Study Protocol

Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease

ALL-HEART

Co-sponsor	University of Dundee / NHS Tayside
Funder	NIHR HTA
Funding Reference Number	HTA 11/36/41
Chief Investigator	Prof Isla S Mackenzie
EudraCT Number	2013-003559-39
CTA Number	21726/0284/001-0001
MREC Number	13/ES/0104
ISRCTN Number	ISRCTN32017426
Version Number and Date	ALL-HEART protocol V5 (15-02-2019)

CONTENTS

PROTOCOL APPROVAL

Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease

EudraCT number 2013-003559-39

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

Professor Isla Mackenzie **Chief Investigator**	Signature	18 June 2019 Date
Professor Ian Ford **Trial Statistician**	Signature	19 June 2019 Date
Professor Chris Hawkey **Principal Investigator (Nottingham)**	Signature	26/6/2019 Date

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AE	Adverse event
APTC	Antiplatelet Triallists' Collaboration
CHD	Coronary heart disease
CLRN	Comprehensive Local Research Network
CV	Cardiovascular
DMC	Data Monitoring Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
GP	General practitioner
HTA	Health Technology Assessment
IHD	Ischaemic heart disease
IVRS	Interactive voice response system
LVH	Left ventricular hypertrophy
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
NHS	National Health Service
NIHR	National Institute for Health Research
NYHA	New York Heart Association
PCRN	Primary Care Research Network
PROBE	Prospective Randomised Open-label Blinded Endpoint
QALY	Quality adjusted life year
QOF	Quality Outcome Framework
SAE	Serious adverse event
SPCRN	Scottish Primary Care Research Network
STEMI	ST elevation myocardial infarction
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

SUMMARY
PROFESSIONAL SUMMARY

Design

The study is a multi-centre, controlled, prospective randomised open-label blinded endpoint (PROBE) trial of allopurinol versus no treatment added to usual therapy in patients aged 60 years and over with ischaemic heart disease (IHD). The aim is to establish whether allopurinol improves cardiovascular (CV) outcomes in this population. Approvals will be obtained for the trial from ethics committees, the Medicines and Healthcare products Regulatory Agency (MHRA) and local research and development departments. Primary care practice lists and secondary care clinic lists will be searched for suitable subjects with IHD who will be invited to participate. At a screening visit, written informed consent will be taken, inclusion and exclusion criteria checked and blood samples taken for baseline full blood count, urea and electrolytes, creatinine, eGFR and urate. Patients will be randomised via a web portal or interactive voice response system (IVRS) to either allopurinol or no drug to be given in addition to their usual medications. In patients who are randomised to allopurinol and have a screening visit eGFR ≥60mL/min/1.73m^2, allopurinol will be started at 100-150mg daily for 2 weeks (100mg should be the usual starting dose; 150mg may be used as the starting dose in the event of a local shortage of 100mg tablets), then titrated to 300mg daily for 2 weeks, then titrated to 600mg daily if tolerated. In patients who are randomised to allopurinol and have a screening visit eGFR 30-59mL/min/1.73m^2, allopurinol will be started at 100-150mg daily for 2 weeks, then titrated to 300mg daily if tolerated.

In patients randomised to allopurinol, bloods will be taken for full blood count, urea and electrolytes, creatinine, eGFR and urate 6 weeks (+/- 1 week) after starting study medication. Patients will be asked to report any treatment-related adverse events, particularly rash (~1% incidence with allopurinol) and gout flares, and any serious adverse events. Study medications will be prescribed by the GP. An eCRF and dedicated study web portal will be used to collect study data and aid pharmacovigilance reporting and trial management.

Health technologies being assessed - Allopurinol up to 600mg daily

Allopurinol is a xanthine oxidase inhibitor. Xanthine oxidase promotes inflammation and atherosclerosis via the production of reactive oxygen species. Xanthine oxidase levels are raised in several conditions including coronary artery disease. Allopurinol is usually given in daily doses of between 100mg and 900mg. Allopurinol has several beneficial effects in CV disease. Allopurinol improves endothelial function in patients with heart failure, type 2 diabetes and smokers, reduces left ventricular hypertrophy, increases exercise time in angina and reduces myocardial ischaemia-reperfusion injury. Allopurinol reduces oxidative stress and improves oxygen and energy supply to tissues. Allopurinol also reduces blood pressure, arterial stiffness and may reduce low density lipoprotein cholesterol levels. Observational studies suggest that allopurinol may improve CV outcomes. A study in patients with chronic kidney disease showed that allopurinol reduced CV events. Some studies have suggested that higher doses of allopurinol (600mg) are necessary to achieve some of these positive CV effects, which is why a dose of 600mg daily has been chosen for the current study for patients with normal renal function (screening visit eGFR ≥60mL/min/1.73m^2). A maximum dose of 300mg daily will be given to patients with screening visit eGFR 30-59mL/min/1.73m^2. It is documented in the summary of product characteristics for allopurinol that in patients with severe renal impairment (creatinine clearance 10-20mL/min) a daily dose of 300mg allopurinol leads to equivalent levels of oxipurinol (the active metabolite of allopurinol) as a daily dose of 600mg allopurinol in patients with normal renal function (33). It has previously been demonstrated that allopurinol at doses of 600mg daily can be given safely in patients with angina.

Setting

Further interventions for patients with IHD are best tested in the real-life setting of patients already taking usual therapy. This is a pragmatic streamlined clinical trial within the primary care setting of the UK NHS. Follow-up will primarily be by electronic record-linkage using unique identifiers to collect data on hospitalisations and mortality centrally without the need for study follow-up visits. This approach significantly reduces the cost of the trial.

Target Population

The study population will be patients 60 years and over with IHD (angina or myocardial infarction). Exclusions will include patients with gout, known severe renal impairment (eGFR <30 mL/min/1.73m^2), moderate to severe heart failure (NYHA III-IV), significant hepatic disease, already taking part in another interventional clinical trial of an investigational medicinal product or medical device (or taken part in one in the previous 3 months), patients with previous allergy to allopurinol or a previous serious adverse cutaneous (skin) reaction to any drug and patients already taking urate lowering therapy, azathioprine, mercaptopurine, ciclosporin or theophylline.

Sample size

5,215 patients need to be randomised to give 80% power to detect a 20% reduction in the primary CV endpoint for the intervention (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 has been estimated from previous trials in similar patient groups. The study will end when 631 adjudicated primary endpoints have occurred.

Measurement of costs and outcomes

The primary outcome will be the composite (APTC) CV endpoint of non-fatal myocardial infarction (MI), non-fatal stroke and CV death. It is necessary to use a composite endpoint in this type of trial as event rates for individual events would be too low. The APTC endpoint is well-established and non-subjective. Secondary outcomes will be: non-fatal MI, non-fatal stroke, CV death, all-cause mortality, all CV hospitalisations, hospitalisation for acute coronary syndrome (ACS), coronary revascularisation, hospitalisation for ACS or revascularisation, hospitalisation for heart failure, quality of life and cost-effectiveness of allopurinol. Record-linkage for events will be carried out at least once a year and potential endpoints will be investigated further by obtaining information from medical records. Endpoint packages will be adjudicated by an endpoint committee blinded to treatment allocation. Data analysis will be carried out according to a pre-determined data analysis plan. The primary analysis will be intention-to-treat. Results will be reported in peer-reviewed journals and at scientific meetings. Results will also be disseminated to guideline committees, NHS organisations and patient groups. The economic evaluation will estimate costs and benefits over a lifetime horizon using a Markov model approach. Using the cost perspective of the NHS and social services, it will take account of medicines cost, costs of monitoring, impact on hospital admissions (and associated costs after discharge). We will compare this to our estimate of the QALY gain from treatment to produce a net cost per QALY gained for adding allopurinol to usual care.

Project timetables including recruitment rate

There will be a 3 month start-up phase to allow finalisation of regulatory approvals, development of the eCRF and web systems and training materials and recruitment of study staff. During this time, practices will be approached to take part in the study. The recruitment phase will last for approximately 2 years with an average follow-up of around 4 years. These periods may be extended depending on recruitment rates, event rates and additional funding. In the event that the study follow up period for individual patients is extended beyond 5 years, the study team will contact participants affected by this increase in duration, using the contact methods provided by the study participants, to gather their implicit consent to continue in the follow up phase of the study until study completion. There will follow an approximate 6 month period for finalisation of data collection by record linkage, data analysis and preparation of the final study reports. The study end is event-driven therefore it will be important to recruit at a high rate early in the trial to maximise patient years' exposure. IHD is a common disease and recruitment should benefit from our established networks of primary care practitioners and from working with the primary care and comprehensive local research networks to maximise recruitment. Project managers based in Dundee will oversee the project. An independent data monitoring committee will oversee patient safety. A trial steering committee including patient members will guide trial progress.

LAY SUMMARY

Allopurinol is a medication used to prevent gout. 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 the commonest cause of death in people in the UK and treatment of patients with ischaemic heart disease costs the NHS billions of pounds each year. In this study, we want to improve the treatment of patients with ischaemic heart disease. We want to

investigate whether adding allopurinol to these patients' usual medications will reduce their risk of having a stroke, heart attack or of dying due to cardiovascular disease. Patients will usually attend their local primary care centre (general practice) to take part in the study. Patients will be randomly allocated to receive allopurinol or no treatment in addition to their usual medications then will be followed up for a period of around 4 years to count the number of heart attacks, strokes and cardiovascular deaths that occur. The follow up period may be extended with appropriate approvals if this is necessary for the successful completion of the study. For example, this may happen if it takes longer than expected to include the necessary number of patients in the study or if fewer patients than expected have events like heart attacks or strokes. In the event that the study follow up period for individual patients is extended beyond 5 years, the study team will contact participants affected by this increase in duration, using the contact methods provided by the study participants, to gather their implicit consent to continue in the follow up phase of the study until study completion. The numbers of events that occur in the different treatment groups will be compared to see if there is a benefit of adding allopurinol to their other treatment. Most of the follow up data will be collected electronically by accessing centrally held electronic records of hospital admissions and deaths which will make the study easier for patients and more cost-efficient. We will also measure quality of life and whether there is an economic benefit of using allopurinol in patients with ischaemic heart disease using annual questionnaires. The study will be reviewed by an ethics committee prior to starting.

