THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mackenzie I, Ford I, Nuki G, et al. Long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia: a prospective, randomised, open-label, blinded endpoint clinical trial. The Febuxostat versus Allopurinol Streamlined Trial (FAST).

Supplementary Materials

Long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia: a prospective, randomised, open-label, blinded endpoint clinical trial. The Febuxostat versus Allopurinol Streamlined Trial (FAST).

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Table of contents

Supplementary Table S1: Main inclusion/exclusion criteria

Inclusion Criteria	
1	Male or female patients aged 60 years or older with at least one additional cardiovascular risk factor: • Age ≥70 years (male) or ≥75 years (female) • Smoking (current or within the last 2 years) • Diabetes mellitus • Impaired glucose tolerance • Hypertension (SBP >140 mmHg and/or DBP >90 mmHg) or receiving treatment to lower blood pressure • Dyslipidaemia (investigator assessment) • Chronic kidney disease (CKD) • Microalbuminuria or proteinuria • Family history of coronary heart disease or stroke in first degree relative at age <55 years • Inflammatory arthritis (investigator assessment – including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis) • Chronic NSAID therapy (investigator assessment) • Previous cardiovascular (CV) event (MI, cerebrovascular accident [CVA]–or transient ischaemic attack [TIA]) • Peripheral vascular disease (investigator / clinical assessment) • Chronic obstructive pulmonary disease (COPD) • Body mass index >30 kg/m^2
2	Patients who, in the opinion of the recruiting physician, require treatment for chronic hyperuricaemia where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis) fulfilling the recommendation for treatment with urate lowering therapy.
3	Patients who have received ≥60 days treatment with allopurinol, or ≥2 allopurinol prescriptions, within the previous 6 months.
4	Patients, who in the opinion of the recruiting physician or study site coordinator, are eligible for treatment (with reference to the summary of product characteristics) with either allopurinol or febuxostat.
5	Patients who are willing to give permission for their paper and electronic medical records, hospitalisation data, prescribing data, and (in the event of their death) their death certification data to be accessed and abstracted by trial investigators.
6	Patients who are willing to be contacted and interviewed by trial investigators or delegates (suitably trained research nurses), should the need arise (e.g., for adverse event [AE] assessment and to determine whether an episode of acute gout has occurred).

Exclusion Criteria	
1	Patients who have any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics) or any of the components of their formulations.
2	Patients who are not receiving allopurinol as ULT.
3	Patients with severe renal impairment (eGFR <30 mL/min as defined by the Cockroft-Gault formula (http://www.nephron.com/cgi-bin/CGSI.cgi) according to creatinine, age, sex and body weight).
4	Patients with moderate or severe hepatic impairment i.e. cirrhosis with clinical and/or biological decompensation (i.e. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x reference value, ascites, lower limb oedema, icterus or increased prothrombin time >2x reference value).
5	Patients with a life-threatening co-morbidity or with a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol.
6	Patients with a diagnosis of, or receiving treatment for malignancy (excluding minor skin cancer and indolent cancers that are not thought to be life threatening and require no treatment) in the previous 5 years. (Investigator opinion)
7	Patients who have experienced either a myocardial infarction or stroke within the 6 months prior to the screening visit.
8	Patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV.
9	Patients whose behaviour or lifestyle would render them less likely to comply with study medication (i.e., abuse of alcohol, substance misuse, debilitating psychiatric conditions or inability to provide informed consent).
10	Patients with a current acute gout flare or who are within 14 days of the resolution of a gout flare.
11	Patients currently participating in another clinical trial or who have participated in a non-interventional clinical trial in the previous 1 month or an interventional clinical trial in the previous 3 months.

Supplementary Table S2: Additional cardiovascular risk factors

Additional cardiovascular risk factors	• Age ≥70 years (male) or ≥75 years (female) • Smoking (current or within the last 2 years) • Diabetes mellitus • Impaired glucose tolerance • Hypertension (SBP >140 mmHg and/or DBP >90 mmHg) or receiving treatment to lower blood pressure • Dyslipidaemia (investigator assessment) • Chronic kidney disease (CKD) • Microalbuminuria or proteinuria • Family history of coronary heart disease or stroke in first degree relative at age <55 years • Inflammatory arthritis (investigator assessment – including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis) • Chronic NSAID therapy (investigator assessment) • Previous cardiovascular (CV) event (MI, cerebrovascular accident [CVA] or transient ischaemic attack [TIA]) • Peripheral vascular disease (investigator / clinical assessment) • Chronic obstructive pulmonary disease (COPD) • Body mass index >30 kg/m^2

Supplementary Table S3: Definitions used by the Endpoint Adjudication Committee

Extracted from FAST Endpoint Committee Charter version 2.0(14-01-13). (NB full version of charter included later in Appendix)

5 Clinical Event definitions

5.1 Hospitalisation

Hospitalisation is defined as an emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

5.2 Non-fatal events

Date of onset

For purposes of classification, when classifying events that are a cause of hospitalisation, the date of admission will be used as the onset date. In cases where the stated date of admission differs from the date the patient first presented to hospital with the event (e.g. because of a period of observation in an emergency department, medical assessment unit or equivalent), the date of initial presentation to hospital will be used (provided that the patient had not been discharged from hospital in the interim). For events where an admission date is not applicable (e.g. events occurring *during* an ongoing hospitalisation), the date of onset as reported by the treating physician will be used.

5.2.1 Acute myocardial infarction

Note on biomarker elevations:

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL.

Spontaneous acute myocardial infarction:

A rise and/or fall of cardiac biomarkers (troponin or CK-MB) should usually be detected (see note below) with at least one value above the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischaemia (as outlined in Table 1, below) or new left bundle branch block (LBBB).
- Development of pathological Q waves on the ECG (see Table 2, below)

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute myocardial infarction

If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as:

a. One of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia (as outlined in Table 1, below) or new left bundle branch block. [The events committee will adjudicate in the context of the sequential ECG changes that are commonly seen in acute ST elevation/acute non-ST elevation myocardial infarction.]
- New pathological Q waves (see Table 2, below). [The events committee will adjudicate in the context of the sequential ECG changes that are commonly seen in acute ST elevation/acute non-ST elevation myocardial infarction.]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute myocardial infarction

AND

b. Both of the following:

- Evidence that cardiac biomarker values were decreasing (e.g. two samples 3-6 hours apart) prior to the suspected acute myocardial infarction*

- ≥ 20% increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation with the suspected recurrent myocardial infarction and a further sample taken 3-6 hours later

*If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent myocardial infarction is generally not possible.

Percutaneous coronary intervention-related acute myocardial infarction

Peri-percutaneous coronary intervention (PCI) acute myocardial infarction is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

1. Biomarker elevations within 48 hours of PCI:

   • Troponin or CK-MB (preferred) > 3 x URL ***and***

   • No evidence that cardiac biomarkers were elevated prior to the procedure;

   OR

Both of the following must be true:

- ≥ 50% increase in the cardiac biomarker result
- Evidence that cardiac biomarker values were decreasing (e.g. two samples 3-6 hours apart) prior to the suspected acute myocardial infarction

2. New pathological Q waves or new left bundle branch block (LBBB).

   [If the PCI was undertaken in the context of an acute myocardial infarction, the events committee will adjudicate in the context of the sequential ECG changes that are commonly seen in acute ST elevation/acute non-ST elevation myocardial infarction.]

3. Autopsy evidence of acute myocardial infarction

Coronary artery bypass grafting-related acute myocardial infarction

Peri-coronary artery bypass graft surgery (CABG) acute myocardial infarction is defined by the following criteria. Symptoms of cardiac ischemia are not required.

1. Biomarker elevations within 72 hours of CABG:
   - Troponin or CK-MB (preferred) > 5 x URL **and**
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

   OR

   • Both of the following must be true:
   - ≥ 50% increase in the cardiac biomarker result
   - Evidence that cardiac biomarker values were decreasing (e.g. two samples 3-6 hours apart) prior to the suspected acute myocardial infarction

   AND

2. One of the following:
   - New pathological Q-waves (preferably with evidence of persistence)
   - New LBBB (preferably with evidence of persistence)
   - Angiographically documented new graft or native coronary artery occlusion
   - Imaging evidence of new loss of viable myocardium

   OR

3. Autopsy evidence of acute myocardial infarction

Note: For a diagnosis of acute myocardial infarction, elevation of cardiac biomarkers above the upper reference limit (or, if an URL is not available, above the local MI decision limit) should usually be present. If biomarkers are detectable but do not exceed the URL or the local MI decision limit, the classification "biomarker positive acute coronary syndrome" will be used, providing that the definition of this particular event-type (see below) is met.

