ALLOPURINOL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH ISCHAEMIC HEART DISEASE

(ALL-HEART)

STATISTICAL ANALYSIS PLAN
(Final Analysis)

Study Title:	Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease		
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1. INTRODUCTION

1.1. STUDY BACKGROUND

Allopurinol has several positive effects on the cardiovascular system, is inexpensive and is already widely used in patients with gout. Ischaemic heart disease (angina or heart attack) is a common cause of death in people in the UK and treatment of patients with ischaemic heart disease (IHD) costs the NHS billions of pounds each year. The aim of this study is to improve the treatment of patients with IHD and determine whether adding allopurinol up to 600mg daily to these patients' usual medications will reduce their risk of having a stroke, heart attack or of dying due to cardiovascular disease.

1.2. STUDY OBJECTIVES

1.2.1. PRIMARY OBJECTIVES

To determine whether the addition of allopurinol up to 600mg daily to usual therapy improves cardiovascular outcomes.

1.2.2. SECONDARY OBJECTIVES

- To determine the cost-effectiveness of adding allopurinol up to 600mg daily to usual therapy.
- To determine whether the addition of allopurinol up to 600mg daily to usual therapy improves quality of life assessed by:
    - General health survey (EQ-5D)
    - Coronary heart disease-specific questionnaire (Seattle Angina Questionnaire)
- To determine the safety and tolerability of giving allopurinol to patients with IHD (without a history of gout).

1.3. STUDY DESIGN

The study is a multi-centre, controlled, prospective randomised open-label blinded endpoint (PROBE) trial of allopurinol up to 600mg daily vs. no treatment added to usual therapy in patients 60 years and over with ischaemic heart disease (IHD).

1.4. SAMPLE SIZE AND POWER

The original sample size noted at least 5,215 patients would be randomised to give 80% power to detect a 20% reduction in the primary cardiovascular (CV) endpoint (allowing for 4% dropout for withdrawal of consent to follow up and for non-cardiovascular deaths). A 14% event rate over 4 years average follow-up had been estimated from previous trials in similar patient groups and so a target number of 631 adjudicated primary endpoints was planned. During the study, a lower than expected event rate was observed, resulting in the study being extended in duration to allow for as close as

possible to the original target number of adjudicated primary endpoints to be accrued. An extension beyond the original maximum five years of follow-up was granted up until the 31st March 2021, and then a subsequent extension until the 30th September 2021 was also agreed. Where required, additional consent from each participant was sought to allow for continuing follow-up, in line with the relevant study extension(s).

1.5. Study Population

Patients aged 60 and older with a diagnosis of IHD, excluding those with known eGFR < 60ml/min (from February 2014 to April 2016) and, following a protocol amendment, excluding those with known eGFR < 30ml/min (from April 2016 onwards) at general practices across Scotland and England were considered for recruitment.

1.5.1. Inclusion Criteria and Exclusion Criteria

A list of inclusion and exclusion criteria can be found in the current version of the protocol (see section 1.6.3 below).

1.6. Statistical Analysis Plan (SAP)

1.6.1. SAP Objectives

The objective of this SAP is to describe the statistical reporting to be carried out for the final analysis of the ALL-HEART Study.

This SAP does not cover any statistical issues for other interim analyses or any cost-effectiveness analyses. These will be addressed in separate documents if required.

1.6.2. General Principles

All summaries will include results overall and by treatment group (Allopurinol and Usual Care). Categorical variables will be summarised using the number available, number missing and the number and percentage of patients in each category. Continuous variables will be summarised using the number available, number missing, mean, standard deviation (SD), median, 25th and 75th quartiles (Q1 and Q3 respectively), minimum and maximum values as appropriate.

1.6.3. Current Protocol

The current study protocol at the time of writing is version 5, dated 15th February 2019. This SAP has been created in line with the current version of the protocol.

Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. If no changes are required to this SAP following future amendments to the study protocol, this will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.6.4. Deviations To Those Specified In the Protocol

The protocol notes the analysis will be performed on the Intention to Treat population, but we will use a modified Intention to Treat (mITT) population.