The team running this study has a lot of experience in running large clinical studies of this type and have already established good working research relations with a team of more than 700 general practices. The results of this study could have major benefits for patients and result in significant cost savings for the NHS if allopurinol is found to be effective as it would be inexpensive and easy to introduce quickly to patient care within the UK.

1. INTRODUCTION

1.1 BACKGROUND

What is the problem being addressed?
This clinical trial aims to address whether allopurinol improves cardiovascular outcomes in patients with ischaemic heart disease (IHD).

Ischaemic heart disease
IHD is the commonest cause of death in both men and women in the UK (around 1 in 5 men and 1 in 7 women die of IHD). Although death rates from IHD have fallen in the last 10 years, largely due to reductions in smoking and improvements in treatment and secondary prevention, morbidity from IHD is increasing. IHD is more common in Scotland (4.6%) than in England (3.5%) and is more prevalent in lower socioeconomic groups and older age groups. Overall, 4% of men and 0.5% of women in the UK have a history of MI while 14% of men and 8% of women aged 65-74 years have a history of angina.

IHD is usually treated with a combination of medications, some that may improve symptoms e.g. anti-anginals, and some that may improve survival e.g. statins. In addition, interventional procedures such as angioplasty, coronary artery stenting and coronary artery bypass grafting are used in selected patients. Lifestyle improvements such as stopping smoking and exercise programmes are also recommended. Most of the current treatments for IHD have risks that need to be balanced with their benefits e.g. most medications used for IHD carry risks of causing adverse reactions, and interventional procedures carry risks such as bleeding, arrhythmia and coronary artery rupture.

1.2 RATIONALE FOR STUDY

Allopurinol has beneficial effects on various cardiovascular parameters and we hypothesise that it might improve cardiovascular outcomes in patients with IHD. We also hypothesise that it might improve quality of life and be a cost-effective therapy within the NHS in patients with IHD.

Allopurinol
Allopurinol is a xanthine oxidase inhibitor that lowers uric acid and is currently licensed for the prevention of gout and hyperuricaemia. Xanthine oxidase promotes inflammation and atherosclerosis via the production of reactive oxygen species. Xanthine oxidase levels are raised in several conditions including coronary artery disease (1). Allopurinol is usually given in daily doses of between 100mg and 900mg. Allopurinol has several beneficial effects in CV disease. Allopurinol improves endothelial function in patients with heart failure, type 2 diabetes and smokers, reduces left ventricular hypertrophy, increases exercise time in angina and reduces myocardial ischaemia-reperfusion injury. Allopurinol reduces oxidative stress and improves oxygen and energy supply to tissues. Allopurinol also reduces blood pressure, arterial stiffness and may reduce low density lipoprotein cholesterol levels. Observational studies suggest that allopurinol may improve CV outcomes. A study in patients with chronic kidney disease showed that allopurinol reduced CV events. Some studies have suggested that higher doses of allopurinol (600mg) are necessary to achieve some of these positive CV effects (2-4). As a result, a dose of 600mg daily has been chosen for the current study for patients with normal renal function (screening visit eGFR ≥60mL/min/1.73m^2). A maximum dose of 300mg daily will be given to patients with screening visit eGFR 30-59mL/min/1.73m^2. It is documented in the summary of product characteristics for allopurinol that in patients with severe renal impairment (creatinine clearance 10-20mL/min) a daily dose of 300mg allopurinol leads to equivalent levels of oxipurinol (active metabolite of allopurinol) as a daily dose of 600mg allopurinol in patients with normal renal function (33). It has previously been demonstrated that allopurinol at doses of 600mg daily can be given safely in patients with angina (4).

A recent study from the University of Dundee published in the Lancet showed that allopurinol 600mg daily increases exercise time and reduces chest pain in patients with angina (4). This study was carried out in 60 patients with angina with angiographically documented coronary artery disease and no adverse effects of the study treatment were observed. The results are suggestive of an anti-ischaemic effect of allopurinol as discussed further below. More recently, a Medical Research Council funded study carried out at the University of Dundee showed that allopurinol 600mg daily

reduces left ventricular mass compared to placebo in patients with IHD (32). There was also a reduction in augmentation index (a measure of arterial wave reflection associated with arterial stiffness) with allopurinol compared to placebo. Since left ventricular hypertrophy is present in 73% of IHD patients (7) and, after age, left ventricular hypertrophy is said to be the strongest predictor of cardiovascular events and all-cause mortality (8), this is an important finding. Allopurinol has also been shown to regress left ventricular hypertrophy in patients with chronic kidney disease (9). Studies have shown that LVH regression is associated with reductions in all-cause mortality (by 28%), cardiovascular mortality (by 38%), sudden cardiac death (by 19%), MI (by 15%), stroke (by 24%), new congestive heart failure (by 36%) and new onset atrial fibrillation (by 12%), all of which are important cardiovascular outcomes (10-12). These reductions are independent of any changes in blood pressure.

Allopurinol also improves endothelial function in patients with heart failure (13-14), type 2 diabetes (15) and smokers (3). Allopurinol lowers blood pressure (16-17), arterial stiffness (18) and low density lipoprotein cholesterol (unpublished data).

Various mechanisms have been suggested as to how allopurinol may theoretically improve cardiovascular outcomes. Xanthine oxidase is a major source of reactive oxygen species (19). Allopurinol (a xanthine oxidase inhibitor) profoundly reduces oxidative stress by reducing superoxide anions and other free radicals which reduces cardiac hypertrophy, increases tissue oxygenation and reduces atherosclerotic plaque rupture – a key event linked to myocardial infarction (2, 20, 21, 22). Allopurinol may also reduce cardiac afterload by improving arterial compliance (through reduced wave reflection and improved endothelial function). It is not clear whether it is uric acid lowering or other effects of allopurinol that are important although in one study comparing allopurinol with the uricosuric agent probenecid, effects on endothelial function were found to be independent of uric acid lowering (2). Finally, by inhibiting xanthine oxidase activity, allopurinol increases levels of hypoxanthine, which might increase adenosine triphosphate (ATP) levels and thus energy availability to tissues. Extra ATP and oxygen availability produced by allopurinol might prevent downstream ischaemic cardiomyocytes from infarcting and thereby leading to heart failure during an ischaemic insult such as acute coronary syndrome (23, 24).

In observational studies, in patients with hyperuricaemia (25) and heart failure (26, 27) allopurinol was associated with reduced mortality. Smaller randomised studies have found that allopurinol reduces cardiac events in patients with chronic kidney disease (28), and allopurinol reduced the troponin rise in patients undergoing percutaneous coronary intervention following ST elevation MI (STEMI), which is strong evidence that downstream ischaemic cardiomyocytes stay alive better during an ischaemic insult in the presence of allopurinol therapy (29). Preservation of ischaemic cardiomyocytes may be a key factor in preventing future heart failure in such patients.

Several different generic preparations of allopurinol are available for prescription within the UK. Adverse reactions in association with allopurinol are rare in the overall treated population and mostly of a minor nature. The incidence of adverse reactions is thought to be higher in the presence of renal and/or hepatic disorders. The most common adverse reaction to allopurinol is rash (affects around 1% of patients). Usually this is a minor rash that resolves on stopping therapy. Rarely, the rash may be more serious and occasionally serious skin reactions such as Stevens Johnson syndrome or toxic epidermal necrolysis may occur. In the event of a serious skin reaction, allopurinol therapy should be stopped immediately and should not be restarted. Other possible adverse reactions to allopurinol include gastrointestinal disturbance such as nausea or vomiting, asymptomatic increases in liver function tests, hypersensitivity, angioedema and hepatitis. The summary of product characteristics lists other very rare reactions to allopurinol.

Allopurinol will be given orally as tablets at a dose of up to 600mg daily (in patients with screening visit eGFR ≥60mL/min/1.73m^2) throughout the duration of the study (following an initial uptitration phase of 100-150mg daily for 2 weeks (100mg should be the usual starting dose; 150mg may be used as the starting dose in the event of a local shortage of 100mg tablets), then 300mg daily for 2 weeks, then 600mg daily thereafter if tolerated). In patients with screening visit eGFR 30-59mL/min/1.73m^2, allopurinol will be given orally as tablets at a dose of up to 300mg daily throughout the duration of the study (following an initial up-titration period of 100-150mg daily for 2 weeks, then 300mg daily thereafter if tolerated). The titration phase has been included (as in previous clinical trials of allopurinol in patients with heart disease) to ensure tolerability and minimise the risk of adverse events upon introduction of allopurinol therapy. Safety bloods will be checked 6 weeks (+/-

1 week) after starting allopurinol therapy in patients randomised to allopurinol. Patients will be asked to contact the study team if they develop any adverse reactions to allopurinol at any time and will be advised to stop therapy immediately and seek further medical advice if they develop a rash on allopurinol therapy. The chosen dose of 600mg daily (for patients with screening visit eGFR ≥60mL/min/1.73m^2) lies within the licensed dose range for use of allopurinol in patients with gout (100-900mg daily) and is the dose that is likely to be effective based upon the findings of previous studies of the effects of allopurinol on cardiovascular parameters and on exercise time in patients with angina. The chosen dose of 300mg daily (for patients with screening visit eGFR 30-59mL/min/1.73m^2) should give roughly equivalent (or lower) drug levels in patients with renal impairment due to altered renal excretion of allopurinol and its metabolites.

