo 100mg for 2 weeks, with dosing after each dialysis session only. They can have FMD, PWV and PWA measurements taken. All participants will be offered the opportunity to opt in or out of the FMD, PWV and PWA measurements, which are secondary outcome measures only.

If study drugs are tolerated, the dose would be increased at weekly intervals after the 200mg dose to the allopurinol dose chosen by the dose escalation study, if greater than 200mg. Baseline blood samples will be taken for routine bloods including full blood count, renal function, liver function, random blood glucose, haemoglobin A1C, lipids, calcium and phosphate. These blood tests will be repeated at 6, 9 and 12 months. Routine safety bloods (including U+Es and LFTs) will be taken pre-dialysis at visits throughout the study. Subjects will be followed at baseline, week 2, week 6, month 6, month 9 and month 12. Research bloods and urate levels will be taken at baseline, week 6, months 6, 9 and 12. However, to ensure blinding throughout urate results will not be made available to the investigators until the end of the trial. BP is recorded as part of standard care and will be available for analysis. Pre and post-dialysis readings will be recorded. Other variables such as weight and fluid removed during dialysis are also noted as part of routine care and will be available for analysis. 24-hour BP will be performed at the start and end of the study if participants agree. Cardiac MRI scans will be performed at the start and at the end of the 12 month study period. Patients will continue with all their usual medication, which will remain unchanged throughout unless clinically indicated.

5.0 Sample Size

In powering MRI studies of LVH regression, it is recommended that they are powered for a 10gm change in LV mass (= 4.8g/m2 change in LVMI). Grothues et al recommend this as this size of effect should reduce future CV events. We have powered this study based on two published studies where 12 months of treatment were given, as planned here. In Edwards et al, there was a 10g reduction in LV mass with a standard deviation of 12g in CKD patients. Based on these values, we would need 32 patients per group to have 90% power at $p<0.05$ to detect this magnitude of change in LV mass. In the only MRI study which we have done involving one year of treatment, we saw an LV mass fall of 14 $\pm$ 14 g, which would give us a very similar power calculation.

(Unfortunately our allopurinol in mild CKD study only involved 9 months treatment and time is known to be crucial when a treatment is trying to regress LV mass : a larger effect is anticipated here with 12 months therapy). If we anticipate a 10% death or transplantation rate/year and a 10% dropout rate, then we will need a total of 76 patients to be recruited, we will recruit approximately 80 patients. Glasgow has 650 dialysis patients Dundee 200, and Ayrshire and Arran has 180 so that our planned recruitment should be achievable, especially since these patients are well aware of their poor prognosis and hence usually very willing to volunteer for potentially lifesaving research from which they may well personally benefit in the long term.

6.0 General Considerations

6.1 Timing of Analyses

The final analysis will be performed after all data have been entered and the database has been locked.

6.2 Analysis Populations

The main analysis population will be all available subjects on an intention-to-treat basis for the outcome measures. A secondary study population will be complete cases.

6.3 Missing Analysis

This is an intention to treat study so all non-compliers, withdrawn patients and missing data will be analysed by imputation if such data found to be missing at random. If data is not missing at random (e.g. a pattern is identified like a specific patient group is missing), then the impact will be discussed and a decision on replacement (or not) will be taken. Transplanted patients will, however, be analysed separately as having a renal transplant is an entirely different entity to being on haemodialysis. We will also do a completed case only analysis.

7 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), number of missing records, mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by subject and treatment and where appropriate by visit number within subject.

All summary tables will be structured with a column for each treatment in the order (Intervention, Control) and an additional column for the total population relevant to that table/treatment, including any missing observations.

7.1 Demographic and Baseline Variables

Baseline characteristics for participants which will be considered as co-variates are mean pre-dialysis systolic blood pressure for month 0, mean ultrafiltration volumes for month 0 and baseline LVMI as they may be confounding factors in allopurinol's effects on LVMI.