In addition, the secondary efficacy outcomes have been reordered in this document to reflect the hierarchical order in which testing will be carried out. If the primary outcome is statistically significant at the 5% significance level, testing will continue on the secondary outcomes in the order specified here until an outcome becomes non-statistically significant at the 5% level.

1.6.5. Additional Analyses To Those Specified In the Protocol

Whilst the primary analysis will utilise the mITT population we will also include an on-treatment analysis, which will censor patients in the mITT population at an earlier date (defined in section 2.2 below) for all efficacy outcomes.

Additional subgroup analyses from those specified in the protocol will also be included. These are noted in section 2.5.6 below and include the following information collected at baseline: sex, diabetes, myocardial infarction, heart failure, peripheral arterial disease, cerebrovascular accident/stroke, transient ischaemic attack.

1.6.6. Software

All analyses will be performed using SAS for Windows v9.3 or higher, or R version 3 or higher.

2. Analysis

2.1. Study Populations and Analysis Sets

The Screened population will consist of all patients with valid consent who attended a screening visit for the study.

The mITT population will consist of all randomised patients, excluding those invalidly randomised.

The Safety population will consist of all members of the mITT population in the usual care arm, and all patients randomised to allopurinol, excluding those where there was evidence that they did not take at least one dose of study medication.

2.2. Censoring

The censoring time for the main analysis will be defined using the earliest of:

- the date of withdrawal of consent from the study;
- the date of death;
- the end of study follow-up date, to be the 30th September 2021 unless patients have opted to cease participation after 5 years of follow-up, or on the 31st March 2021, as per the study extensions detailed in section 1.4 above.

The censoring time for the on-treatment analysis will be defined using the earliest of:

- the last withdrawal from treatment date + 28 days;
- the date of withdrawal of consent from the study;
- the date of death;

- the end of study follow-up date, to be the 30th September 2021 unless patients have opted to cease participation after 5 years of follow-up, or on the 31st March 2021, as per the study extensions detailed in section 1.4 above.

2.3. SUBJECT DISPOSITION

The following information, which will help to prepare the CONSORT diagram, will be summarised:

- The number of patients in the screening population
- The number of patients that did not meet the inclusion and exclusion criteria as assessed prior to randomisation
- The number of patients randomised
- The number of patients not randomised
- The number of patients excluded post-randomisation, from the randomised population, and the reasons for exclusion
- The number and percentage in the mITT population overall and by treatment group
- The number in the Safety population overall and by treatment group
- The number and percentages that withdrew from all follow-up (excluding the deaths), and the reasons for withdrawal (of those included in the mITT population) overall and by treatment group
- The number and percentages of patients that died following randomisation (of those included in the mITT population) overall and by treatment group
- The number and percentages of patients that completed the study overall and by treatment group.
- The number and percentages that permanently withdrew from treatment, and the reasons for withdrawal from treatment, where permanent withdrawal from treatment is not due to death (of those included in the mITT population)

Time to withdrawal from all follow-up (excluding deaths) will be summarised overall and by treatment group, and also displayed using cumulative incidence plots. Time on treatment for the allopurinol group will also be summarised and displayed using a cumulative incidence plot.

2.4. BASELINE CHARACTERISTICS

In the mITT population, overall and by treatment group, summaries will be provided of the following baseline characteristics as included in the eCRF:

- Age and sex;
- Race;
- Smoking and alcohol habits;
- CV medical history;
- Other medical history;
- SBP, DBP and heart rate;
- height, weight and BMI;
- concomitant medications tabulated by WHO ATC with additional tabulation of the following categories of drugs (antiplatelet agents, statins, ezetimibe, anticoagulants, beta-blockers, ACE inhibitors, angiotensin receptor antagonists,

calcium channel blockers, other anti-anginal medications [including long-acting nitrates, nicorandil, ranolazine, etc.], loop diuretics, thiazide/thiazide-like diuretics, insulin diabetic medication, non-insulin diabetic medication, NSAIDs);