Allopurinol is already widely prescribed in the NHS; 3,260,500 prescriptions for allopurinol were dispensed in England in 2008 (5). The current British National Formulary price for a 28-day supply of allopurinol 300mg is £1.17 (allopurinol 600mg would be £2.34 for a 28-day supply) (6). Therefore, this is an inexpensive drug therapy.

Ischaemic heart disease (IHD)
IHD is a common cause of death in both men and women in the UK (around 1 in 5 men and 1 in 7 women die of IHD). IHD is more common in Scotland (4.6%) than in England (3.5%) and is more prevalent in lower socioeconomic groups and older age groups. Overall, 4% of men and 0.5% of women in the UK have a history of MI while 14% of men and 8% of women aged 65-74 years have a history of angina.

Ischaemic heart disease may be diagnosed based upon typical symptoms e.g. exercise-related central dull chest pain relieved by rest (typical of angina) or severe crushing central chest pain radiating down the left arm and into the jaw (typical of myocardial infarction). Often, further evidence of the diagnosis is also present e.g. ECG changes, troponin changes, abnormal exercise tolerance test, abnormal coronary angiogram, echocardiogram or other imaging. Most general practices hold registers of patients with 'Coronary Heart Disease' (i.e. IHD) for Quality Outcome Framework (QOF) and other purposes, created using READ codes for manifestations of IHD (G3…00, G3…11, G3…12, G3…13). These registers should contain all patients with diagnosed occlusive coronary artery disease.

Why is the research important in terms of benefits to patients and the NHS?
This research will establish whether the administration of allopurinol to patients with IHD improves cardiovascular outcomes (stroke, MI and cardiovascular death). A 20% reduction in the primary CV endpoint would be a worthwhile improvement and the study has been powered to detect this level of effect.

Benefits to patients
Patients with IHD often have reduced quality of life due to symptoms including chest pain, reduced exercise tolerance and limitation of activities. The diagnosis of IHD also causes a significant psychological impact on patients due to concerns about mortality and impairment of lifestyle. A simple intervention that could be prescribed easily on the NHS and could improve symptoms and reduce the risk of serious events such as myocardial infarctions, strokes and cardiovascular deaths in this patient group would be of great benefit to patients.

Benefits to the NHS
IHD causes a significant cost burden on the NHS and costs are likely to increase further as the population ages. In 2006, cardiovascular disease cost the NHS around £14.4 billion. Hospital care accounted for 72% of these costs and drug therapies accounted for 20%. Any simple inexpensive measure that could further reduce the morbidity associated with IHD, and could easily be implemented into routine care, would result in significant cost savings for the NHS. If allopurinol improves cardiovascular outcomes and were to be prescribed more widely based on the results of this study, the minimal cost of this generic medication would likely be greatly outweighed by the cost savings of reductions in IHD morbidity for the NHS. Our economic analysis will quantify the health economic benefits.

Evidence explaining why this research is needed now
As the UK population ages, more patients will be living with IHD and its resultant morbidity. Likewise the costs of IHD to the NHS are likely to increase as people live longer. With the strong background

supportive evidence that allopurinol improves various cardiovascular parameters in randomised studies and in observational studies, it is timely to now do a large randomised prospective trial in patients within their usual care setting to determine whether the addition of allopurinol to their usual treatment improves cardiovascular outcomes. In these times of economic difficulty, the ability to add a cheap and established medication to patients' treatment regimes that would reduce morbidity and the cost of treating patients with IHD for the NHS is highly attractive.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

We aim to study patients aged 60 years and over with IHD in the UK.

2.1.1 Primary Objective

To determine whether the addition of allopurinol to usual therapy improves cardiovascular outcomes.

2.1.2 Secondary Objectives

To determine the cost-effectiveness of adding allopurinol 600mg daily (or 300mg daily) to usual therapy.

To determine whether the addition of allopurinol 600mg daily (or 300mg 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).

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The primary outcome is the composite (APTC) CV endpoint of non-fatal MI, non-fatal stroke and CV death. It is necessary to use a composite endpoint in this type of trial as event rates for individual events would be too low. The APTC endpoint is well-established and non-subjective.

2.2.2 Secondary Endpoints

1. Non-fatal MI
2. Non-fatal stroke
3. CV death
4. All-cause mortality
5. All CV hospitalisations
6. Hospitalisation for acute coronary syndrome (ACS) (includes hospitalisation for MI and for troponin-negative cardiac chest pain)
7. Coronary revascularisation
8. Hospitalisation for ACS or coronary revascularisation
9. Hospitalisation for heart failure
10. Quality of life (EQ-5D and Seattle Angina Questionnaire)
11. Cost-effectiveness of allopurinol

The secondary clinical outcomes were selected to include important clinical events for patients, for the NHS in terms of costs and service usage and also to capture whether allopurinol improves symptomatic endpoints, survival endpoints and endpoints related to both symptoms and survival in patients with IHD.
We will also collect data on the safety and tolerability of allopurinol in patients with IHD, in particular discontinuations of allopurinol due to adverse events including gout flares and serious adverse skin reactions.

3. STUDY DESIGN

Research Plan / Methods

Design and theoretical/conceptual framework

The study is a multi-centre, controlled, prospective, randomised, open-label, blinded endpoint (PROBE) trial of allopurinol 600mg daily (or 300mg daily) vs. no treatment added to usual therapy in patients 60 years and over with ischaemic heart disease (IHD). The aim is to establish whether allopurinol improves cardiovascular (CV) outcomes in this population. Approvals will be obtained for the trial from ethics committees, the Medicines and Healthcare products Regulatory Agency (MHRA) and local research and development departments.

Primary care practice lists will be searched for suitable subjects with IHD who will be invited to participate. Other patients with IHD who volunteer to participate in the study may also be included, and patients may be invited to participate from secondary care clinics, in which case their GP will be contacted by the study team with the patient's consent. Patients who have registered on consented research databases such as UK Biobank, Go-SHARE and the Scottish Diabetes Research Network research register may also be approached to participate, with the necessary approvals. At a screening visit, written informed consent will be taken, inclusion and exclusion criteria checked and blood samples taken and sent to local NHS labs for baseline full blood count, urea and electrolytes, creatinine, eGFR and urate. Patients will be randomised at this stage via a web portal or interactive voice response system (IVRS), to either allopurinol or no drug to be given in addition to their usual medications. On confirmation that the screening visit eGFR result is ≥30 mL/min/1.73m^2 allopurinol therapy will be started in those patients randomised to allopurinol. In patients with screening visit (eGFR ≥60mL/min/1.73m^2), allopurinol will be started at 100-150mg daily for 2 weeks (100mg should be the usual starting dose; 150mg may be used as the starting dose in the event of a local shortage of 100mg tablets), then titrated to 300mg daily for 2 weeks, then 600mg daily if tolerated. In patients with screening visit eGFR 30-59mL/min/1.73m^2, allopurinol will be started at 100-150mg daily for 2 weeks, then titrated to 300mg daily if tolerated.

Therefore, the maximum dose of allopurinol will be 600mg daily (taken as 300mg twice daily) in patients with screening visit eGFR ≥60mL/min/1.73m^2 and the maximum dose of allopurinol will be 300mg daily in patients with screening visit eGFR 30-59mL/min/1.73m^2. The allopurinol will be prescribed by the GP.

Patients randomised to the allopurinol arm of the study, or to the no additional therapy arm of the study with a screening visit eGFR <30mL/min/1.73m^2 will be withdrawn from the study before any study medication is administered.

In patients randomised to allopurinol, bloods will be taken for full blood count, urea and electrolytes, creatinine, eGFR and urate 6 weeks (+/- 1 week) after starting study medication. Blood tests will be sent to local NHS labs and results will be checked and entered into the eCRF by study nurses. GPs will be alerted to any abnormal blood results. All patients will be asked to report any treatment-related adverse events, particularly rash (~1% incidence with allopurinol) or gout flares. GPs will also be asked to report any serious adverse events that come to their attention during the trial.

According to the summary of product characteristics for allopurinol, undesirable effects are usually rare and mostly of a minor nature; the incidence is higher in the presence of renal and/or hepatic disorders. We plan to exclude patients with severe renal impairment (screening visit eGFR<30 mL/min/1.73m^2), significant hepatic disease or a history of severe adverse cutaneous (skin) reaction to any drug from the study to minimize the risks of adverse events, particularly severe skin reactions to allopurinol within the trial. We will also limit the maximum daily dose of allopurinol to 300mg daily in patients with screening visit eGFR 30-59mL/min/1.73m^2. We will check safety bloods on all patients started on allopurinol 6 weeks (+/- 1 week) after starting therapy. Any patient developing a rash on allopurinol will be advised to stop the drug immediately to minimize the risk of patients developing severe skin reactions. We will collect and report data on reasons for discontinuation of allopurinol within the trial.

Record-linkage for events will be carried out at least once a year. This will allow us to obtain information on all hospitalisations and deaths in patients within the trial. Potential endpoints will be investigated further by obtaining information from medical records. Endpoint packages will be prepared, removing identifying patient details and details of randomised treatment then adjudicated by an endpoint committee blinded to treatment allocation.

Any serious adverse events and suspected unexpected serious adverse events occurring during the trial will be reviewed by members of a pharmacovigilance group and reported to the sponsor, the MHRA and the ethics committees according to Good Clinical Practice procedures. Some of these events will be picked up by record-linkage and additional information will be obtained from the medical case notes where required.