7.2 Other Important Medical History

Other concurrent illnesses will be recorded and listed but not coded and analysed. We will also present data on baseline demographics to include gender, age, race, cause of ESRD, renal replacement therapy (including transplantation and peritoneal dialysis) vintage, haemodialysis vintage, previous transplant status, transplant list status, vascular access at screening visit, any self reported problems with vascular access at screening, BP (mean pre and post dialysis in month 0 and randomisation pre- and post- dialysis BP and screening 24 hour BP if available), randomisation Hb, randomisation albumin, randomisation phosphate, baseline urate, URR (month pre-randomisation), baseline presence or absence of cardiovascular disease, diabetes, self-reported urine volumes, hypertension, peripheral vascular disease, previous CVA or TIA, and raised cholesterol. Baseline use of the following medication classes will also be reported: beta-blockers, ACE Inhibitors or angiotensin receptor blockers, calcium channel blockers, statins, epo and vitamin D. Between group differences of these variables will be assessed and documented as per section 7.1.

7.3 Prior and Concurrent Medications

Prior medications are all medications which are currently taken by the patient but commenced prior to trial start. Concomitant medications are all medications commenced during the trial, and all changes to the dosing of prior medications.

Both prior and concomitant Medication will be analysed by drug class and number of medications taken.

7.4 Treatment Adherence

Treatment adherence is calculated from the number of pills handed out, the number of pills returned and the number of pills expected to be taken. Adherence (%) is calculated as (Number of drugs issued minus Number of drugs returned) divided by (Number of drugs that should have been taken x 100).

Compliance will be checked and documented using tablet counts at each visit. Should compliance be poor the patient will be advised by the research fellow on the importance of correct compliance. Should compliance be persistently less than 70%, they will be withdrawn from treatment but remain in the study for intention to treat analysis.

7.4.1 Treatment Adherence Subgroup Analysis

We will also consider compliance by looking at change in urate level from baseline. Although all patients will be included in the main intention to treat analysis, we will also perform a separate analysis where participants who were on active treatment but who did not achieve a reduction of urate of 10% from baseline are excluded as this may in addition reflect poor IMP compliance.

8 Efficacy Analysis

Data for continuous outcome measures will be assessed for normality prior to analysis. Transformations of the outcome variables will be used where necessary if these are not normally distributed.

If data are normally distributed, outcome measures will be assessed by multiple linear regression. Initial comparisons will be between treatment groups (allopurinol vs placebo) at the final visit (12 months +- 2 weeks), adjusted for site and baseline measure of the outcome.

In addition, the baseline variables systolic blood pressure, ultrafiltration volumes and baseline LVMI will be assessed for impact on the outcome parameter and adjusted for in the model.

Where data are not normally distributed and cannot be transformed into a normal distribution, data will be analysed using non-parametric methods in addition to multiple linear regression.

All analyses will be implemented in SPSS.

8.1 Primary Efficacy Analysis

The primary outcome measure will be analysed as described above and presented as the between group difference in change in LVMI between baseline and 12 months. The LVMI is calculated using the mean of the two blinded MRI LVMI readings at baseline to determine baseline LVMI and the two blinded MRI LVMI readings at follow up (month 12) to determine follow up LVMI.

8.2 Secondary Efficacy Analysis

All secondary outcomes will be analysed in the same manner as the primary outcome. Results will be presented as:

- Between group difference in change in the continuous variables LV mass, LV end systolic volume, LV end diastolic volume, and LVEF. The average of the two blinded readings taken at baseline and at follow up will be used to calculate this.

- Between group differences in change in FMD and/or PWA (all that are available) between baseline, month 9 and month 12 (final visit). A repeated measure analysis will be used when month 9 is included. A straight baseline and month 12 analysis will also be performed.

- Between group difference in change in blood markers between baseline, visit 4 (week 6), month 6, month 9 and month 12 (final visit). A repeated measure analysis will be used to compare these multiple groups. A straight baseline and month 12 analysis will also be performed.

- Between group difference in change in BP control. This will be measured as the change in BP control from baseline to month 12 (final visit) using mean ambulatory BP results for those participants who completed this optional part of the study. For all participants including those who did not complete ambulatory BP monitoring, this will also be measured by change in mean monthly pre and post dialysis BPs for the month prior to study commencement to the mean monthly pre and post dialysis BPs for the month prior to the month 12 (final visit).

8.3 Safety Analysis

Reporting of adverse events will be done in tabular form.

Presence or absence of any adverse events and serious adverse events will be presented for both treatment allocations. Whether a serious adverse event led to treatment discontinuation or not and whether any relation to study drug was suspected or not will also be reported.