However, myocardial infarction may be adjudicated for an event that has characteristics which are very suggestive of acute infarction but which does not meet the strict definition because biomarkers are not available (e.g. not measured) or are non-contributory (e.g. may have normalized).

Suggestive characteristics are:

- Typical cardiac ischemic-type pain/discomfort
  (except for suspected acute myocardial infarction occurring in the context of PCI or CABG where this requirement need not apply)

AND

- New ECG changes* or other evidence to support a diagnosis of acute myocardial infarction (e.g. imaging evidence of new loss of viable myocardium/new regional all motion abnormality or angiography demonstrating occlusive coronary thrombus)

*If ECG tracings are not available for review, the CEC may adjudicate on the basis of reported ECG changes that have been clearly documented in the case records or in the case report form.

<u>Clinical classification of different types of myocardial infarction</u>

Myocardial infarctions will be clinically classified as:

Type 1
Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

Type 2
Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

Type 3

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a
Myocardial infarction associated with PCI.

Type 4b

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy.

Type 5
Myocardial infarction associated with CABG.

Myocardial infarctions will be further sub-classified as:

1. ST segment elevation myocardial infarction (STEMI).

or

2. Non-ST segment elevation myocardial infarction (NSTEMI).

or

3. Myocardial infarction, type (i.e. STEMI or NSTEMI) unknown.

Table 1: ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy and left bundle branch block)

ST elevation

New ST elevation at the J-point in two anatomically contiguous leads with the cut-off

points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

ST depression and T wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two

contiguous leads; and/or new T wave inversion ≥ 0.1 mV in two contiguous

leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

Table 2: Pathological Q waves:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF) a

A The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

5.2.2 Biomarker positive acute coronary syndrome (ACS)

Note: This does not include acute myocardial infarction which will be classified separately (see above).

For the diagnosis of biomarker positive ACS, the following criteria should be fulfilled:

There should be:

1 Clinical presentation consistent with ischaemia (e.g. typical cardiac ischaemic-type pain or discomfort).

and

2 Detectable cardiac biomarkers but without the fulfilment of the biomarker criteria outlined above for acute myocardial infarction.

[i.e. not exceeding the upper reference limit or, if an upper reference limit is not available, not exceeding the MI decision limit for the particular laboratory.

and

3 The need for treatment with parenteral (intravenous, intra-arterial, buccal, transcutaneous or subcutaneous) anti-ischaemic/antithrombotic therapy and/or coronary revascularisation.

Note: The following are considered supportive of the diagnosis and, in general, at least one of these [(a), (b) or (c)] is expected to be present. However, this is not mandatory if the criteria 1 to 3 (above) are met and provided that the adjudicator is satisfied that the totality of the information is consistent with the diagnosis.

(a) New and/or reversible ST segment or T wave changes on the ECG.

(b) Investigations undertaken in view of the event (e.g. exercise ECG or stress myocardial perfusion scan) showing evidence of reversible myocardial ischaemia,

(c) Coronary angiography showing angiographically significant coronary disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take precedence.]

*5.2.3 Hospitalisation for angina**

For the diagnosis of hospitalisation for angina, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

1 Clinical presentation consistent with ischaemia (e.g. typical cardiac ischaemic-type pain or discomfort) but without the fulfilment of the above diagnostic criteria for acute myocardial infarction or biomarker positive acute coronary syndrome.

and

2 The need for treatment with new or increased anti-anginal therapy (excluding sublingual nitrate therapy) and/or coronary revascularisation

and

3 (a) New and/or reversible ST segment or T wave changes on the ECG

Or

3 (b) Investigations undertaken in view of the event (e.g. exercise ECG or stress myocardial perfusion scan) showing evidence of reversible myocardial ischaemia,

Or

3 (c). Coronary angiography showing angiographically significant coronary disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take precedence.]

and

4 The CV-CEC should be satisfied that angina was the primary reason for hospitalisation.

*5.2.4 Hospitalisation for other chest pain**

There should be:

- Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay i.e. a date change) due to chest pain but where the definitions (above) of acute myocardial infarction, biomarker positive ACS or angina are not met.
- The CV-CEC should be satisfied that chest pain was the primary reason for

  Hospitalisation.

*These events are not study endpoints but the definitions provided for these events will be used by the CEC to categorise reported myocardial infarction, biomarker positive ACS, angina and chest pain events that do not meet the study definitions of acute myocardial infarction or biomarker positive acute coronary syndrome.

5.2.5 Stroke

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

For the diagnosis of for stroke, the following 4 criteria should usually be fulfilled:

1. **Rapid onset* of a focal/global neurological deficit with at least one of the following:**
   - Change in level of consciousness
   - Hemiplegia
   - Hemiparesis
   - Numbness or sensory loss affecting one side of the body

- Dysphasia/aphasia
- Hemianopia (loss of half of the field of vision of one or both eyes)
- Complete/partial loss of vision of one eye
- Other new neurological sign(s)/symptom(s) consistent with stroke

*If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation.

2. **Duration of a focal/global neurological deficit ≥ 24 hours**

   or

   < 24 hours if

   (i) this is because of at least one of the following therapeutic interventions:

   (a) pharmacologic i.e. thrombolytic drug administration.

   (b) non-pharmacologic i.e. neurointerventional procedure (e.g. intracranial angioplasty).

   or

   (ii) brain imaging available clearly documenting a new haemorrhage or infarct.

   or

   (iii) the neurological deficit results in death

3. **No other readily identifiable non-stroke cause for the clinical presentation** (e.g. brain tumour, hypoglycaemia, peripheral lesion).

4. **Confirmation of the diagnosis by at least one of the following****:

   a) neurology or neurosurgical specialist.

   b) brain imaging procedure (at least one of the following):

   (i) CT scan.

   (ii) MRI scan.

   (iii) cerebral vessel angiography.

   c) lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial haemorrhage).

**If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone but *full CEC consensus will be mandatory.*

Strokes will be further sub-classified as:

- Ischaemic (non-haemorrhagic) stroke

  (ie caused by an infarction of central nervous system tissue)

or

- Haemorrhagic stroke

  (ie caused by nontraumatic intraparenchymal, intraventricular or subarachnoid haemorrhage)

or

- Stroke type (i.e. haemorrhagic or ischaemic) unknown (i.e when imaging/other investigations are unavailable or inconclusive).

5.2.6 Hospitalisation for heart failure

For the diagnosis of hospitalisation for heart failure, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

1. clinical manifestations of new or worsening heart failure including at least one of the following:
   - New or worsening dyspnoea on exertion
   - New or worsening dyspnoea at rest
   - New or worsening fatigue/decreased exercise tolerance
   - New or worsening orthopnoea
   - New or worsening PND (paroxysmal nocturnal dyspnoea)
   - New or worsening lower limb or sacral oedema
   - New or worsening pulmonary crackles/crepitations
   - New or worsening elevation of JVP (jugular venous pressure)
   - New or worsening third heart sound or gallop rhythm

And

2. Investigative evidence of structural or functional heart disease (<u>if available</u>) with at least *one* of the following:

    - Radiological evidence of pulmonary oedema/congestion or cardiomegaly.
    - Imaging (e.g. echocardiography, cardiac magnetic resonance imaging, radionuclide ventriculography) evidence of an abnormality (e.g. left ventricular systolic dysfunction, significant valvular heart disease, left ventricular hypertrophy).
    - Elevation of BNP or NT-proBNP levels.
    - Other investigative evidence of structural or functional heart disease (e.g evidence obtained from pulmonary artery catheterisation).

    And

3. Need for new/increased therapy***** *specifically <u>for the treatment of heart failure</u>* including at least one of the following:

    - New or increased oral therapy for the treatment of heart failure
    - (See note on oral therapy, below)
    - Initiation of intravenous diuretic, inotrope, vasodilator or other recognised intravenous heart failure treatment or uptitration of such intravenous therapy if already receiving it
    - Mechanical or surgical intervention (e.g. mechanical or non-invasive ventilation, mechanical circulatory support, heart transplantation, ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, dialysis or other mechanical or surgical intervention that is specifically directed at treatment of heart failure.

    *****If time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the CEC will adjudicate on clinical presentation and, if available, investigative evidence.