The economic evaluation will estimate costs and benefits over a lifetime horizon using a Markov model approach. Using the cost perspective of the NHS and social services, it will take account of medicines cost, costs of monitoring, impact on hospital admissions (and associated costs after discharge). We will compare this to our estimate of the QALY gain from treatment to produce a net cost per QALY gained for adding allopurinol to usual care.

Patients will complete quality of life questionnaires at the screening visit, after 1 year and at the end of the trial. Two different questionnaires will be used – the EQ-5D to assess general health outcomes and the Seattle Angina Questionnaire to assess coronary artery disease-specific quality of life.

The EQ-5D (30) is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

The Seattle Angina Questionnaire is a disease-specific self-administered functional status measure for patients with coronary artery disease (31). It measures five clinically important dimensions of health in patients with coronary artery disease (anginal stability, anginal frequency, physical limitation, treatment satisfaction, quality of life) and is sensitive to clinical change over time. We will use the (UK) English version.

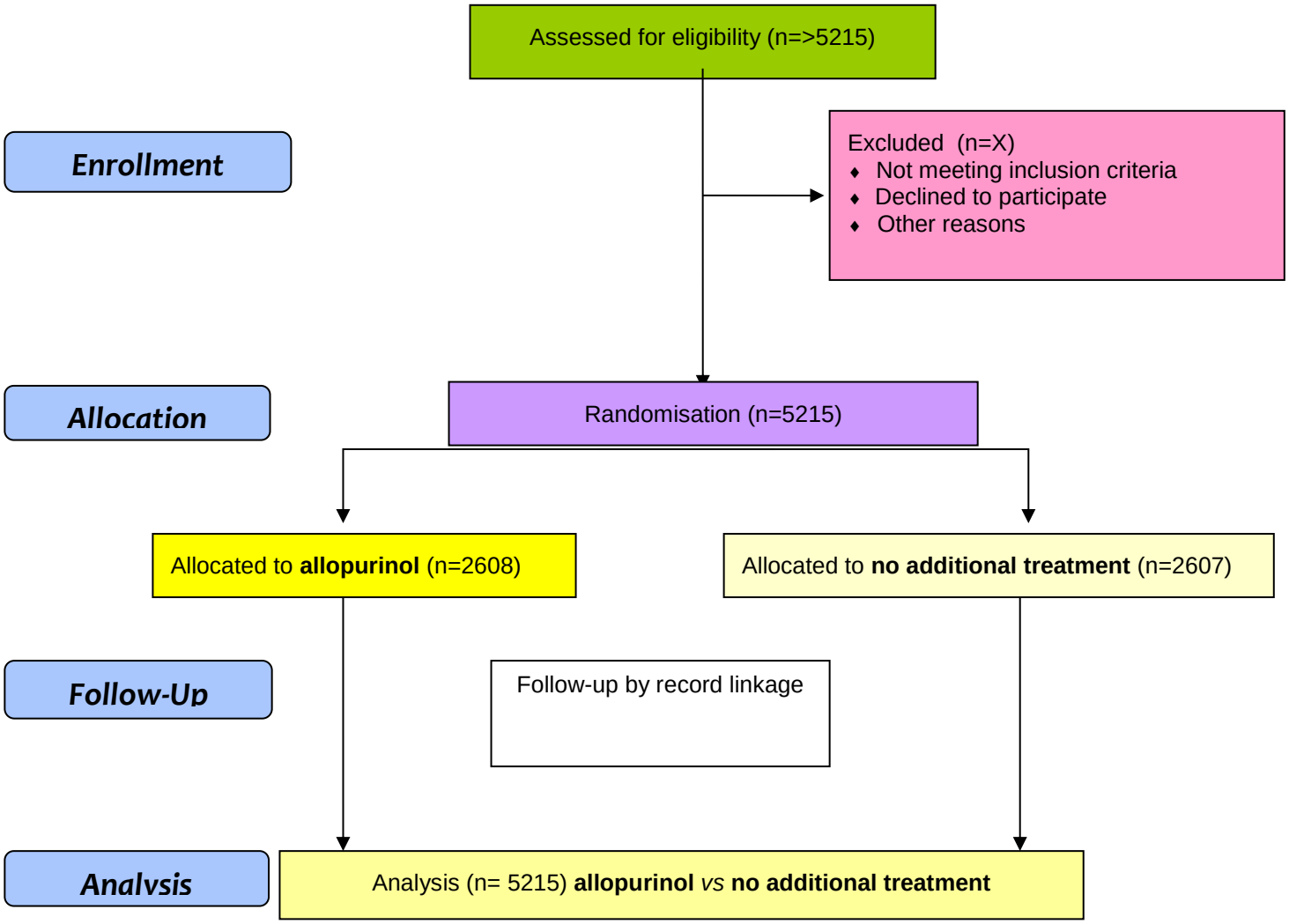
Data on health service usage will be collected at 1 year and at the end of the trial from all participants (and from a randomly selected 25% of participants at annual intervals during the trial) by email/online where possible or otherwise by postal questionnaire or telephone. The patient will be asked to report the number of visits they have made to a GP, practice nurse, physiotherapist and hospital outpatient clinics over the last year. The number of hospitalisations will be collected via the electronic record-linkage system along with other outcome data.

The willingness of patients to complete the questionnaires electronically will be assessed during the first year of the trial.

Project timetables including recruitment rate

There will be a 3 month start-up phase to allow finalisation of regulatory approvals, development of the eCRF and web systems and training materials and recruitment of study staff. During this time, practices will be approached to take part in the study. The recruitment phase will last for approximately 2 years with an average follow-up of around 4 years. These periods may be extended depending on recruitment rates, event rates and additional funding. There will follow an approximate 6 month period for finalisation of data collection by record linkage, data analysis and preparation of the final study reports. The study end is event-driven therefore it will be important to recruit at a high rate early in the trial to maximise patient years exposure.

Study flow diagram



4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

5,215 patients who meet the inclusion and exclusion criteria will be randomised to allopurinol or no additional treatment. Patients will be recruited from the UK. Approximately 200-300 GP sites will be involved, co-ordinated by 2 main study sites (Dundee and Nottingham). Recruitment is expected to last for approximately 2 years with an average follow-up period of around 4 years. These periods may be extended depending on recruitment rates, event rates and additional funding.

4.2 INCLUSION CRITERIA

1. Male or female patients aged 60 years and over.
2. Ischaemic heart disease (IHD) defined as a diagnosis of angina or myocardial infarction (MI) at any time or other evidence of ischaemic heart disease (investigator opinion).

4.3 EXCLUSION CRITERIA

1. History of gout
2. Known severe renal impairment (eGFR <30 mL/min/1.73m^2).
3. Moderate to severe heart failure (NYHA III-IV).
4. Significant hepatic disease (e.g. ALT >3 x upper limit of normal, cirrhosis, ascites) (investigator opinion)
5. Patients currently taking part in another interventional clinical trial of an investigational medicinal product or medical device (or taken part in one within the last 3 months).
6. Previous allergy to allopurinol
7. Previous serious adverse cutaneous (skin) reaction to any drug (e.g. Stevens Johnson syndrome, toxic epidermal necrolysis, hospitalisation due to skin reaction to drug) (investigator opinion)
8. Patients already taking urate lowering therapy (including allopurinol, febuxostat, sulfinpyrazone, benzbromarone, probenecid, rasburicase).
9. Patients taking azathioprine, mercaptopurine, ciclosporin or theophylline.
10. Malignancy (except non-metastatic, non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years (investigator opinion).

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential study participants will be identified from their GP practice by carrying out a search for patients aged 60 years and over with a diagnosis of ischaemic heart disease, excluding those patients with known severe renal impairment (eGFR <30 mL/min/1.73m^2), patients with a history of gout and patients already taking allopurinol. This search will be carried out by a member of the practice staff or a suitable trained nurse or delegate under Caldicott guardian approval or equivalent. A list of potential patients who appear to meet the study inclusion criteria will be produced. This will be examined by one or more practice physicians in order to remove from the list any patients who based on the inclusion and exclusion criteria and in the opinion of the physician should not be invited to take part in the study. The final list will then be signed by a physician attesting that in his/her opinion the patients meet the study inclusion criteria.

Practices will be encouraged to repeat the screening process periodically during the recruitment period to identify new potential patients. Other patients with ischaemic heart disease who volunteer to take part in the trial may be included, and patients may be invited to participate from secondary care clinics, in which case, their GP will be informed with the patient's consent. Patients who have registered on consented research databases such as UK Biobank, Go-SHARE and the Scottish Diabetes Research Network research register may also be approached to participate with the necessary approvals.

We already work with a large network of >700 GP practices participating in two randomised clinical trials. In addition to working with the Scottish Primary Care Research Network (SPCRN) and the

Primary Care Research Networks (PCRN) and Comprehensive Local Research Networks (CLRN) in England we will use our established networks to recruit GP practices to take part in the study. We aim to recruit 100-150 practices in Scotland and 100-150 practices in England, co-ordinating the trial from two main study centres – Dundee and Nottingham.

Our model will maximise use of the SPCRN, PCRN and CLRN support where available and supplement this with centrally based research nurses (three in Dundee and one in Nottingham) as well as enabling interested practice nurses to participate in study activities with appropriate study training and support from our centrally based nurses and the SPCRN/PCRN/CLRN. By using this hybrid model, we ensure quality, adequate support and also achieve the goal of increasing primary care staff skills and input into research.