Events leading to death will be reported with deaths further divided into death from a cardiovascular cause or a non-cardiovascular cause. Non-cardiovascular deaths will be further divided into infection and otherwise non-specified deaths.

Rashes and any episodes of gout will be listed separately as they may be related to allopurinol. An overview table of number of adverse events will be presented.

8.4 Deaths, Serious Adverse Events and other Significant Adverse Events

Serious Adverse Events (SAE) will be reported with all other AEs as described in section 8.3. However, they will be reviewed for the trial report on a case by case basis by the PI.

8.5 Clinical Laboratory Evaluations

Clinical Laboratory data will be reported in accordance with the guidelines in section 8. Differences to baseline will be calculated and incorporated into the tables. For categorical variables, shift tables showing a change from baseline will be created.

8.6 Additional Outcomes of Interest

8.6.1 T1 Mapping

During the study a subgroup of patients from NHS GGC and Ayrshire & Arran underwent an additional MRI sequence called T1 mapping. This is a technique under development, which may potentially be a surrogate marker of cardiac tissue abnormalities such as cardiac fibrosis. Cardiac fibrosis is intrinsically linked to left ventricular hypertrophy and is therefore of interest in this study. Although this was not formally a study outcome at study commencement the relationships between T1 time and LVM and study drug will additionally be assessed. This will be done as follows as a subgroup analysis (where available):

- Correlation of T1 and change in T1 with LVM, LVMI, EF, EDV, ESV, BP, ultrafiltration volumes at baseline and follow up (in whole group, and treatment allocations)
- Effect of allopurinol on change of T1 from baseline to follow up
- We will also consider change in T1 time corrected for LV mass to determine if there may be any change in density of tissue abnormalities in any treatment group

8.6.2 Pulse Wave Velocity

As highlighted in section 8.2, a subgroup of patients underwent optional PWA. This includes an assessment of pulse wave velocity using applantion tonometry.

Pulse wave velocity can also be estimated from images of flow through the aorta. As a substudy we will compare the values for PWV obtained via MRI with those obtained with traditional PWA. For all patients with an MRI PWV we will assess overall change in PWV from baseline to follow up for all patients, and consider if treatment had an effect on results using methods as per those described in section 8.

- We will also consider any correlation of MRI PWV and change in MRI PWV with LVM, LVMI, EF, EDV, ESV, BP, ultrafiltration volumes at baseline and follow up (in whole group, and treatment allocations)

9 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.

10 Technical Details

All analysis will be performed using the latest SPSS version. All data, analysis programs and output will be kept securely backed up on an encrypted hard drive.

Analysis programs will be required to run without errors or warnings. The analysis will be carried out by Elaine Rutherford (study PI). Once the output has been created the methods used and output will be sent to the study CI (Prof Allan Struthers) and a TCTU trial statistician (Petra Rauchhaus) for checking.

Supplemental Methods

1. Study Population

Amendments to inclusion criteria

At the study outset participants were restricted to those under 80 years of age and patients with echocardiographic evidence of LVH. Following full regulatory and ethical review an amendment to protocol was made to allow recruitment of patients over 80 years of age and those who did not have LVH as recruitment was more challenging than originally anticipated and it was considered that these changes could be made without affecting the integrity of the study.

Amendments to exclusion criteria

At the study outset participants who had any history of gout, those who were taking warfarin and patients with above ankle amputations were excluded from participation. These exclusion criteria were removed in an amendment following regulatory and ethical review in an effort to improve study recruitment without impeding trial integrity.

2. CMR Methods

An ECG gated fast imaging steady-state free precession (SSFP) sequence was used to acquire cine images in both long axis and short axis planes. Each short axis slice was 6mm thick with an 4mm gap between each slice. Typical cine acquisition parameters included: repetition time 47.88ms, flip angle=45°, echo time = 1.5ms, matrix = 216 x 256 pixels and voxel size = 1.4 x 1.4 x 6mm, slice thickness = 6mm, band-with= 930Hz/pixel.

A single blinded observer analyzed acquired anonymized images in a random order using dedicated software (Siemens Argus, Erlangen, Germany) to determine cardiac indices including LVM and function.