    <u>Note on oral therapy</u>: In general, for an event to qualify as *heart failure requiring hospitalisation* on the basis of *oral* heart failure therapy (i.e. in cases where none of the intravenous or non-pharmacological therapies listed above have been utilised), the new or increased oral therapy should include oral diuretics. However, in special cases, other new or increased oral therapy (e.g. hydralazine/long acting nitrate, aldosterone antagonist) may be accepted provided that the adjudication committee is satisfied that:

a) the new or increased oral therapy was primarily directed at treating clinical manifestations of new or worsening heart failure (rather than, for example, initiation or uptitration of heart failure therapy as part of the routine optimisation of medical therapy)

and

b) the totality of the evidence indicates that heart failure, rather than any other disease process, was the primary cause of the clinical presentation.

And

4. The CEC should be satisfied that heart failure was the primary disease process accounting for the clinical presentation.

5.2.7 Hospitalisation with arrhythmia

[Excluding hospitalisation for resuscitated cardiac arrest which is a separate endpoint – see note below]

For this diagnosis, there should be:

1. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

2. Documented ECG evidence of the arrhythmia/conduction disturbance.

[If ECG tracings are not available for review, the CEC may adjudicate on the basis of a reported arrhythmia/conduction disturbance that has been clearly documented in the case records.]

Arrhythmias will be categorised by the CEC as follows:

1) The primary reason for hospitalisation

   (arrhythmias deemed to be secondary to acute myocardial infarction/biomarker positive ACS will not be included in this category)

2) A contributing reason for hospitalisation

   (includes arrhythmias deemed to be secondary to acute myocardial infarction/biomarker positive ACS if the arrhythmia is adjudged to have contributed to the hospitalisation)

3) Other (i.e. arrhythmia present on admission but whether or not it contributed to the hospitalisation is uncertain).

Arrhythmias will be further subclassified as follows:

- Atrial fibrillation/flutter
- Atrial tachycardia
- Other supraventricular tachycardia
- Ventricular tachycardia
  - Non-sustained
  - Sustained
  - VT type (i.e. non-sustained or sustained) unknown

- Ventricular fibrillation
- Bradycardia/heart block
- Other arrhythmia/conduction disturbance

NOTE: If an arrhythmia event is deemed to meet the definition of hospitalisation for resuscitated cardiac arrest (see below), then “hospitalisation due to resuscitated cardiac arrest” will be the classification verdict recorded (i.e. to avoid “double counting”, the event will not also be classified as “hospitalisation with arrhythmia”).

5.2.8 Hospitalisation for resuscitated cardiac arrest*

For this diagnosis, there should be:

1. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

2. Sudden cardiac arrest or sudden cardiac death (see definition of sudden cardiac death, below) from which the patient is successfully resuscitated by cardiopulmonary resuscitation, cardioversion, defibrillation or other advanced cardiac life support measures (e.g. emergency cardiac pacing) with recovery of consciousness and survival for more than 72 hours post resuscitation.

And

3. The cause of the cardiac arrest should not be due to another adjudicated cause (e.g. acute myocardial infarction).

And

4. The CEC should be satisfied that the event was the primary reason for hospitalisation.

Identified causes of transient loss of consciousness, such as seizures or vasovagal episodes that do not reflect significant cardiac dysfunction, are excluded.

*Should any “non-hospitalised” resuscitated cardiac arrest events occur (i.e. events of sudden cardiac arrest [with successful resuscitation] that do not result in a hospitalisation), these will also be adjudicated by the CEC according to criteria 2 and 3, above.

5.2.9 Hospitalisation for deep venous thrombosis (DVT)

For this diagnosis, there should be:

1. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

2. Documented confirmatory evidence of DVT e.g. imaging (such as ultrasonography, venography, etc.).

And

3. The need for pharmacological therapy (e.g. anticoagulation) or mechanical/surgical intervention (e.g. placement of a vena cava filter, percutaneous/surgical thrombectomy) directed at venous thromboembolism.

And

4. The CEC should be satisfied that DVT was the primary reason for hospitalisation. [In cases of hospitalisation due to venous thromboembolism where there is documented evidence of both deep venous thrombosis and pulmonary embolism, the CEC will decide which was the primary reason for hospitalisation and classify the hospitalisation accordingly.]

5.2.10 Hospitalisation for pulmonary embolism

For this diagnosis, there should be:

1. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

2. Documented confirmatory evidence of pulmonary embolism e.g. imaging (such as computed tomographic pulmonary angiography, conventional (invasive) pulmonary angiography, ventilation-perfusion scanning, etc.) or autopsy evidence.

And

3. The need for pharmacological therapy (e.g. anticoagulation, thrombolysis) or mechanical/surgical intervention (e.g. placement of a vena cava filter, percutaneous/surgical embolectomy) directed at venous thromboembolism.

And

4. The CEC should be satisfied that pulmonary embolism was the primary reason for hospitalisation. [In cases of hospitalisation due to venous thromboembolism where there is documented evidence of both deep venous thrombosis and pulmonary embolism, the CEC will decide which was the primary reason for hospitalisation and classify the hospitalisation accordingly.]

5.2.11 Hospitalisation for chronic critical lower limb ischaemia (due to obstructive atherosclerotic arterial disease)

Note that the term *chronic* critical limb ischaemia implies that the clinical manifestations *usually* have been present for greater than 2 weeks as opposed to *acute* critical limb ischaemia where there is a sudden, catastrophic change in a previously adequately perfused limb (see definition of acute critical limb ischaemia below).

For the diagnosis of chronic critical limb ischaemia, there should be:

1. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

2. Chronic (*usually* > 2 weeks) history of lower limb rest pain or non-healing ulcers or gangrene.

And

3. Documented confirmatory evidence of lower limb arterial occlusive disease e.g. haemodynamic/physiological (such as ankle systolic blood pressure, ankle-brachial index, toe pressure, transcutaneous oxygen tension ($tcPO_2$) or imaging (such as duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, conventional (invasive) angiography) that is considered to be responsible for the clinical presentation.

And

4. The need for treatment directed specifically at chronic critical limb ischaemia such as revascularisation (endovascular or surgical), pharmacological therapy (e.g. prostanoids), amputation or other recognised therapy directed at this diagnosis.

And

5. The CEC should be satisfied that chronic critical limb ischaemia was the primary reason for hospitalisation.

5.2.12 Hospitalisation for acute critical limb ischaemia (due to arterial embolism or thrombosis)

Note that the term acute critical limb ischaemia refers to a sudden decrease in limb perfusion that could threaten limb viability and where the presentation is *usually* within 2 weeks of the acute event (as opposed to chronic critical limb ischaemia – see definition above).

For this diagnosis, there should be:

1. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).
2. New or worsening (*usually* within 2 weeks of presentation) clinical manifestations of significant limb ischaemia (e.g. pain, pulselessness, pallor, paraesthesia, paralysis).

And

3. Either

    a) Documented confirmatory evidence of an arterial occlusion such as haemodynamic/physiological (e.g. doppler signals) or imaging (e.g. duplex ultrasonography, computed tomographic angiography, magnetic resonance angiography, conventional [invasive] angiography) that is considered to be responsible for the clinical presentation.

    Or

    b) Clinical history consistent with an acute loss of blood flow to a peripheral artery with documented evidence supporting a likely embolic source e.g. documented atrial fibrillation (including paroxysmal), imaging evidence of a potential cardioembolic source (e.g. mural thrombus), documented arterial aneurysm, etc. or other evidence supportive of the diagnosis of acute critical limb ischaemia (e.g. findings in theatre if the patient is taken straight to theatre).

    And

4. The need for treatment specifically directed at acute critical limb ischaemia such as intravenous anticoagulation (e.g. continuous intravenous heparin infusion), catheter-directed thrombolytic therapy, percutaneous thrombectomy/embolectomy, surgical revascularisation procedure or amputation.

    And

5. The CEC should be satisfied that acute critical limb ischaemia was the primary reason for hospitalisation.

Note: Acute critical limb ischaemia events will be further subclassified as:

- Embolic

or

- Thrombotic

or

- Acute critical limb ischaemia, type (i.e. embolic or thrombotic) unknown (e.g. when imaging/other investigations are unavailable or inconclusive).

5.2.13 Other cardiovascular event

This category includes any cardiovascular event that does not fit any of the above definitions (e.g. cardiovascular operation/procedure, ruptured aortic aneurysm, endocarditis).

Such events will not be adjudicated by the CEC but will be reviewed by the CEC coordinating physician to ensure that potential endpoint events that would require CEC adjudication have not been missed.

5.3 Fatal events

In cases where a patient experiences an event and later dies due to that event, the event causing death and the death will be considered as separate events *only* if they are separated by a change in calendar day. If the event causing death and the death occur on the same calendar day, death will be the only event classified.