5.2 CONSENTING PARTICIPANTS

Potential participants will receive a written patient information sheet with details of the study. Participants will have the chance to discuss the study and ask any questions they may have before informed consent is taken. Participants will give written informed consent. Consent will be taken by a suitably trained nurse or doctor in this study.

In the event that the study follow up period for individual participants is extended beyond 5 years, the study team will contact participants affected by this increase in duration, using the contact methods provided by the study participants, to gather their implicit consent to continue in the follow up phase of the study until study completion. Consent for ongoing follow up will be recorded on the study portal and may be obtained from the patient using electronic, written or verbal means depending upon the contact methods provided by the study participants. A reminder email and/or letter will be sent if no response is received to the original email/letter. If there is no response to either email or letter (or the patient prefers telephone contact), the study team will try to contact the participant by telephone. If consent for ongoing follow up is obtained verbally, this will be recorded in writing on the study portal by a member of the research team. If a participant prefers to finish the trial after 5 years involvement, arrangements will be made to stop their study medication if relevant. If a patient does not provide consent to continue their involvement beyond 5 years, their inclusion will be censored at 5 years from the date of their screening visit.

5.3 SCREENING FOR ELIGIBILITY

Potential participants will attend a screening visit to assess eligibility to participate in the study. Following informed consent being taken, subjects will be asked questions about their medical history, current health and their medications and the inclusion and exclusion criteria will be checked. The subject will complete two short questionnaires about their quality of life. A blood sample will be taken for full blood count, urea and electrolytes, eGFR and urate. If a subject has known severe renal impairment (eGFR<30mL/min/1.73m^2) at this stage, they will be excluded from the study.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Participants who are not randomised to the study will continue to receive usual care for their medical condition.

5.5 RANDOMISATION

5.5.1 Randomisation

Randomisation will be performed during the screening visit using a central randomisation facility, contacted either online or by telephone (IVRS). Randomisation will be stratified according to GP site, history of MI and history of stroke. Randomised therapy of allopurinol or no additional treatment will be assigned in a 1:1 ratio. Patients and study staff will be aware of their randomisation decision as there is no blinding to treatment allocation.

Before any patient is prescribed allopurinol, screening visit blood results will be checked to ensure that the eGFR is ≥30mL/min/1.73m^2. Blood results will normally become available 1-3 days after the screening visit. If the screening visit eGFR is ≥30mL/min/1.73m^2 and there are no safety concerns

regarding the other screening visit blood results, the study nurse will arrange for an allopurinol prescription to be issued. The patient will be asked by the study nurse to collect their prescription for allopurinol and then present it to their local pharmacy or dispensary. The patient will be asked to start their study medication at the earliest date convenient for them. If patients are likely to be unable to start their study medication within 2 weeks (for health or social reasons), this will be recorded on the study database. If a patient's screening visit eGFR is <30mL/min/1.73m^2, the study nurse will advise them of this and inform them that they will be withdrawn from the study and that they should not start study medication.

5.5.2 Treatment Allocation

Allopurinol therapy will be prescribed using the standard NHS prescribing system in this study. For patients randomised to allopurinol therapy, the GP will issue a prescription for allopurinol.
In patients with screening visit eGFR ≥60mL/min/1.73m^2, the GP will issue a prescription for allopurinol 100-150mg once daily for 2 weeks (100mg should be the usual starting dose; 150mg may be used as the starting dose in the event of a local shortage of 100mg tablets), then 300mg once daily for 2 weeks then 600mg daily (given as 300mg twice daily) if tolerated. The prescription will then be continued at 600mg daily thereafter until the end of the study, unless randomised therapy is withdrawn or the dose is decreased due to tolerability problems, in which case, patients will continue to take their maximum tolerated dose of allopurinol and this dose will be recorded.

In patients with screening visit eGFR 30-59mL/min/1.73m^2, the GP will issue a prescription for allopurinol 100-150mg once daily for 2 weeks (100mg should be the usual starting dose; 150mg may be used as the starting dose in the event of a local shortage of 100mg tablets), then 300mg once daily if tolerated. The prescription will then be continued at 300mg daily thereafter until the end of the study, unless randomised therapy is withdrawn or the dose is decreased due to tolerability problems, in which case, patients will continue to take their maximum tolerated dose of allopurinol and this dose will be recorded.

Participants will be advised to inform the study nurse if they stop randomised therapy or their dose of allopurinol is changed during the study. Patients randomised to allopurinol will receive an instruction leaflet detailing how to take their allopurinol.

5.5.3 Emergency Unblinding Procedures

This study is not blinded so this does not apply.

5.5.4 Withdrawal procedures

Stopping of randomised allopurinol therapy (this does not necessarily entail withdrawal from the trial)
A study participant may stop allopurinol therapy before the end of the trial for several different reasons including tolerability problems, treatment-related adverse events, serious adverse events, patient choice or medical advice.

Any study participant stopping allopurinol therapy will be asked to inform the study nurse. The study nurse will record on the eCRF the date allopurinol was stopped and the reason for stopping therapy. If the patient has suffered a treatment-related adverse event or serious adverse event, the nurse will arrange for this to be formally reported and for the patient to receive any necessary medical advice or review if required from either the study doctor or GP.

Any study participant stopping allopurinol therapy will be asked for permission to continue the usual follow-up procedures including electronic record-linkage for the rest of the trial.

Study participants stopping allopurinol therapy will not be replaced.

Temporary withdrawals from randomised therapy will be allowed at the discretion of the investigator and the reason recorded in the eCRF.

Withdrawal from the study

A study participant may withdraw consent to take part in the study before the end of the trial for several different reasons including tolerability problems, treatment-related adverse events, serious adverse events, patient choice or medical advice.

The study nurse will record on the eCRF the date the patient withdrew from the study, and if one is offered, the reason for withdrawal. If the patient has suffered a treatment-related adverse event or serious adverse event, the nurse will arrange for this to be formally reported and for the patient to receive any necessary medical advice or review if required from either the study doctor or GP.
No further follow-up procedures will be conducted on patients who choose to fully withdraw consent to take part in the study.

Study participants withdrawing from the study will not be replaced.

In addition, a study participant may choose to withdraw from receiving the annual follow up questionnaires, but retain consent for follow up by record-linkage. Any such withdrawals will be recorded on the study eCRF.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification
Allopurinol tablets
Generic allopurinol tablets will be prescribed in the study.

6.1.2 Study Drug Manufacturer
There are several different manufacturers of generic allopurinol in the UK. Because the allopurinol will be prescribed using the standard NHS prescribing system, any of the available preparations may be used within the study.

6.1.3 Marketing Authorisation Holder
There are several different manufacturers of generic allopurinol in the UK. Because the allopurinol will be prescribed using the standard NHS prescribing system, any of the available preparations may be used within the study.

6.1.4 Labelling and Packaging
Allopurinol will be prescribed using the standard NHS prescribing system and standard labelling and packaging will be used.

6.1.5 Storage
Standard storage conditions apply (store at less than 25^{o}C). Allopurinol has a shelf life of around 3 years.

6.1.6 Summary of Product Characteristics
Several different preparations of generic allopurinol are available in the UK. Current Summaries of Product Characteristics (SmPC) for allopurinol are available online (see Appendix 1).
Licensed indications for allopurinol are prophylaxis of gout and of uric acid and calcium oxalate renal stones; prophylaxis of hyperuricaemia associated with cancer chemotherapy.
In this study, allopurinol will be used out with its licensed indications but within the licensed dose range.
Contraindications: acute gout attack
Expected side effects: Rash, nausea, vomiting, hypersensitivity, drowsiness, diarrhoea. See full list in SmPC in Appendix 1.

6.2 PLACEBO
There is no placebo in this study. Allopurinol will be compared to no additional therapy.

6.3 DOSING REGIME

In patients with screening visit eGFR ≥ 60mL/min/1.73m^2, following randomisation, allopurinol will be given at 100-150mg daily for 2 weeks (100mg should be the usual starting dose; 150mg may be used as the starting dose in the event of a local shortage of 100mg tablets), increasing to 300mg daily for 2 weeks, then 600mg daily thereafter. These participants will continue allopurinol at 600mg daily for the duration of the study (average of 4 years).

Patients with reduced renal function may be at increased risk of hypersensitivity to allopurinol. For this reason, patients with a screening visit eGFR of 30-59mL/min/1.73m^2, following randomisation, will be given allopurinol at 100-150mg daily for 2 weeks, increasing to 300mg daily thereafter. These participants will continue allopurinol at 300mg daily for the duration of the study (average of 4 years).

6.4 DOSE CHANGES

The dose of allopurinol may be reduced at the discretion of the study doctor or another doctor if the patient fails to tolerate a higher dose during the up-titration phase or at any time during the study. Allopurinol will be continued at the maximum tolerated dose until the end of the study. Temporary withdrawals of allopurinol therapy will be allowed at the discretion of the investigator and a reason documented on the eCRF.

6.5 PARTICIPANT COMPLIANCE

Compliance with allopurinol will be assessed at the 6 week visit and as part of the annual follow-up contact made with the patient.

6.6 OVERDOSE

Ingestion of up to 22.5g allopurinol without adverse effect has been reported. Symptoms and signs of overdose may include nausea, vomiting, diarrhoea and dizziness. General supportive measures should be implemented, adequate hydration should be maintained and haemodialysis may be considered. Any patient thought to have taken an overdose should be discussed immediately with medical staff and advice from a toxicology/poisons information unit should be obtained without delay.

6.7 OTHER MEDICATIONS

6.7.1 Permitted Medications

Patients may take most other medications during the study as usual but should tell any doctor who is treating them that they are taking allopurinol.