The reproducibility of LVM assessment was derived by the same observer from the above repeated blinded measurements at both time points and an intra-class correlation of 0.998 (95% confidence interval 0.996-0.999) was achieved. The LVMI was calculated using the mean of the two blinded CMR LVMI readings at baseline to determine baseline LVMI and the two blinded CMR LVMI readings at follow up (month 12) to determine follow up LVMI.

3. Flow Mediated Dilation Methods

A secondary outcome of this study was to determine if there is a difference in endothelial function with allopurinol compared with placebo, measured by flow mediated dilation (FMD).

Place and Timing of FMD

FMD was performed at baseline, month 9 and month 12 of the study. Reactivity Task Force guidelines and was in line with FMD practices performed at both Dundee and Glasgow Universities.[3,4]

FMD Acquisition

FMD was measured using a Siemens Accuson Sequoia 512 ultrasound system with an 8 MHz linear array probe. FMD was performed at randomisation, month 9 and month 12. FMD was an optional part of the study and not all participants consented to this aspect of the study. Patients with previous bilateral arteriovenous vascular access surgeries were unable to participate. FMD was either performed immediately prior to a haemodialysis session or on a post-dialysis day. For each individual participant, the timing of FMD in relation to their haemodialysis session was kept consistent throughout the study.

FMD was performed in a dark and quiet room. After arrival patients lay supine for ten minutes. Their non-fistula upper limb was held supine at a 90° angle level with the heart. The brachial artery was located using the ultrasound probe which was then held securely in place using a pneumatic probe holder. A blood pressure cuff was placed around the forearm 10cm distal to the brachial artery recording site. To

minimise interference of the naturally occurring variability of diameter of the brachial artery throughout the cardiac cycle, all ultrasound recordings were ECG-gated. A baseline recording of the brachial artery was taken for 5 minutes. Following this, the blood pressure cuff was then rapidly inflated to either 200mmHg or 30mmHg above the participants' systolic blood pressure (if that was higher than 200mmHg). The cuff was then held inflated for 5 minutes before the pressure was rapidly released. Following this, a 5-minute recording was taken. After this recording of endothelial dependent vasodilation, there were 5 minutes of recovery time. Thereafter, a further 2-minute baseline recording of the artery was taken prior to the administration of 400mcg of sublingual glyceryl trinitrate (GTN). One minute after administration of GTN a further 5-minute recording of the brachial artery was made to record endothelial independent vasodilation.

FMD Analysis

FMD analysis was performed offline using dedicated Vascular Research Tools software (Medical Imaging Applications LLC, Coralville, IA, USA). FMD was recorded as the percentage change in maximal diameter achieved after the cuff was deflated relative to the baseline average brachial artery diameter. As well as the percentage change, the absolute change in brachial artery diameter in millimetres from the baseline average to maximal diameter post cuff deflation was recorded. The same recordings were made for the pre- and post- GTN images with an average of the baseline being compared to the maximal post GTN brachial artery diameter. All FMD acquisition and analysis was performed by a single trained observer (ER) who was blinded to study allocation.

4. Pulse Wave Analysis and Pulse Wave Velocity

A secondary outcome of this study was to determine if there was a difference in endothelial function with allopurinol compared with placebo, measured by pulse wave analysis. Pulse wave velocity and augmentation indices were undertaken at baseline, month 9 and month 12 of the study. These tests were an optional component of this study and were only undertaken in participants who chose also to undergo FMD analysis. The pulse wave tests took place in the same room as FMD at each centre immediately prior to FMD being performed. Participants with a history of bilateral upper limb vascular access procedures were not able to participate. All pulse wave acquisition was performed by a single observer (ER) who was blinded to treatment allocation.

Augmentation Indices

Analysis was undertaken using the SphygmoCor® Vx machine (AtCor Medical, Sydney, Australia) using a highly sensitive micro-manometer. Participants lay supine for 5 minutes prior to the analysis being performed. The radial artery of the non-fistula arm was used to acquire peripheral pressure waveforms by applanation tonometry. The SphygmoCor software then automatically calculated the central aortic pressure. The difference between the first and second systolic peaks from the calculated aortic pressure wave were then used to calculate the augmentation index. The adjusted augmentation index was automatically normalised to a heart rate of 75 beats per minute.