- Quality of Life: EQ-5D (utility score, individual questions and VAS);
- Quality of Life: Seattle Angina Questionnaire (SAQ domains: physical limitation, angina stability, angina frequency, treatment satisfaction and disease perception);
- Lab results (Haemoglobin, White Cell count, Platelet count, Mean Corpuscular Volume, Neutrophil count, Lymphocyte count, Monocyte count, Eosinophil count, Basophil count, Sodium, Potassium, Urea, Creatinine, eGFR, Urate);

Formal comparisons of baseline characteristics will be provided using chi-square test or Fisher's exact test for categorical variables as required and Wilcoxon rank sum test for continuous variables.

2.5. STUDY OUTCOMES

2.5.1. PRIMARY OUTCOME

The primary outcome is the composite of cardiovascular (CV) death, non-fatal stroke and non-fatal myocardial infarction (MI) and this will be analysed as time to first event analysis using a Cox Proportional Hazards model. Predictor variables will be randomised treatment and the stratification variables (history of MI and history of stroke). Treatment effects will be estimated in the form of hazard ratios, for allopurinol vs. usual care, with corresponding 95% confidence intervals and p-values (Wald Statistic). The results will be summarised graphically using a cumulative incidence plot of events by treatment group. The number of patients with first events, crude percentage of patients with events, rates of events / 100 patient years of follow-up will also be summarised by treatment group.

2.5.2. SECONDARY OUTCOMES

Secondary outcomes include:

1. Non-fatal MI
2. CV death
3. Non-fatal stroke
4. All-cause mortality
5. Hospitalisation for heart failure
6. Hospitalisation for ACS or coronary revascularisation
7. Hospitalisations for acute coronary syndrome (ACS)
8. Coronary revascularisation
9. All CV hospitalisations
10. Quality of life as assessed by the EQ-5D
11. Quality of life as assessed by the SAQ

The secondary outcomes 1 to 9 noted above will be analysed as time to first event analysis, as per the analysis detailed above for the primary outcome.

Secondary outcomes 10 and 11 will be summarised overall and by treatment group at each time point; change from baseline will also be summarised. The EQ-5D individual

questions will be used to obtain the utility score. The EQ-5D visual analogue scale (VAS), utility score and the SAQ domains will be analysed using linear regression models with the change from baseline as the outcome and predictor variables of treatment, the stratification variables (history of MI and history of stroke) and the corresponding outcome baseline value.

These will be analysed at two time points, one year post-randomisation and the final year, and for each outcome at each time point, the analysis will include:

1. Complete case analysis (of those alive). Note, for the EQ-5D utility score, patients who have died by the time point for analysis will have a value of 0 imputed and will be included in this analysis.
2. Missing follow-up values will be imputed with a 0 if the patient has died, or using multiple imputation (only if missing follow-up AND baseline value is available).

The treatment effect estimate (allopurinol – usual care), corresponding 95% confidence interval and p-value will be reported to determine the main effect of treatment.

2.5.3. ADJUDICATED OUTCOME DEFINITIONS

The primary outcome, and secondary outcomes (as listed in 2.5.2) 1 to 5 and 7, as well as the hospitalisation for ACS aspect of secondary outcome 6, are adjudicated by the endpoint adjudication committee. Secondary outcome 8, and the corresponding part of secondary outcome 6, are confirmed by the endpoint adjudication chair. Each of these outcomes is identified from the adjudication committee final adjudication form as follows:

1. All-cause mortality – any adjudicated death

2. CV mortality – any adjudicated death that has been adjudicated as 'cardiovascular death' (regardless of sub-classification), or 'undetermined cause of death'.

3. Non-fatal MI – any adjudicated non-fatal event that has been adjudicated as either an acute myocardial infarction OR a biomarker positive ACS.