6.7.2 Prohibited Medications

Patients should not be taking urate lowering therapy (including allopurinol, febuxostat, sulfinpyrazone, benzbromarone, probenecid, rasburicase) at the time of randomisation. Patients (particularly in the non-allopurinol arm of the study) may take these medications if they are deemed clinically necessary e.g. if they develop gout, during the study.

Patients should not be taking azathioprine, mercaptopurine, ciclosporin or theophylline at the time of randomisation as the plasma levels of these medicines may be increased by allopurinol therapy. These medications may be given under specialist direction during the study but doses should be adjusted in patients taking allopurinol and monitoring of levels may be necessary.

7. STUDY ASSESSMENTS

Study assessments are detailed in the schedule of events below.

VISIT: **PROCEDURE**	Screening[a], Randomisation[b] and Treatment Allocation[d]	Check safety bloods[c] / Confirm if safe to start study Medication (Screening +1-3 days)	Week 6 (+/-1 week) post- randomisation[e] (allopurinol group)	Annual contact via email, post or telephone
Informed Consent	X			
Inclusion / Exclusions	X			
Demographics	X			
Medical History	X			
Lifestyle Factors	X			
Concomitant Medication	X		X	
Height	X			
Weight	X			
Vital Signs	X			
Haematology	X		X	
Biochemistry including eGFR and urate	X		X	
Check screening blood results		X[c]		
Seattle angina questionnaire	X			X[g]
EQ-5D questionnaire	X			X[g]
Resource usage questionnaire				X[h]
IVRS	X			

Allopurinol prescription		X	X (continue)	X (continue)
Confirm with patient if safe to start study medication		X[c]		
Adverse Events[f]			X	X
Skin reactions			X	X
Gout flares			X	X
Compliance			X	X

A. At a screening visit, informed consent will be taken, inclusion and exclusion criteria checked and blood samples taken for baseline full blood count, urea and electrolytes, creatinine, eGFR and urate.
B. Patients will be randomised via a web portal or interactive voice response system (IVRS) to either allopurinol or no drug to be given in addition to their usual medications.
C. Screening blood results will be checked once they are available (normally screening visit + 1-3 days). At this stage, it will be confirmed by research nurse (or study doctor in the event of abnormal blood results) if it is safe for patient to start allopurinol. This will be communicated to the patient and to the GP. An eGFR value <30mL/min/1.73m^2 will automatically exclude any patient from starting allopurinol. All other results will be judged on an individual patient basis, with clinical support offered to research nurse in the event of abnormal blood result(s).
D. Patients randomised to allopurinol (with screening eGFR ≥60mL/min/1.73m^2) will be given allopurinol started at 100-150mg daily for 2 weeks, then 300mg daily for 2 weeks, then 600mg daily if tolerated. Patients randomised to allopurinol (with screening eGFR 30-59mL/min/1.73m^2) will be given allopurinol started at 100-150mg daily for 2 weeks, then 300mg daily if tolerated. Patients randomised to allopurinol, or to no addition to their usual medication, with a baseline eGFR <30mL/min/1.73m^2 will be withdrawn from the study before taking any study medication. Study medication will be prescribed by the GP.
E. Only in patients randomised to allopurinol, bloods will be taken for full blood count, urea and electrolytes, creatinine, eGFR and urate 6 weeks (+/- 1 week) after starting study medication.
F. AEs are to be collected during the treatment period by record linkage and GP or patient reporting.
G. Quality of life data (Seattle angina questionnaire and EQ-5D) will be collected at screening, 1 year and end of trial.
H. Resource usage data will be collected at 1 year and end of trial from all participants and at interim annual intervals from a randomly selected 25% of participants.

8. DATA COLLECTION

An eCRF and dedicated study web portal will be used to collect study data and aid pharmacovigilance reporting and trial management. These systems will be developed by the Robertson Centre for Biostatistics (the Data Centre and Biostatistics arm of the UKCRC fully registered Glasgow Clinical Trials Unit) who have experience in such systems for large clinical trials. Nurses will enter data at the screening visit and at the 6 week follow-up visit for safety bloods. Data entered directly on the eCRF will be considered to be source data. Quality of life data will be collected at the screening visit, at 1 year and at the end of the trial. Data on health service usage will be collected at 1 year and at the end of the trial from all participants (and from a randomly selected 25% of participants at annual intervals during the trial) by email/online where possible or otherwise by postal questionnaire or telephone. At the time of annual contact, patients will be asked to confirm whether they are still taking randomised therapy and will be asked whether they have had any serious skin reactions, gout flares or other adverse reactions or serious adverse events. Any data collected on paper will be entered and verified into the study database by the Robertson Centre for Biostatistics team.

Patients will complete quality of life questionnaires at the screening visit, after 1 year and at the end of the trial. Two different questionnaires will be used – the EQ-5D to assess general health outcomes and the Seattle Angina Questionnaire to assess coronary artery disease-specific quality of life.

The EQ-5D (30) is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

The Seattle Angina Questionnaire is a disease-specific self-administered functional status measure for patients with coronary artery disease (31). It measures five clinically important dimensions of health in patients with coronary artery disease (anginal stability, anginal frequency, physical limitation, treatment satisfaction, quality of life) and is sensitive to clinical change over time. We will use the (UK) English version.

Data on health service usage will be collected from the patient by asking about number of visits to GP, practice nurse, physiotherapist and hospital outpatient clinics over the last year. The number of hospitalisations will be collected via the electronic record-linkage system along with other outcome data.

9. STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

5,215 patients need to be randomised to give 80% power to detect a 20% reduction in the primary CV endpoint for each intervention (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 has been estimated from previous trials in similar patient groups. The study will end when 631 adjudicated primary endpoints have occurred.

In order to estimate likely recruitment and event rates and reassure us that our study design is viable, we have used different sources of data to guide the development of this proposal. Although in some cases, it is difficult to make accurate estimates based on observational datasets with imprecisions in coding and certainty of diagnosis, these numbers have been helpful in supporting our approach to recruitment. According to ISD Scotland data, the prevalence of CHD in patients aged 65-74 years is 16.85% in men and 8.26% in women (overall 12.27%) and in those aged 75+ years the prevalence is 22.47% in men and 12.46% in women (overall 16.3%). Using local Tayside and Fife data (MEMO database) we estimate that there are 26,943 patients in the region aged 60 years and over with IHD – this is around 25% of the over 60 years population. In the Clinical Practice Research Datalink (CPRD) which includes English and Scottish practices, 72% of men with IHD and 85% of women with IHD are over the age of 60 years. Finally, looking at practice level data in one local general practice (Montrose), 294 out of 6,600 patients (4.5%) are on the coronary heart disease practice register of whom 92% are over 60 years of age.

We conclude from these estimates that an average general practice with around 5,000 patients on their list will have at least 200 potentially suitable patients for this study. If around 13-14% of these patients are actually randomised into the study (a conservative but realistic estimate based on our other studies), we would need around 200 general practices to participate, each contributing 26 randomised patients to the trial. We plan to spread recruitment across around 100-150 practices in Scotland and 100-150 in England, although this may be modified depending on interest and uptake of the study in different regions. It is estimated that recruitment will be completed within 2 years from the start of patient recruitment.

9.2 PROPOSED ANALYSES

Main cardiovascular outcomes
Data analysis will be carried out according to a pre-determined data analysis plan. The primary analysis will be intention-to-treat. The primary outcome and its individual components (CV death, non-fatal stroke and non-fatal myocardial infarction) will be analysed as cause-specific time to first event outcomes using Cox proportional hazards models. Treatment effects will be estimated in the form of hazard ratios (allopurinol vs. no treatment) with 95% confidence intervals and p-values (Wald statistic). Results will be summarised graphically using cumulative incidence functions. Pre-specified sub-group analyses will be carried out by investigating the effects of treatment within each subgroup with heterogeneity of treatment effect across subgroup levels assessed by fitting interaction terms to the overall Cox models. Pre-specified subgroups will include splitting patients into three groups by urate at baseline, patients with eGFR ≥60mL/min/1.73m^2 versus patients with eGFR 30-59mL/min/1.73m^2 at screening visit, patients age <70 years versus those aged ≥70 years. Results for other cardiovascular outcomes and all-cause mortality will be analysed in a similar manner. Time to discontinuation of allopurinol treatment will be described. Serious adverse events will be coded using MedDRA and tabulated according to system organ class and preferred term.

Health economic assessment and analysis
Design
The economic evaluation will reflect the comparison in the randomised controlled trial and assess the cost-effectiveness of adding allopurinol to usual care alone.

The perspective on costs will be that of the NHS plus social services. Benefits will be measured in Quality-Adjusted Life Years (QALYs) as well as cost savings. We thus intend to carry out a cost-utility analysis comparing the change in costs (net of savings) with the change in QALYs.

We plan to estimate the lifetime costs and benefits of treatment using a Markov modelling approach. We anticipate the states in the model will be: no event, events of different types (e.g. alive after stroke, alive after MI and so on), and death (cardiovascular disease and other). We will estimate transition probabilities from the trial data using an appropriate cycle length (e.g. 3 months) and use this to make projections over the lifetime of the patients.

Data collection and preparation
The following data for the economic evaluation will be collected:
(i) Use of medicines
(ii) Hospital admissions
(iii) Use of other NHS services (other than hospital admissions)
(iv) Cardiovascular events and deaths
(v) Quality of life

We consider these in turn as follows:

(i) Use of medicines – the trial will record doses of allopurinol and we will apply the cost per dose from MIMS. We assume no change in use of other medicines but will carry out a sensitivity analysis to assess the impact.

(ii) Hospital admissions – we will collect these through electronic data linkage and this will give us information on the admission and length of stay; we will also collect Healthcare Resource Group (HRG) codes. We will value each HRG using the English NHS tariffs and compare this to the Scottish NHS tariff in a sensitivity analysis.