Pulse Wave Velocity

Radial and carotid waveforms were obtained using ECG gating. The distance between the radial artery and the carotid was measured and inputted. The SphygmoCor system calculates the time from the R wave of the ECG to the arterial wave forms. Using these times and the distance between the two measurement sites allows calculation of the pulse wave velocity.

5. Safety and Trial withdrawals

At each study visit participants were monitored for any potential side effects of allopurinol and pre-dialysis safety blood tests were taken (full blood count, renal function, liver function, random blood glucose, hemoglobin A1C, lipids, calcium and phosphate). If there was any significant deterioration in safety blood tests, then the trial medication was stopped and no further medication issued. Urate was also measured at study visits 2,4,5,6 and 7 but to ensure blinding, the results were not made available to investigators until after unblinding at the end of the trial.

Rash was considered the main potential side effect of allopurinol and the protocol specified that participants would stop trial medication if a rash was marked as persistent. If other concerns arose, then at the discretion of the trial team, the trial medication dose could be reduced to the dose last tolerated and the participant remain in the trial. Unless patients underwent kidney transplantation, participants who stopped trial medication during the study were invited to continue with all trial protocol visits for intention to treat analysis.

Supplemental Table 1. Breakdown of medication use at study baseline

Baseline Medication (%)	**Allopurinol (n=39)**	**Placebo (n=40)**	**p value**
Vitamin D	89.8	82.5	0.352
Beta Blocker	43.6	47.5	0.727
Statin	59.0	45.0	0.214
Non-calcium containing phosphate binders	71.8	70.0	0.861
Intravenous Iron	94.9	80.0	0.087
CCBs	30.8	35.0	0.689
ESAs	87.2	85.0	0.780
Loop diuretics	23.1	32.5	0.350
ARBs	20.5	5.0	0.048
Calcium containing phosphate binders	30.8	32.5	0.869
ACE Inhibitors	10.3	17.5	0.352

Abbreviations: ACE – angiotensin converting enzyme, ARBs – angiotensin receptor blockers, CCBs – calcium channel blockers, ESAs erythropoietin stimulating agents.

Supplemental Table 2 – Breakdown of baseline characteristics for completed cases

Baseline Characteristics	**Allopurinol (n=28)**	**Placebo (n=25)**	**p valu**
Age (years)	56.5 ± 11.3	58.8 ± 13.4	0.51
Gender (% male)	44.0	60.7	0.28
Ethnicity White Caucasian (%) Other (%)	 96.4 3.6	 100 0	 0.53
Pre-Systolic BP (mmHg)	141 ± 23	142 ± 23	0.93
Pre-Diastolic BP (mmHg)	68 ± 12	74 ± 13	0.09
Ultrafiltration volume (l)	1.8 ± 0.9	1.7 ± 0.9	0.44
Weight (kg)	72.5 (60.7 – 85.4)	78.0 (66.0 – 94.0)	0.41
BMI (kg/m^2)	25.6 (21.3 - 29.6)	28.9 (22.6 – 33.5)	0.25
RRT (months)	32 (16 – 115)	39 (23 – 82)	0.81
Duration hemodialysis (months)	30 (13 – 69)	36 (17 – 52)	0.90
Dialysis Access (%) Fistula or Graft Line	 92.9 7.1	 84.0 16.0	 0.44
Primary renal disease (%) Diabetic nephropathy ADPKD Glomerulonephritis Renovascular disease Chronic pyelonephritis Other/Unknown Hypertension	 28.6 10.7 25.0 3.6 0.0 28.5 3.6	 8.0 20.0 24.0 4.0 16.0 28.0 0.0	 0.06 0.29 0.59 0.73 0.04 0.59 0.53
Past medical history (%) Diabetes Hypertension Cerebrovascular disease Peripheral vascular disease Ischemic heart disease Dyslipidemia	 32.1 82.1 32.1 25.0 17.9 53.6	 16.0 64.0 8.0 4.0 24.0 32.0	 0.38 0.12 0.03 0.04 0.42 0.10
Smoking History (%) Ex/Current Never	 57.2 42.8	 44.0 56.0	 0.48
Hemoglobin(g/dL)	11.6 (11.3 – 12.6)	111 (10.5 – 11.8)	0.27
URR (%)[a]	76.6 ± 5.5	74.0 ± 8.4	0.22
Albumin (g/L)	35 (32 – 37)	33 (31 – 36)	0.36
Urate[b] (mmol/L)	342 ± 68	360 ± 90	0.44
Phosphate[a] (mmol/L)	1.53 ± 0.38	1.68 ± 0.44	0.20