4. Non-fatal stroke – any adjudicated non-fatal event that has been adjudicated as a stroke.

5. Hospitalisations for ACS – any adjudicated non-fatal event that has been adjudicated as either an acute myocardial infarction, OR a biomarker positive ACS (but only when the acute MI or biomarker positive ACS events were a cause of hospitalisation), OR a hospitalisation for angina.

6. Hospitalisation for heart failure – any adjudicated non-fatal event that has been adjudicated as a hospitalisation for heart failure.

2.5.4. ADJUDICATED OUTCOMES

Causes of adjudicated deaths will be summarised overall and by treatment group, including detail on whether the adjudicated deaths were cardiovascular, non-

cardiovascular or an undetermined cause. The cardiovascular deaths will be further summarised using the sub-classification causes of death.

Non-fatal adjudicated outcomes will be summarised overall and by treatment group using the information available from the adjudication for both the first type of event and separately for all events.

2.5.5. NON-ADJUDICATED OUTCOMES

CV hospitalisations are defined as hospital admissions involving an overnight stay that had a CV reason for admission.

2.5.6. SUBGROUP ANALYSIS

The numbers and percentages of subjects with primary endpoints within each sub-group will be given split by treatment. The hazard ratios, 95% CIs and p-values for the treatment effects will be calculated from Cox models within each subgroup. The model used for the primary outcome will be extended to include a subgroup variable and the interaction between the subgroup and the treatment effect. A p-value for the interaction will be calculated

The following subgroup analyses for the primary outcome will be provided:

- Baseline Urate (split by tertiles)
- eGFR (<60mL/min / ≥ 60mL/min)
- Age (< / ≥ 70 years)
- Sex (Male/Female)
- Diabetes reported in other medical history at baseline (yes/no)
- Myocardial Infarction reported in cardiovascular history at baseline (yes/no)
- Heart Failure reported in cardiovascular history at baseline (yes/no)
- Peripheral arterial disease reported in cardiovascular history at baseline (yes/no)
- Cerebrovascular accident/Stroke reported in cardiovascular history at baseline (yes/no)
- Cerebrovascular accident/Stroke OR Transient Ischaemic Attack reported in cardiovascular history at baseline (yes/no)

A forest plot will be provided for the subgroup analyses.

2.5.7. ASSUMPTION CHECKING

The proportional hazards assumption for the primary outcome and secondary outcomes 1 to 9 will be tested informally by review of the cumulative incidence plots, and formally by adding a log(time)*treatment covariate in each of the Cox Proportional Hazards models and assessing the statistical significance at the 5% significance level. If the extent of any deviation from proportional hazards is minor, the proportional hazards model results will be reported with a caveat that the hazard ratio represents approximately the average treatment effect over the follow-up period. If there is more extensive deviation, for instance clear evidence of the survival curves crossing, a further analysis will be stratified within appropriate time intervals.

2.5.8. Safety Outcomes

All safety outcomes will be provided for the safety population.

2.5.8.1. Treatment Related Adverse Events

All reported treatment related adverse events will be provided when they occurred:

1. At any point post-randomisation up to end of study follow-up date

2. Prior to permanent withdrawal from randomised allopurinol treatment + 28 days

Treatment related adverse events will be reported only for the allopurinol group by system organ class and preferred term as classified by MedDRA (for all events and for the severe events only) for:

1. All recorded events
2. Rash events (regardless of event description)
3. Gout events (regardless of event description)

For each scenario, the number of patients with first events and corresponding crude percentages of patients with events, as well as the total number of events and rates of events / 100 patient years of follow-up will be summarised.

Cumulative incidence plots for the allopurinol group will be produced for the time to first event, for each of the rash and gout events separately.

2.5.8.2. Serious Adverse Events

Serious adverse events and fatal serious adverse events will be reported by treatment group, by system organ class and preferred term as classified by MedDRA. These will be reported for all patients and additionally split by relatedness (any or none) and separately the SAE's where treatment was withdrawn (for the allopurinol arm only). The number of patients with first events and corresponding crude percentages of patients with events, as well as the total number of events and rates of events / 100 patient years of follow-up will be summarised by treatment group.