(iii) Use of other NHS services (e.g. GP and community nurse contacts) – because the trial emphasises the electronic collection of data from routine sources there are limited opportunities to collect data on use of other NHS services. Over the period of study follow up we do not anticipate significant changes across the whole trial population although by preventing CV events we certainly anticipate differences for individual patients. This is even more of an issue for use of rehabilitation services after MI or stroke: the potential savings per case avoided are high but the effect will be difficult to detect at the level of the whole trial population.
Our proposed solution is two-fold:
(a) We will ask patients about their use of resources such as GPs, practice nurses and community nursing at 1 year and the end of the trial. This will cover the preceding 12 months. At interim years 2 3, 4, etc we will contact a randomly selected 25% sample of patients for the same information. Patients will be contacted by email where possible (or by post or telephone). We will infer missing values for non-responders and assess the impact in a sensitivity analysis.
(b) For the use of resources after an event (i.e. after discharge from hospital for acute care) we will review recent HTA reports and research publications at the time of the analysis for UK-based cost estimates of lifetime costs for the relevant events (MI, stroke, CV death, etc.). For the base case we will select values based on the following criteria: relevance to the UK, based on observational data, up-to-date, and comprehensive. We will use the range of values we identify in our search as the basis for sensitivity analysis.

(iv) Cardiovascular events and deaths will be taken from the records of the randomised controlled trial and we will use them as the basis of lifetime projections of costs and benefits as described above.

(v) Quality of life – as noted elsewhere in the application, we propose to measure quality of life at baseline, 1 year and the end of the trial. We will convert EQ-5D data into utility values and compare the change from baseline in each treatment arm using 'area-under-the-curve' analysis. For the Markov model we will use a similar approach to that described for resource use: we will search the literature and HTA reports for examples of utility values after events such as MI or stroke. In the base case we will give priority to values obtained directly from UK patients using a validated technique such as the EQ-5D. We will use the range of values found in our search as the basis for a sensitivity analysis.

Other considerations
Valuing resource use – for hospital resource use we will use data from the tariffs for England and for Scotland. For resource use such as GP consultations we will use the Unit Costs of Health and Social Care, published annually by the University of Kent.

Missing data – we anticipate that with the planned follow-up period of several years and regular data collection then we will need a plan to deal with missing data. We propose to use multiple imputation techniques to estimate the values for missing data. More details will be provided in the data analysis plan.

Discounting for time preference – we will apply the relevant UK approved rate at the time of analysing the data to future costs and benefits; at present this is 3.5% per annum.

Sub-group analyses
A particular feature of this application is that it has other data available on phenotyping that will allow sub-groups of patients to be analysed. Pre-specified subgroup analyses will include uric acid at baseline split into thirds of its distribution, baseline eGFR 30-59 mL/min/1.73m^2 vs baseline eGFR ≥ 60 mL/min/1.73m^2 and patients aged <70 years vs those aged ≥70 years.

Sensitivity analysis
We recognise that there will be uncertainty in our data, including sampling variation where we can measure data directly, and the selection of data from previous studies (e.g. costs and disutility of events). We propose to carry out a range of sensitivity analysis including a cost-effectiveness acceptability curve (CEAC), but also using threshold analysis and simpler scenario analyses as appropriate. While we recognise a CEAC is most meaningful to a statistical audience we anticipate clinicians will engage to a greater extent with simpler analyses.

Planned interim data analyses for the Independent Data Monitoring Committee (IDMC)
Planned interim data analyses will be performed for review by the IDMC (see Appendix 3). The IDMC will have the opportunity to make a recommendation of early stopping because of overwhelming evidence of benefit from study treatment based on interim analyses after approximately 50% and 75% of the target number of adjudicated study outcomes have been observed. Overwhelming evidence of benefit is defined as evidence of benefit of allopurinol over usual care ($P<0.001$). Because of the conservative nature of this test, these interim analyses will have no impact on the overall sample size calculations.

10. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the trial drug can be found in the relevant Summary of Product Characteristics (SmPC) in Appendix 1.

Participants should be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All reported events that occur after joining the trial must be recorded in detail in the eCRF. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

In the ALL-HEART study, only ***treatment-related non-serious adverse events*** will be collected and reported (ie thought to be definitely, probably or possibly related to allopurinol therapy). ***All serious adverse events (whether treatment-related or not)*** will be collected and reported.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

An **adverse reaction** (AR) is where it is suspected that an AE has been caused by a reaction to a trial drug

A **serious adverse event** (SAE), **serious adverse reaction** (SAR) or **suspected unexpected serious adverse reaction** (SUSAR) is any AE, AR or UAR that at any dose:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs.

10.2 DETECTING AEs AND SAEs

All ARs and SAEs must be recorded from the time a participant consents to join the study until the study ends.

The Investigator should ask about the occurrence of ARs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant should be used to enquire about AR/SAE occurrence. Participants should also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AR, the event should be recorded. ARs and SAEs may also be detected and notified to the study team by the GP or notified directly to the study team by the patient, in which case the study team will ensure that these are correctly reported. Some SAEs will be detected by electronic record-linkage. More information will be obtained by accessing case records where necessary to aid pharmacovigilance reporting.

10.3 RECORDING ARs AND SAEs

Depending on severity, when an AR/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator should then record all relevant information in the CRF and on the AR/SAE form.

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.4 EVALUATION OF AEs AND SAEs

Seriousness, causality, severity and expectedness should be evaluated as though the participant is taking active drug. Cases that are considered serious, possibly, probably or definitely related to drug and unexpected (i.e. SUSARs) are likely to be unblinded. (This is not relevant in the ALL-HEART study as treatment is not blinded so patients and investigators will know which patients are taking allopurinol at the time of any event).

10.4.1 Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

Unrelated: where an event is not considered to be related to the study drug.

Possibly: although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug.

Definitely: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that study drug is the most likely cause.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the study drug will be considered as ARs/SARs. All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the study drug and another drug will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

10.4.3 Assessment of Severity

The Investigator should make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.
Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.4.4 Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

10.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, they must report the information to the Pharmacovigilance Sponsor within 24 hours of becoming aware of the event. The SAE form must be completed as thoroughly as possible with all available details of the event, signed (or electronic equivalent) by the Investigator or designee. If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

The SAE report must provide an assessment of causality and expectedness at the time of the initial report to the Pharmacovigilance sponsor according to Sections 10.4.2, Assessment of Causality and 10.4.4, Assessment of Expectedness.

The SAE form should be sent to the address given in the current version of *NHS Tayside Guidelines on: Pharmacovigilance in Clinical Trials of Investigational Medicinal Products*.

10.6 REGULATORY REPORTING REQUIREMENTS

An Annual Safety Report will be submitted to the MHRA and the main REC listing all SARs and SUSARs. The Chief Investigator is responsible for submitting annual safety reports to the MHRA and the main REC on the anniversary of the Clinical Trial Authorisation approval.

NHS Tayside Pharmacovigilance is responsible for informing the MHRA and the main REC of these safety issues. Fatal or life threatening SUSARs will be reported to MHRA no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after the Pharmacovigilance Sponsor is first aware of the reaction.

10.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator is required to follow each participant until resolution. Follow up information on an SAE should be reported to the Pharmacovigilance Sponsor.

Unless otherwise stated in the protocol, ARs and SAEs should be followed up until resolution, the death of the trial subject, or 30 days after the end of the study.

11. PREGNANCY

Pregnancy is not considered an AE or SAE however the investigator must collect pregnancy information for female trial subjects or female partners of male trial subjects who become pregnant while participating in a study. The Investigator should record the information on a Pregnancy Notification Form and submit this to the Pharmacovigilance Sponsor within 14 days of being made aware of the pregnancy.

Any pregnancy that occurs in a trial subject or a trial subject's partner during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 PROJECT MANAGEMENT GROUP

The trial will be coordinated by a Project Trial Management Group (TMG), consisting of the Chief Investigator, selected other Investigator(s), Trial Project Manager(s) and coordinating nurse(s).

12.2 TRIAL MANAGEMENT

Trial Project Managers will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.3 CENTRAL TRIAL OFFICE

The Central Trial Offices will provide support to each site. They will be responsible for randomisation, collection of data in collaboration with the research nurses, data processing and analysis. Publication and dissemination of the study results will be coordinated by the Chief Investigator and Investigators.

12.4 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial (Appendix 2).

12.5 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of subjects in the trial (Appendix 3).

12.6 INSPECTION OF RECORDS

Principal Investigators and institutions involved in the study will permit trial related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation.

12.7 STUDY MONITORING

The Sponsor has determined the appropriate extent and nature of monitoring for the trial and will appoint appropriately qualified and trained monitors. Risk-based and remote monitoring will be employed in this study where possible.

A monitoring plan will be developed and documented separately (see Appendix 4)

12.8 RISK ASSESSMENT

A study risk assessment was carried out by the TASC Research Governance Manager prior to Sponsorship approval being granted (see Appendix 5).

12.8.1 Potential Risks

The main clinical risk of the study is side effects of allopurinol in patients randomised to allopurinol. Although allopurinol is generally well tolerated, there is a risk of serious skin reaction (thought to occur at a rate of between 1 in 1,000 to 1 in 10,000 patients). The risk of a serious skin reaction occurring with allopurinol is thought to be more likely in patients with renal or hepatic impairment. There are other very rare but potentially serious side effects such as hypersensitivity reactions and blood disorders.