LVM (g)	124.3 ± 34.4	115.4 ± 39.9	0.39
LVMI (g/m^2)	67.0 ± 16.2	60.8 ± 19.3	0.22
End Diastolic Volume (ml)	154.2 ± 32.9	160.7 ± 44.8	0.56
End Systolic Volume (ml)	62.1 ± 22.9	68.0 ± 28.3	0.41
Ejection Fraction (%)	60.6 ± 8.9	58.4 ± 10.0	0.41
Post systolic BP (mmHg)	126(116 – 146)	118 (109 – 139)	0.33
Post-diastolic BP (mmHg)	65 ± 13	67 ± 15	0.65
24h systolic BP[c] (mmHg)	129 ± 14	133 ± 20	0.64
24h diastolic BP[c] (mmHg)	73 ± 15	78 ± 12	0.47
FMD – baseline cuff (% change)[d]	3.8 ± 2.2	3.7 ± 4.4	0.95
FMD – baseline GTN (% change)[d]	11.3 ± 6.0	14.1 ± 7.3	0.30
PWV (m/s)[e]	7.4 ± 1.5	7.5 ± 2.2	0.91
Aix (%)[e]	25.2 ± 10.1	22.6 ± 19.5	0.70

Data presented as mean ± standard deviation, or median (inter quartile range) if non-parametric
Data available for [a]50, [b]52,[c]16, [d]28, [e]25 participants

BMI - body mass index, RRT – renal replacement therapy, ADPKD – autosomal dominant polycycstic kidney disease, URR – urea reduction ratio, LVM – left ventricular mass, LVMI – left ventricular mass indexed to body surface area, BP – blood pressure, FMD – flow mediated dilation, PWV – pulse wave velocity, Aix – augmentation index

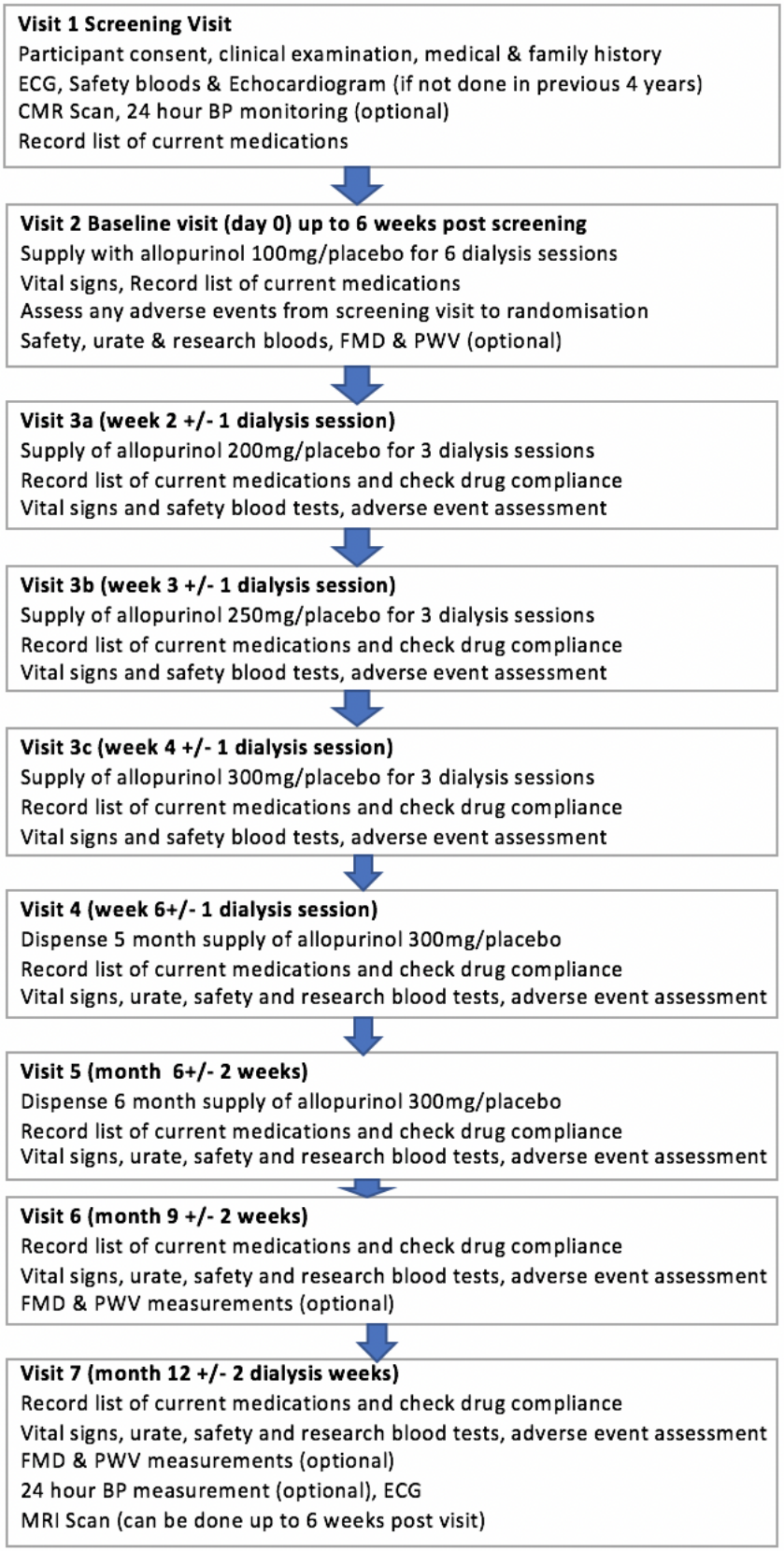
Supplemental Table 3. Breakdown of all Adverse Events in the Study