5.3.1 Cardiovascular deaths

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke and death due to other cardiovascular causes as follows:

Death due to Acute Myocardial Infarction refers to a death usually occurring up to 30 days after a documented acute myocardial infarction (verified either by the diagnostic criteria outlined above for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus) due to the myocardial infarction or its immediate consequences (e.g. progressive heart failure) and where there is no conclusive evidence of another cause of death.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and other (e.g. ECG, angiographic, autopsy) evidence.

NOTE: This category will include sudden cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation*, or left new left bundle branch block*, or evidence of fresh thrombus in a coronary artery by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood (i.e. acute myocardial infarction Type 3 – see section 5.2, above).

*If ECG tracings are not available for review, the CEC may adjudicate on the basis of reported new ECG changes that have been clearly documented in the case records or in the case report form.

Death resulting from a procedure to treat an acute myocardial infarction [percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)], or to treat a complication resulting from acute myocardial infarction, should also be considered death due to acute myocardial infarction.

Death resulting from a procedure to treat myocardial ischemia (angina) or death due to an acute myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation that was not undertaken to treat an acute myocardial infarction or its complications should be considered as a death due to other cardiovascular causes.

Sudden Cardiac Death refers to a death that occurs unexpectedly in a previously stable patient. The cause of death should not be due to another adjudicated cause (e.g. acute myocardial infarction Type 3 – see section 5.2 above).

The following deaths should be included.

a. Death witnessed and instantaneous without new or worsening symptoms

b. Death witnessed within 60 minutes of the onset of new or worsening symptoms unless a cause other than cardiac is obvious.

c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor), or unwitnessed but found on implantable cardioverter-defibrillator review.

d. Death in patients resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, including acute myocardial infarction, and who die (without identification of a non-cardiac aetiology) within 72 hours or without gaining consciousness; similar patients who died during an attempted resuscitation.

e. Unwitnessed death without any other cause of death identified (information regarding the patient's clinical status in the 24 hours preceding death should be provided, if available)

Sudden cardiac death events will be further subclassified by the CEC as:

1) Sudden cardiac death due to a documented arrhythmia

   (i.e. arrhythmia adjudged to be the primary terminal event ***and*** documented evidence of the arrhythmia)

2) "Other" sudden cardiac death (i.e. not classifiable as being due to a documented arrhythmia)

   [e.g. insufficient evidence to suggest that an arrhythmia was the primary terminal event and/or no documented evidence of an arrhythmia]

Death due to Heart Failure refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death (e.g. acute myocardial infarction).

Death due to heart failure should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of heart failure include any of the following:

a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure

Note: If time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the CEC will adjudicate on clinical presentation and, if available, investigative evidence.

b. Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary oedema.

c. Confinement to bed predominantly due to heart failure symptoms.

d. Pulmonary oedema sufficient to cause tachypnoea and distress **not** occurring in the context of an acute myocardial infarction, worsening renal function (that is not wholly explained by worsening heart failure/cardiac function) or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

e. Cardiogenic shock **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

Death due to Stroke refers to death after a documented stroke (verified by the diagnostic criteria outlined above for stroke or by typical post mortem findings) that is either a direct consequence of the stroke or a complication of the stroke and where there is no conclusive evidence of another cause of death.

NOTE: In cases of early death where confirmation of the diagnosis cannot be obtained, the CEC may adjudicate based on clinical presentation alone.

Death due to a stroke reported to occur as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories [e.g. pulmonary embolism, cardiovascular intervention (other than one performed to treat an acute myocardial infarction or a complication of an acute myocardial infarction – see definition of death due to myocardial infarction, above), aortic aneurysm rupture, or peripheral arterial disease]. Mortal complications of cardiac surgery or non-surgical revascularisation should be classified as cardiovascular deaths.

5.3.2 Non-cardiovascular deaths

A non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. There should be unequivocal and documented evidence of a non-cardiovascular cause of death.

Further subclassification of non-cardiovascular death will be as follows:

- Pulmonary
- Renal
- Gastrointestinal
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Malignancy
- Haemorrhage, not intracranial
- Accidental/Trauma
- Suicide
- Non-cardiovascular surgery
- Other non-cardiovascular, specify

5.3.3 Undetermined cause of death

This refers to any death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause (e.g. due to lack of information such as a case where the only information available is “patient died”). It is expected that every effort will be made to provide the adjudicating committee with enough information to attribute deaths to either a cardiovascular or non-cardiovascular cause so that the use of this category is kept to a minimal number of patients.

Supplementary Table S4: Summary of baseline cardiovascular risk factors – Randomised set (n = 6128)

	Allopurinol (N = 3065)	Febuxostat (N = 3063)	All Subjects (N = 6128)
At least one cardiovascular risk factor	3065 (100·0%)	3063 (100·0%)	6128 (100·0%)
Cardiovascular Risk Factors			
Age $\geq$ 70 years (male) or $\geq$ 75 years (female)	1430 (46·7%)	1463 (47·8%)	2893 (47·2%)
Smoking (current or within the last two years)	322 (10·5%)	345 (11·3%)	667 (10·9%)
Diabetes mellitus	719 (23·5%)	661 (21·6%)	1380 (22·5%)
Impaired glucose tolerance	438 (14·3%)	414 (13·5%)	852 (13·9%)
Hypertension	2619 (85·4%)	2575 (84·1%)	5194 (84·8%)
Dyslipidaemia	1729 (56·4%)	1819 (59·4%)	3548 (57·9%)
Chronic kidney disease stage 1-3	481 (15·7%)	485 (15·8%)	966 (15·8%)
Microalbuminuria or proteinuria	584 (19·1%)	598 (19·5%)	1182 (19·3%)
Family history of coronary heart disease or stroke	455 (14·8%)	473 (15·4%)	928 (15·1%)
Inflammatory arthritis	146 (4·8%)	153 (5·0%)	299 (4·9%)
Chronic NSAID therapy	265 (8·6%)	234 (7·6%)	499 (8·1%)
Previous CV event (MI, Cerebrovascular accident or TIA)	576 (18·8%)	575 (18·8%)	1151 (18·8%)
Peripheral vascular disease	148 (4·8%)	147 (4·8%)	295 (4·8%)
Chronic obstructive pulmonary disease	228 (7·4%)	211 (6·9%)	439 (7·2%)
Body mass index > 30kg/m^2	1680 (54·8%)	1646 (53·7%)	3326 (54·3%)

Supplementary Table S5: Allopurinol daily dose being taken immediately prior to randomisation – Randomised set (N = 6128)

		Allopurinol (N = 3065)	Febuxostat (N = 3063)	All Subjects (N = 6128)
Allopurinol dose prior to randomisation (mg)				
	50	2 (0·1%)	1 (0·0%)	3 (0·0%)
	75	0 (0·0%)	1 (0·0%)	1 (0·0%)
	100	299 (9·8%)	331 (10·8%)	630 (10·3%)
	150	11 (0·4%)	9 (0·3%)	20 (0·3%)
	200	734 (23·9%)	763 (24·9%)	1497 (24·4%)
	250	0 (0·0%)	1 (0·0%)	1 (0·0%)
	300	1536 (50·1%)	1497 (48·9%)	3033 (49·5%)
	400	360 (11·7%)	348 (11·4%)	708 (11·6%)
	450	8 (0·3%)	5 (0·2%)	13 (0·2%)
	500	59 (1·9%)	53 (1·7%)	112 (1·8%)
	600	49 (1·6%)	46 (1·5%)	95 (1·6%)
	700	3 (0·1%)	5 (0·2%)	8 (0·1%)
	800	0 (0·0%)	1 (0·0%)	1 (0·0%)
	900	4 (0·1%)	2 (0·1%)	6 (0·1%)

Supplementary Table S6: Gout flare prophylaxis and gastric protectants dispensed during the trial by treatment group and overall - Safety analysis set (N = 6051)

	Allopurinol (N = 3050)	Febuxostat (N = 3001)	All participants (N = 6051)
Colchicine	1603 (52·6%)	2223 (74·1%)	3826 (63·2%)
Naproxen	97 (3·2%)	177 (5·9%)	274 (4·5%)
Diclofenac	2 (0·1%)	2 (0·1%)	4 (0·1%)
Meloxicam	0 (0·0%)	1 (0·0%)	1 (0·0%)
Omeprazole	119 (3·9%)	181 (6·0%)	300 (5·0%)
Ranitidine	3 (0·1%)	8 (0·3%)	11 (0·2%)

Data are number of patients dispensed medication (%) as gout flare prophylaxis or gastric protection to cover NSAID use at any time during the study·

Supplementary Table S7: Withdrawals from all follow-up reasons excluding deaths (randomised population)