An additional table will be created at the system organ class level for the period from randomisation to end of study follow-up date. Comparisons between treatment groups for the percentages of patients with at least one SAE for each system organ class will be made assuming Binomial distributions. Estimates of the difference in percentages between groups and corresponding 95% Confidence Intervals will be provided.

Cumulative incidence plots by treatment group will be produced for the time to first serious adverse event, as well as a log-rank test.

A table of the non-benign incident cancers will also be reported by treatment group, by site of cancer.

2.5.8.3. RASH AND GOUT EVENTS

The number of patients at each annual visit experiencing at least one event within the previous 12 months (new skin rash and attack of gout) as recorded in the annual questionnaire, will be summarised overall and by treatment group.

2.5.8.4. FOLLOW-UP LAB DATA

Follow-up lab data was recorded six weeks after starting study medication in the allopurinol group only. In the population with lab data available at six weeks, the follow-up, baseline and the change from baseline results will be summarised.

2.5.8.5. EXPOSURE TO ALLOPURINOL WITHIN THE ALLOPURINOL ARM

Allopurinol dose at 6 weeks post-randomisation, and at each annual follow-up post-randomisation will be summarised in all patients randomised to allopurinol, who are noted as remaining on treatment at each time point respectively. In addition, the dose summaries will also be provided split by the patients' baseline eGFR (<60 mL/min / $\geq$ 60 mL/min).

2.5.8.6. DROP-INS TO ALLOPURINOL

The number of patients initiating on allopurinol who were randomised to the usual care group will also be summarised, along with the indication, average starting dose and average last dose.

2.5.9. OTHER OUTCOMES

All other outcomes will be reported for the mITT population.

2.5.9.1. HEALTHCARE SERVICE USAGE

The number of contacts with healthcare services for the preceding 12 months, reported within annual questionnaires at the first year of follow-up and at the end of the study, will be summarised for all patients overall and by treatment group for each of the collected healthcare services:

- General Practitioner
- Practice or community nurse
- Physiotherapist
- Doctor at a hospital outpatient clinic

Formal analysis to compare each of the four healthcare service usages detailed above between treatment groups, at each of the first year of follow-up and at the end of study, will be provided using stratified Wilcoxon tests to account for the stratification variables.

In addition, a subset of 25% of patients were selected to record this data at all of their annual visits. For these patients, the same principles as those above will be used, but the data will be summarised at each annual visit.

2.5.9.2. RECURRENT EVENTS

The total numbers of events and rates of events / 100 patient years of follow-up will be summarised by treatment group, for the primary outcome and secondary outcomes 1, 3, 5, 6, 7, 8 and 9. Treatment effects will be estimated using the method of Lin, Wei, Ying and Yang to obtain rate ratios for allopurinol vs. usual care, corresponding 95% confidence intervals and p-values.

3. TABLES AND FIGURES

Dummy reports will be produced and reviewed by the chief investigator. Approval of the content of the final statistical outputs will be documented prior to the database lock.

4. LISTINGS

Listings of all derived datasets will be produced as excel spreadsheets. In addition, listings (as excel spreadsheets) will be produced containing the information used for each output table and figure in the report.

5. DOCUMENT HISTORY

This is version 1.1 of the ALL-HEART final analysis SAP, dated 17th May 2022. Version 1_0 was updated on this day to:

1. Identify the population in which all safety outcomes will be reported (section 2.5.8).

2. Part of section 2.5.8.3 (rash and gout events) has been moved to section 2.5.8.1 (treatment related adverse events) for clarity as to which data is being summarised since rash and gout information is collected under both the treatment related adverse events and the patient annual questionnaires.

3. The rash and gout events section noted above that has been moved to section 2.5.8.1 has also been reduced to only report these events at any time during the study, rather than additionally within each year of follow-up.

4. Identify the population in which all other outcomes will be reported (section 2.5.9) and correct the numbering of the sub-sections.