12.8.2 Minimising Risk

The risk of patients in the trial developing serious skin reactions to allopurinol has been minimised in several ways:

Patients with known significant renal impairment (eGFR <30 mL/min/1.73m^2) and significant hepatic impairment will be excluded from the study. Patients with screening visit eGFR 30-59 mL/min/1.73m^2 will receive a lower maximum daily dose of allopurinol (300mg daily) than patients with normal screening visit eGFR (≥60mL/min/1.73m^2).

Patients with a history of a serious skin reaction to any drug (e.g. Stevens Johnson syndrome, toxic epidermal necrolysis, skin reaction to a drug resulting in hospitalisation) will be excluded from the study.

Patients with allergy to allopurinol will be excluded from the study.

Allopurinol will be started at low dose and titrated up over a four week period. All patients randomised to allopurinol will have a visit with the study nurse 6 weeks (+/- 1 week) after starting therapy during which safety blood samples will be taken and any adverse reactions or serious adverse events will be collected.

Patients will be advised to contact the study team if they develop any side effects they think may be due to allopurinol.

Patients will be specifically advised to stop taking allopurinol immediately and contact the study team or their GP for further advice if they develop a rash after starting to take allopurinol. The risk of developing a serious skin reaction on allopurinol is reduced if treatment is stopped as soon as any rash develops.

13. GOOD CLINICAL PRACTICE MODULE

13.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).
A favourable ethical opinion will be obtained from the appropriate REC and local NHS R&D approval will be obtained prior to commencement of the study.

13.2 REGULATORY COMPLIANCE OF THE STUDY

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

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant should be performed by the Investigator or designated person and must cover all the elements specified in the Participant Information Sheet/Informed Consent.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant should be informed and agree to their medical records being inspected by regulatory authorities but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant should sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant should receive a copy of this document and a copy should be filed in the Investigator Site File (ISF).

The original copy of the consent form will be stored in the Investigator Site File, a copy will be stored in the GP/medical record, a copy given to the patient and a scanned electronic copy uploaded to the study webportal and stored on a secure database.

13.3.2 Study Site Staff
The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording
The Investigator is responsible for the quality of the data recorded in the eCRF.

13.3.4 Investigator Documentation
Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the Sponsor, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);

- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The Chief Investigator, with the agreement of the Sponsor, will ensure all other documents required for compliance with the principles of GCP are retained in a Trial Master File and that appropriate documentation is available in local ISFs.

13.3.5 GCP Training
All study staff must hold evidence of appropriate GCP training or undergo GCP training.

13.3.6 Confidentiality
All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection
All Investigators and study site staff involved with this study must comply with the requirements of GDPR and the updated Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14. STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS
Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Chief Investigator. Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

14.2 PROTOCOL VIOLATIONS AND DEVIATIONS

The Investigator should not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC, Regulatory Authority and R&D approval except where necessary to eliminate an immediate hazard to trial participants.

In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation should be recorded in the CRF. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

14.3 STUDY RECORD RETENTION

All study documentation will be kept for at least 5 years after the end of the study. If the data is to be used to support a Marketing Authorisation, it will be retained for a minimum of 15 years after the end of the study.

14.4 END OF STUDY

The end of study is defined as the point at which the required number of primary endpoints (631) is estimated to have been achieved and is expected to be five-seven years after the start of patient recruitment.

The Investigators and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

14.5 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Allopurinol therapy will be discontinued at the end of the study because allopurinol is not currently a licensed therapy for ischaemic heart disease.

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team, Chief Investigator Prof Isla Mackenzie. On completion of the study, the study data will be analysed and a study report will be prepared.

15.2 PUBLICATION

The study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study with the approval of the Chief Investigator and Trial Steering Committee.

15.3 PEER REVIEW

This study has been peer reviewed internally by the Tayside Clinical Trials Unit and externally by the NIHR HTA program.

16. REFERENCES

(1) Spiekermann S et al. Electron spin resonance characterization of vascular xanthine and NAD(P)H oxidase activity in patients with coronary artery disease: relation to endothelium-dependent vasodilation. Circulation 2003;107:1383-9.
(2) George J et al. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation 2006;114:2508-16.
(3) Guthikonda S et al. Xanthine oxidase inhibition reverses endothelial dysfunction in heavy smokers. Circulation 2003:107:416-21.
(4) Noman A et al. High dose allopurinol prolongs exercise in chronic stable angina: a randomised placebo controlled trial. Lancet 2010;375:2161-7.
(5) Prescription Cost Analysis England 2008. The NHS Information Centre. Government Statistical Service.ISBN:978-1-84636-292-7.
http://www.ic.nhs.uk/webfiles/publications/PCA%202008/PCA%202008v2.pdf (accessed 22.4.11).
(6) British National Formulary March 2012. http://www.medicinescomplete.com/mc/bnf/current/5316.htm (accessed 3.7.12).
(7) Ang DS et al. The cardiovascular risk factor, left ventricular hypertrophy, is highly prevalent in stable, treated angina pectoris. American J Hypertension 2007;20:1029-35.
(8) Gosse P. Left ventricular hypertrophy – the problem and possible solutions. J Int Med Res 2005;33 Suppl 1:3A-11A.
(9) Kao MP et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. J Am Soc Nephrol 2011;22:1382-9.
(10) Devereux RB et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA 2004;292:2350-6.
(11) Okin PM et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. JAMA 2006;296:1242-8.
(12) Okin PM et al. Regression of electrocardiographic left ventricular hypertrophy is associated with less hospitalization for heart failure in hypertensive patients. Ann Intern Med 2007;147:311-9.
(13) Doehner W et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002;105:2619-24.
(14) Farquharson CA et al. Allopurinol improves endothelial dysfunction in chronic heart failure. Circulation 2002;106:221-6.
(15) Butler R et al. Allopurinol normalises endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension 2000;35:746-51.
(16) Feig DI et al. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008;27;300:924-32.
(17) Kanbay M et al. Effect of treatment of hyperuricaemia with allopurinol on blood pressure, creatinine clearance and proteinuria in patients with normal renal function. Int Urol Nephrol 2007;39:1227-33.
(18) Khan F et al. Allopurinol treatment reduces arterial wave reflection in stroke survivors. Cardiovascular Therapeutics 2008;26:247-52.
(19) Berry CE et al. Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications. J Physiol 2004;555:589-606.
(20) Rajagopalan S et al. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. J Clin Invest 1996;98:2572-9.
(21) Takimoto E et al. Role of oxidative stress in cardiac hypertrophy and remodelling. Hypertension 2007;49:241-8.
(22) Rajendra NS et al. Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. J Am Coll Cardiol 2011;58:820-8.
(23) Khatib SY et al. Allopurinol enhances adenine nucleotide levels and improves myocardial function in isolated hypoxic rat heart. Biochemistry (Mosc.) 2001;66:328-33.
(24) Hirsch GA et al. Allopurinol acutely increases adenosine triphosphate energy delivery in failing human hearts. J Am Coll Cardiol 2012;59:802-8.
(25) Luk AJ et al. Allopurinol and mortality in hyperuricaemic patients. Rheumatology (Oxford) 2009;48:804-6.
(26) Thanassoulis G et al. Gout, allopurinol use, and heart failure outcomes. Arch Intern Med 2010;170:1358-64.

(27) Wei L et al. Association between allopurinol and mortality in heart failure patients: a long-term follow up study. Int J Clin Pract 2009;63:1327-33.
(28) Goicoechea M et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol 2010;5:1388-93.
(29) Rentoukas E et al. The prognostic impact of allopurinol in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. Int J Cardiol 2010;145:257-8.
(30) http://www.euroqol.org/eq-5d/what-is-eq-5d.html (accessed 10.7.12).
(31) Spertus JA et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-41.
(32) Rekhraj S, Gandy S, Szwejkowski BR, Nadir MA, Noman A, Houston JG, Lang CC, George J, Struthers AD. High dose allopurinol reduces left ventricular mass in patients with ischaemic heart disease. J Am Coll Cardiol 2013 (in press).
(33) Summary of product characteristics – allopurinol.
https://www.medicines.org.uk/emc/medicine/25728 (accessed 22.7.15)

APPENDIX 1: SUMMARY OF PRODUCT CHARACTERISTICS

The current online summaries of product characteristics for allopurinol preparations are available online on the electronic Medicines Compendium (http://www.medicines.org.uk/emc/default.aspx) .

Several different generic formulations of allopurinol are currently available for prescription in the UK and may be prescribed in this study. Where the exact formulation of allopurinol given to a participant is unknown, the Chief Investigator will have discretion over the version of summary of product characteristics of allopurinol to be consulted during the trial.

APPENDIX 2: TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to provide overall supervision for the trial and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The NIHR HTA programme director will vet the nominees and appoint the chair and members of the TSC according to their standard procedures.

Processes and procedures for the TSC will be detailed in a trial-specific document.

APPENDIX 3: DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to monitor un-blinded comparative data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue.

The NIHR HTA programme director will vet the nominees and appoint the chair and members of the IDMC according to their standard procedures.

Processes and procedures for the IDMC will be detailed separately in a trial-specific document.

APPENDIX 4: MONITORING PLAN, QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring will be carried out by TASC, University of Dundee and NHS Tayside. The monitoring plan will be detailed in a separate trial-related document. Risk-based and remote monitoring will be employed in this study where possible.

APPENDIX 5: RISK ASSESSMENT

A study risk assessment was carried out by the TASC Research Governance Manager prior to Sponsorship approval being granted. This is detailed separately.

APPENDIX 6: ENDPOINT COMMITTEE

A trial endpoint committee will be established. The endpoint committee will adjudicate all primary endpoints within the trial and selected categories of secondary endpoints and will be blinded to treatment allocation. Processes and procedures for the endpoint committee will be detailed in a separate trial-specific document.