		Allopurinol (N = 3065)	Febuxostat (N = 3063)	All Subjects (N = 6128)
Withdrawals from all follow-up (% of randomised)		169 (5·5%)	189 (6·2%)	358 (5·8%)
Reason for withdrawal (% of withdrawn)	n (missing)	169 (0)	189 (0)	358 (0)
	Adverse Event	11 (6·5%)	28 (14·8%)	39 (10·9%)
	Serious Adverse Event	9 (5·3%)	12 (6·3%)	21 (5·9%)
	Doctor's Recommendation	17 (10·1%)	20 (10·6%)	37 (10·3%)
	Moved from study area	26 (15·4%)	15 (7·9%)	41 (11·5%)
	Protocol violation	6 (3·6%)	5 (2·6%)	11 (3·1%)
	Patient's request	98 (58·0%)	107 (56·6%)	205 (57·3%)
	Lost to follow-up	1 (0·6%)	2 (1·1%)	3 (0·8%)
	Other	1 (0·6%)	0 (0·0%)	1 (0·3%)

Supplementary Table S8: Serious Treatment Emergent Adverse Events by preferred term occurring with frequency ≥3% in either treatment group. Safety analysis set (n=6051)

Preferred Term	Allopurinol (n = 3050)	Febuxostat (n = 3001)	All subjects (n = 6051)
ATRIAL FIBRILLATION	151 (4·95%)	148 (4·93%)	299 (4·94%)
CATARACT	140 (4·59%)	127 (4·23%)	267 (4·41%)
CHEST PAIN	94 (3·08%)	74 (2·47%)	168 (2·78%)
PNEUMONIA	136 (4·46%)	113 (3·77%)	249 (4·12%)
OSTEOARTHRITIS	109 (3·57%)	103 (3·43%)	212 (3·50%)

Supplementary Table S9: Malignant neoplasms reported during study by treatment group· Safety analysis set (n=6051)

Malignant Neoplasm	Allopurinol (N= 3050)	Febuxostat (N= 3001)	All subjects (N= 6051)
Any Malignant Neoplasm	384 (12·6%)	322 (10·7%)	706 (11·7%)
Skin neoplasms malignant and unspecified	103 (3·4%)	81 (2·7%)	184 (3·0%)
Gastrointestinal neoplasms malignant and unspecified	69 (2·3%)	63 (2·1%)	132 (2·2%)
Reproductive cancers	87 (2·9%)	63 (2·1%)	150 (2·5%)
Renal and urinary tract neoplasms malignant and unspecified	38 (1·2%)	34 (1·1%)	72 (1·2%)
Respiratory and mediastinal neoplasms malignant and unspecified	35 (1·1%)	26 (0·9%)	61 (1·0%)
Haematological/blood cancers	24 (0·8%)	35 (1·2%)	59 (1·0%)
Miscellaneous and site unspecified neoplasms malignant and unspecified	17 (0·6%)	17 (0·6%)	34 (0·6%)
Hepatobiliary neoplasms malignant and unspecified	9 (0·3%)	14 (0·5%)	23 (0·4%)
Nervous system neoplasms malignant and unspecified NEC	14 (0·5%)	4 (0·1%)	18 (0·3%)
Breast neoplasms malignant and unspecified (including nipple)	12 (0·4%)	4 (0·1%)	16 (0·3%)
Metastases	6 (0·2%)	6 (0·2%)	12 (0·2%)
Ocular neoplasms	6 (0·2%)	4 (0·1%)	10 (0·2%)
Endocrine neoplasms malignant and unspecified	3 (0·1%)	3 (0·1%)	6 (0·1%)
Mesotheliomas	1 (0·0%)	2 (0·1%)	3 (0·0%)
Skeletal neoplasms malignant and unspecified	1 (0·0%)	1 (0·0%)	2 (0·0%)
Soft tissue sarcomas	1 (0·0%)	0 (0·0%)	1 (0·0%)

Supplementary Table S10: Adjudicated causes of death – Randomised set (n = 6128)

	Allopurinol (N = 3065)	Febuxostat (N = 3063)	All subjects (N = 6128)
All deaths	263 (8·6%)	222 (7·2%)	485 (7·9%)
Cardiovascular deaths	122 (4·0%)	117 (3·8%)	239 (3·9%)
Death due to myocardial infarction	6 (0·2%)	11 (0·4%)	17 (0·3%)
Death due to stroke	13 (0·4%)	10 (0·3%)	23 (0·4%)
Sudden cardiac death	42 (1·4%)	39 (1·3%)	81 (1·3%)
Death due to heart failure	17 (0·6%)	20 (0·7%)	37 (0·6%)
Death due to cardiovascular procedure/operation	2 (0·1%)	1 (0·0%)	3 (0·0%)
Death due to other cardiovascular cause	10 (0·3%)	9 (0·3%)	19 (0·3%)
Undetermined cause of death	32 (1·0%)	27 (0·9%)	59 (1·0%)
Non-cardiovascular deaths	141 (4·6%)	105 (3·4%)	246 (4·0%)

Supplementary Table S11: Summary of urate levels and changes from baseline during the study (safety population), by year of follow-up and treatment group.

Variable	Statistic	Allopurinol	Febuxostat
Baseline urate (umol/L)	n	3050	3000
	Mean (SD)	297·1 (45·5)	297·1 (48·3)
	n	2751	2306
Year 1 urate (umol/L)	Mean (SD)	301·9 (56·6)	218·7 (67·6)
Change from baseline	Mean (SD)	4·6 (43·9)	-78·4 (71·4)
	n	2547	2121
Year 2 urate (umol/L)	Mean (SD)	299·0 (56·5)	215·9 (67·0)
Change from baseline	Mean (SD)	1·8 (46·1)	-81·3 (72·1)
	n	1851	1505
Year 3 urate (umol/L)	Mean (SD)	297·0 (60·3)	213·1 (65·5)
Change from baseline	Mean (SD)	0·1 (51·6)	-85·5 (70·8)
	n	1223	1034
Year 4 urate (umol/L)	Mean (SD)	296·5 (60·7)	214·2 (71·0)
Change from baseline	Mean (SD)	-0·4 (55·6)	-83·4 (77·1)
	n	799	695
Year 5 urate (umol/L)	Mean (SD)	295·9 (64·5)	209·5 (68·7)
Change from baseline	Mean (SD)	-0·7 (59·8)	-86·9 (74·8)
	n	406	347
Year 6 urate (umol/L)	Mean (SD)	292·0 (64·5)	209·0 (72·4)
Change from baseline	Mean (SD)	-7·8 (61·3)	-84·7 (79·0)
	n	85	83
Year 7 urate (umol/L)	Mean (SD)	282·4 (59·3)	210·9 (79·4)
Change from baseline	Mean (SD)	-9·6 (56·5)	-84·0 (92·1)

Supplementary Table S12: Analysis of urate levels comparing proportions < 0·297 mmol/L (< 5mg/dL) and < 0·357 mmol/L (< 6mg/dL) between treatment groups for each year of follow-up (randomised population). Analysis by logistic regression providing the odds ratio, 95% confidence interval (CI) and p-value for febuxostat relative to allopurinol

	Allopurinol		Febuxostat		
Urate	**N**	**n events (%)**	**N**	**n events (%)**	**OR (95% CI), P**
Year 1: less than 0·297 mmol/L	2751	1270 (46·2%)	2306	2057 (89·2%)	9·8 (8·4, 11·4) , <0·001
Year 1: less than 0·357 mmol/L	2751	2362 (85·9%)	2306	2237 (97·0%)	5·3 (4·1, 6·9) , <0·001
Year 2: less than 0·297 mmol/L	2547	1246 (48·9%)	2121	1936 (91·3%)	11·2 (9·4, 13·2) , <0·001
Year 2: less than 0·357 mmol/L	2547	2192 (86·1%)	2121	2060 (97·1%)	5·5 (4·2, 7·3) , <0·001
Year 3: less than 0·297 mmol/L	1851	948 (51·2%)	1505	1378 (91·6%)	10·5 (8·6, 12·9) , <0·001
Year 3: less than 0·357 mmol/L	1851	1622 (87·6%)	1505	1464 (97·3%)	5·0 (3·6, 7·1) , <0·001
Year 4: less than 0·297 mmol/L	1223	647 (52·9%)	1034	937 (90·6%)	8·8 (6·9, 11·1) , <0·001
Year 4: less than 0·357 mmol/L	1223	1065 (87·1%)	1034	1004 (97·1%)	5·0 (3·4, 7·5) , <0·001
Year 5: less than 0·297 mmol/L	799	429 (53·7%)	695	635 (91·4%)	9·3 (6·9, 12·6) , <0·001
Year 5 less than 0·357 mmol/L	799	692 (86·6%)	695	676 (97·3%)	5·5 (3·4, 9·2) , <0·001
Year 6 less than 0·297 mmol/L	406	229 (56·4%)	347	317 (91·4%)	8·3 (5·5, 12·8) , <0·001
Year 6 less than 0·357 mmol/L	406	360 (88·7%)	347	335 (96·5%)	3·6 (1·9, 7·0) , <0·001
Year 7 less than 0·297 mmol/L	85	55 (64·7%)	83	75 (90·4%)	5·4 (2·3, 13·0) , <0·001
Year 7 less than 0·357 mmol/L	85	76 (89·4%)	83	81 (97·6%)	5·3 (1·1, 25·8) , 0·041

Supplementary Table S13: Sensitivity analysis of the composite outcome of all-cause mortality, non-fatal myocardial infarction/biomarker positive acute coronary syndrome or non-fatal stroke. The table provides the numbers and % with events, the event rates per 100 patient years, the hazard ratios (HR) and 95% confidence intervals (CI) and the p-values for non-inferiority (pNI). Non-inferiority p-values are based on a non-inferiority limit of 1·3.