MedDRA CODING	Allopurinol	Placebo	Grand Total
1. Adverse Events	**81**	**74**	**155**
Blood and lymphatic system disorders		1	1
Cardiac disorders	9	1	10
Endocrine disorders	1		1
Eye disorders	1		1
Gastrointestinal disorders	5	3	8
General disorders and administration site conditions	8	5	13
Hepatobiliary disorders	1		1
Infections and infestations	21	21	42
Injury, poisoning and procedural complications	9	10	19
Investigations	4	4	8
Metabolism and nutrition disorders	2	3	5
Musculoskeletal and connective tissue disorders	2	5	7
Nervous system disorders	1	2	3
Product issues	3	5	8
Renal and urinary disorders	1	1	2
Respiratory, thoracic and mediastinal disorders	5	2	7
Skin and subcutaneous tissue disorders		3	3
Surgical and medical procedures	6	7	13
Vascular disorders	2	1	3
2. Adverse Reactions	**15**	**15**	**30**
Gastrointestinal disorders	5	2	7
General disorders and administration site conditions	1		1
Infections and infestations	2		2
Injury, poisoning and procedural complications		1	1
Investigations		1	1
Metabolism and nutrition disorders	1	1	2
Musculoskeletal and connective tissue disorders	2	1	3
Nervous system disorders	2	5	7
Psychiatric disorders		1	1
Skin and subcutaneous tissue disorders	2	3	5
Serious Adverse Events	**16**	**28**	**44**
Blood and lymphatic system disorders	1		1
Cardiac disorders	1	1	2

Gastrointestinal disorders	2	4	6
Hepatobiliary disorders		1	1
Immune system disorders		1	1
Infections and infestations	3	3	6
Injury, poisoning and procedural complications	1	5	6
Metabolism and nutrition disorders		1	1
Musculoskeletal and connective tissue disorders	1	2	3
Neoplasms benign, malignant and unspecified	1	1	2
Nervous system disorders	3	1	4
Respiratory, thoracic and mediastinal disorders		2	2
Skin and subcutaneous tissue disorders	1		1
Surgical and medical procedures	1	4	5
Vascular disorders	1	2	3
Serious Adverse Reaction		**1**	**1**
Skin and subcutaneous tissue disorders		1	1
GRAND TOTAL	**112**	**118**	**230**

Repetitions of the same adverse event for any given participant have been excluded from this table.

MedDRA – Medical dictionary for regulatory activities



Supplemental Figure 1. Flow chart of patient visits