	Allopurinol (N=3065)		Febuxostat (N=3063)			
Analysis	**n (%)**	**Rate**	**n (%)**	**Rate**	**HR (95%CI)**	**p_{NI}**
On-treatment	328 (10·7%)	2·795	214 (7·0%)	2·144	0·78 (0·65, 0·92)	<0·001
Intention-to-treat	415 (13·5%)	3·341	351 (11·5%)	2·806	0·84 (0·73, 0·97)	<0·001

Supplementary Table S14: Sensitivity on-treatment analysis of the composite outcome of all-cause mortality, non-fatal myocardial infarction/biomarker positive acute coronary syndrome or non-fatal stroke, extending the on-treatment period by 90 days, but maintaining censoring at withdrawal from the study and the end of the study. The table provides the numbers and % with events, the event rates per 100 patient years, the hazard ratios (HR) and 95% confidence intervals (CI) and the p-values for non-inferiority (pNI). Non-inferiority p-values are based on a non-inferiority limit of 1·3.

	Allopurinol (N=3065)		Febuxostat (N=3063)			
Analysis	**n (%)**	**Rate**	**n (%)**	**Rate**	**HR (95%CI)**	**p_{NI}**
On-treatment	257 (8·4%)	2·176	188 (6·1%)	1·847	0·86 (0·71, 1·04)	<0·001

Supplementary Table S15: Sensitivity on-treatment analysis of the composite outcome of all-cause mortality, non-fatal myocardial infarction/biomarker positive acute coronary syndrome or non-fatal stroke, with additional adjustment for age, sex, low density lipoprotein and high density lipoprotein cholesterol levels, high sensitivity troponin I levels, systolic blood pressure, smoking status and histories (yes/no) of each of diabetes, hypertension and cardiovascular disease. The table provides the numbers and % with events, the event rates per 100 patient years, the hazard ratios (HR) and 95% confidence intervals (CI) and the p-values for non-inferiority (pNI). Non-inferiority p-values are based on a non-inferiority limit of 1·3.

	Allopurinol (N=3065)		Febuxostat (N=3063)			
Analysis	**n (%)**	**Rate**	**n (%)**	**Rate**	**HR (95%CI)**	**p_{NI}**
On-treatment	241 (7·9%)	2·054	172 (5·6%)	1·723	0·87 (0·71, 1·05)	<0·001

Supplementary Table S16: FAST Committees, Principal Investigators and other key contributors

		Affiliation
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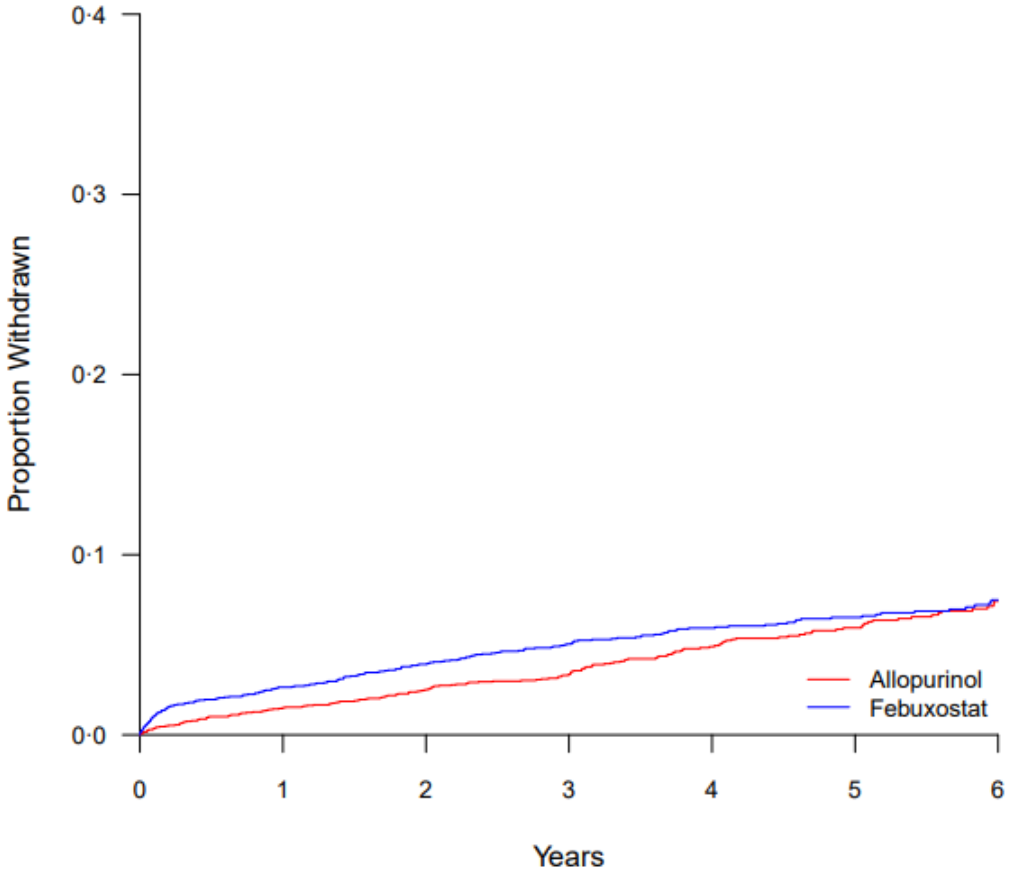
Ellen Kathrine Arve	Denmark Regional Centre	Trial manager, University of Southern Denmark
Morag Maclean	Edinburgh Regional Centre	Trial manager, Edinburgh ECTU

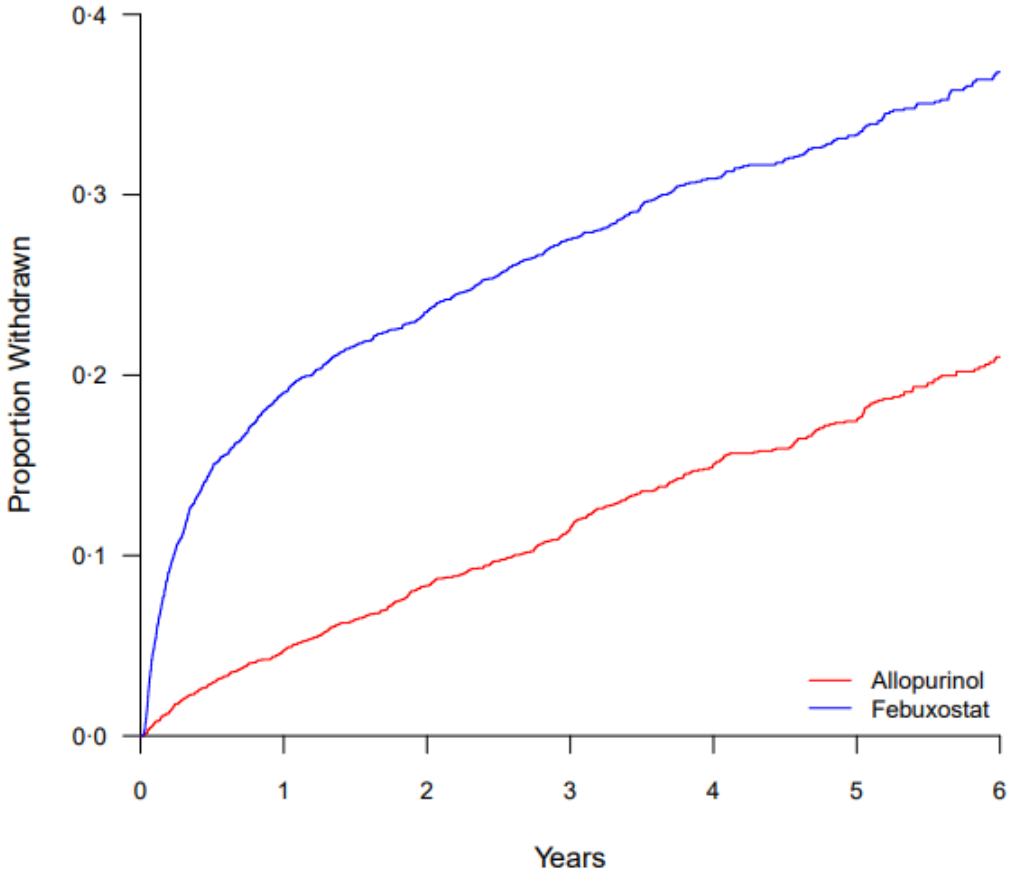
Supplementary Figure S1: Cumulative incidence function - withdrawal of consent from study



Numbers at Risk

Allopurinol	3065	2997	2907	2183	1533	1017	542
Febuxostat	3063	2957	2876	2150	1550	1050	570

Supplementary Figure S2: Cumulative incidence function - withdrawal from randomised medication

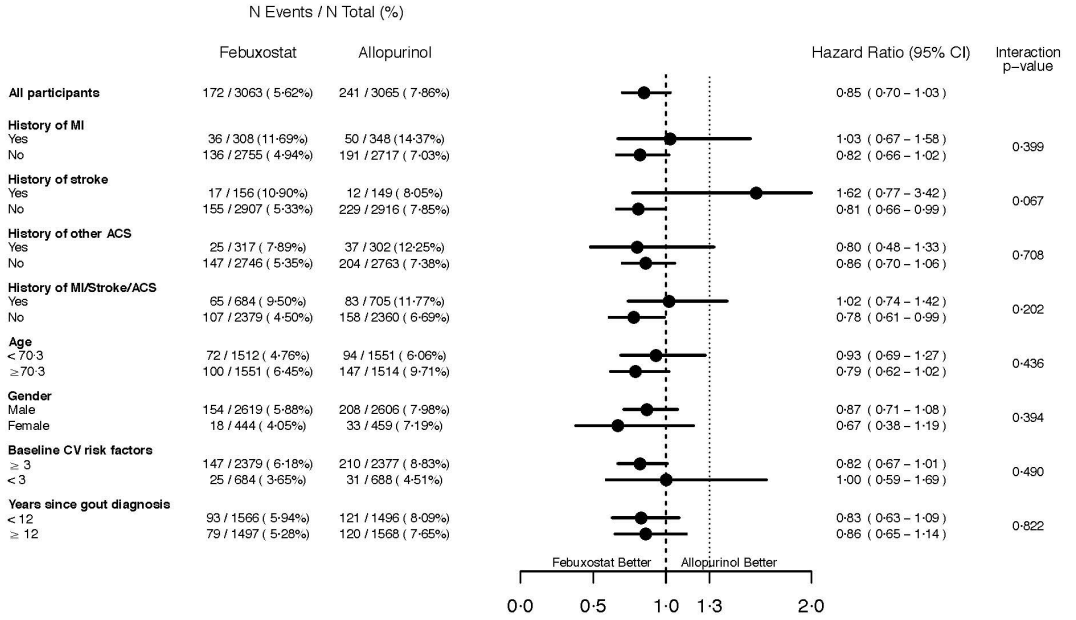


Numbers at Risk

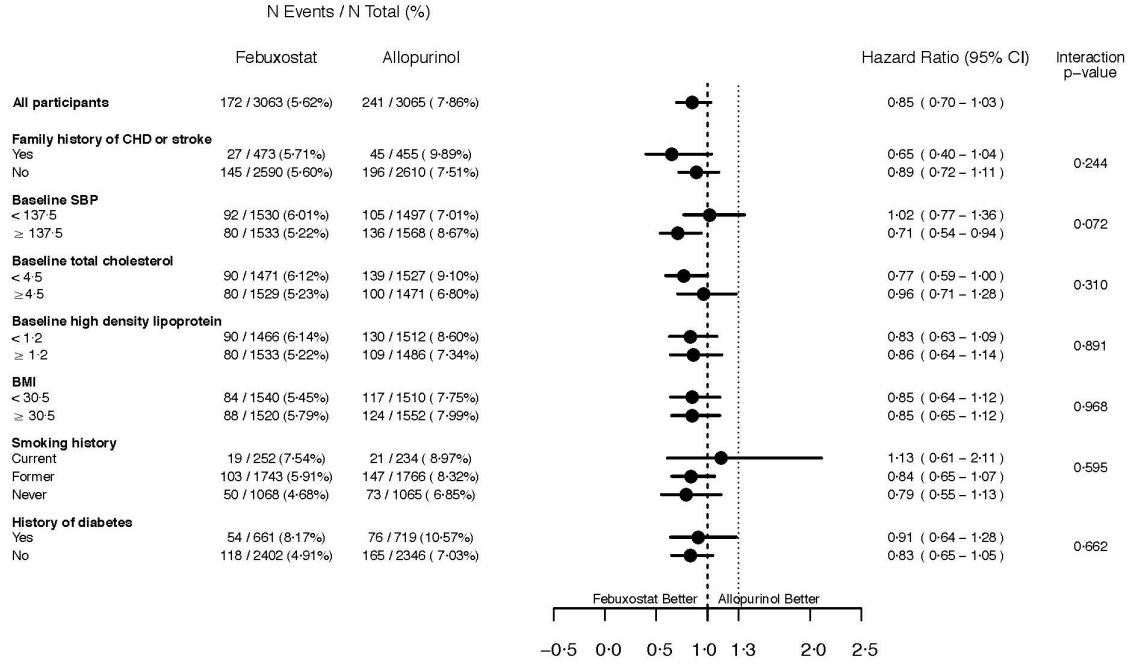
Allopurinol	3050	2892	2745	2023	1391	923	485
Febuxostat	3001	2416	2259	1652	1159	781	411

Supplementary Figure S3: Forest plot for primary endpoint for on-treatment subgroup analysis – Randomised set (n=6128)

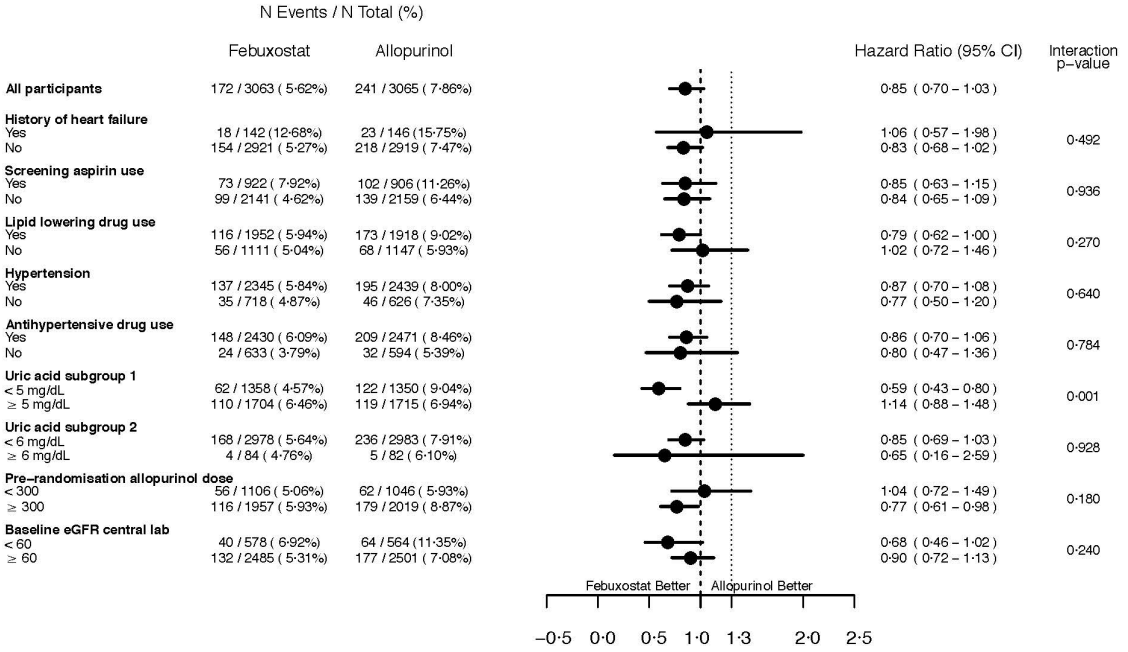
(a)



(b)

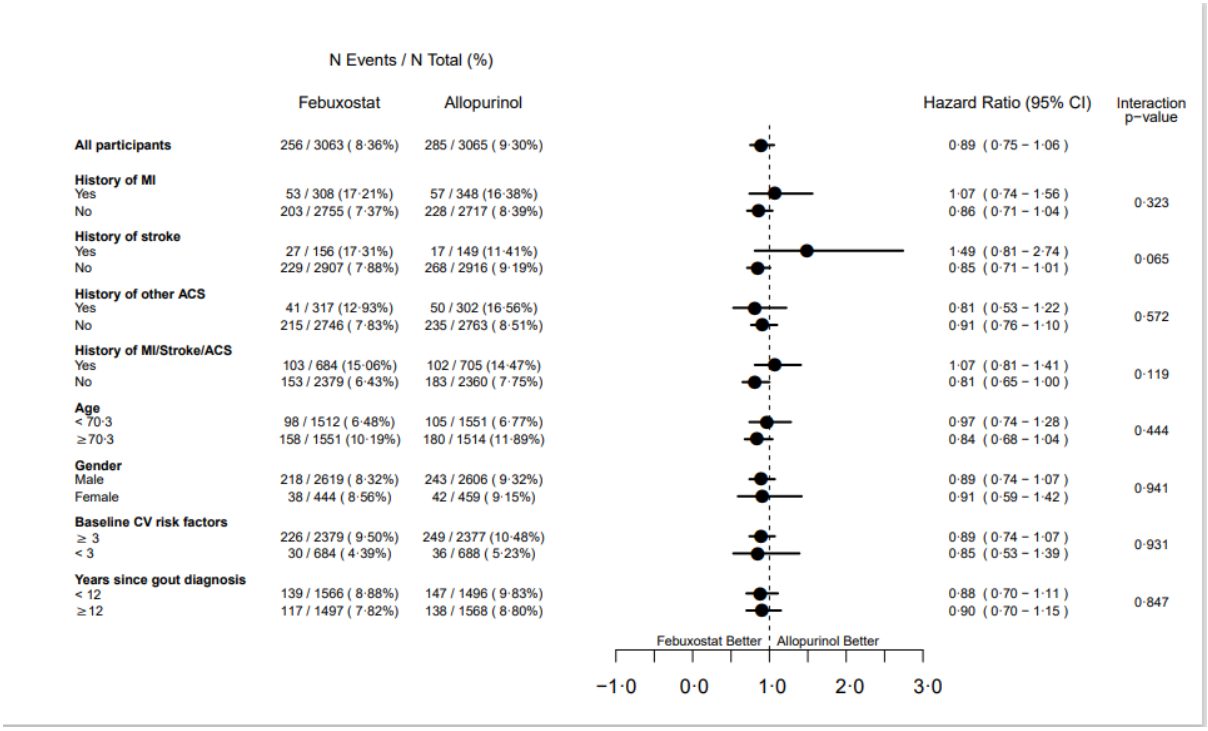


(c)

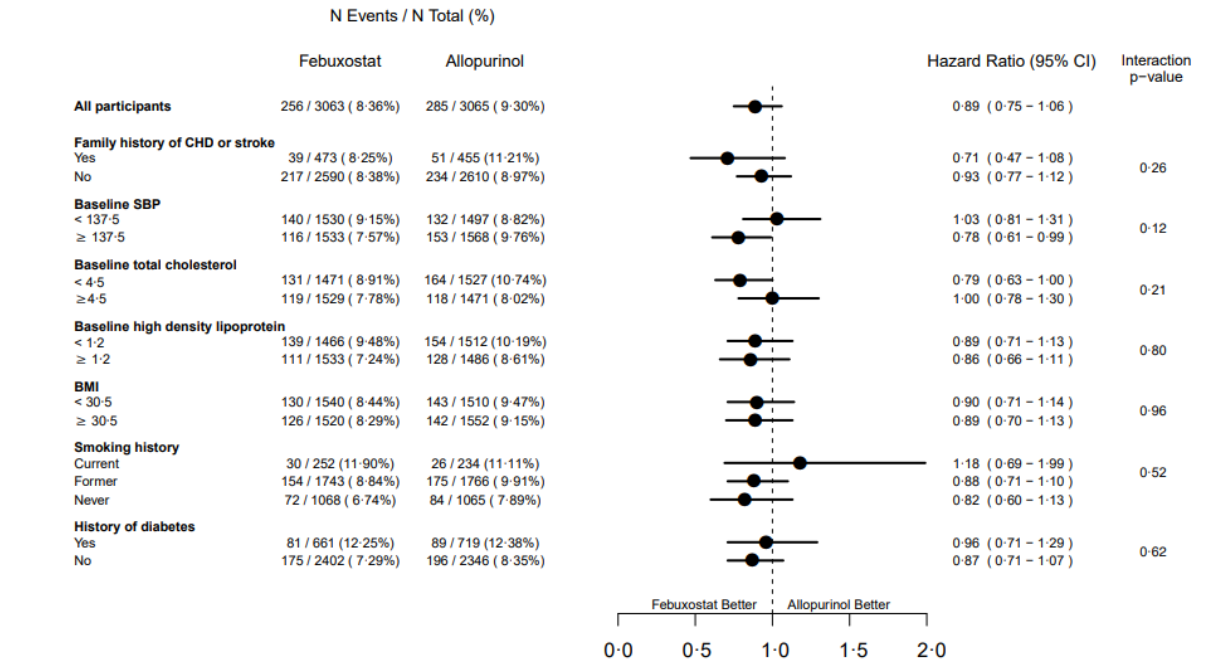

N Events / N Total (%)
Febuxostat
Allopurinol
Hazard Ratio (95% CI)
Interaction p–value
All participants
172 / 3063 (5·62%)
241 / 3065 (7·86%)
0·85 (0·70 – 1·03)
History of heart failure
Yes
18 / 142 (12·68%)
23 / 146 (15·75%)
1·06 (0·57 – 1·98)
No
154 / 2921 (5·27%)
218 / 2919 (7·47%)
0·83 (0·68 – 1·02)
0·492
Screening aspirin use
Yes
73 / 922 (7·92%)
102 / 906 (11·26%)
0·85 (0·63 – 1·15)
No
99 / 2141 (4·62%)
139 / 2159 (6·44%)
0·84 (0·65 – 1·09)
0·936
Lipid lowering drug use
Yes
116 / 1952 (5·94%)
173 / 1918 (9·02%)
0·79 (0·62 – 1·00)
No
56 / 1111 (5·04%)
68 / 1147 (5·93%)
1·02 (0·72 – 1·46)
0·270
Hypertension
Yes
137 / 2345 (5·84%)
195 / 2439 (8·00%)
0·87 (0·70 – 1·08)
No
35 / 718 (4·87%)
46 / 626 (7·35%)
0·77 (0·50 – 1·20)
0·640
Antihypertensive drug use
Yes
148 / 2430 (6·09%)
209 / 2471 (8·46%)
0·86 (0·70 – 1·06)
No
24 / 633 (3·79%)
32 / 594 (5·39%)
0·80 (0·47 – 1·36)
0·784
Uric acid subgroup 1
< 5 mg/dL
62 / 1358 (4·57%)
122 / 1350 (9·04%)
0·59 (0·43 – 0·80)
≥ 5 mg/dL
110 / 1704 (6·46%)
119 / 1715 (6·94%)
1·14 (0·88 – 1·48)
0·001
Uric acid subgroup 2
< 6 mg/dL
168 / 2978 (5·64%)
236 / 2983 (7·91%)
0·85 (0·69 – 1·03)
≥ 6 mg/dL
4 / 84 (4·76%)
5 / 82 (6·10%)
0·65 (0·16 – 2·59)
0·928
Pre–randomisation allopurinol dose
< 300
56 / 1106 (5·06%)
62 / 1046 (5·93%)
1·04 (0·72 – 1·49)
≥ 300
116 / 1957 (5·93%)
179 / 2019 (8·87%)
0·77 (0·61 – 0·98)
0·180
Baseline eGFR central lab
< 60
40 / 578 (6·92%)
64 / 564 (11·35%)
0·68 (0·46 – 1·02)
≥ 60
132 / 2485 (5·31%)
177 / 2501 (7·08%)
0·90 (0·72 – 1·13)
0·240
Febuxostat Better
Allopurinol Better
–0·5
0·0
0·5
1·0
1·3
2·0
2·5

Supplementary Figure S4: Forest plot for primary endpoint for intention to treat subgroup analysis – Randomised set (n=6128)

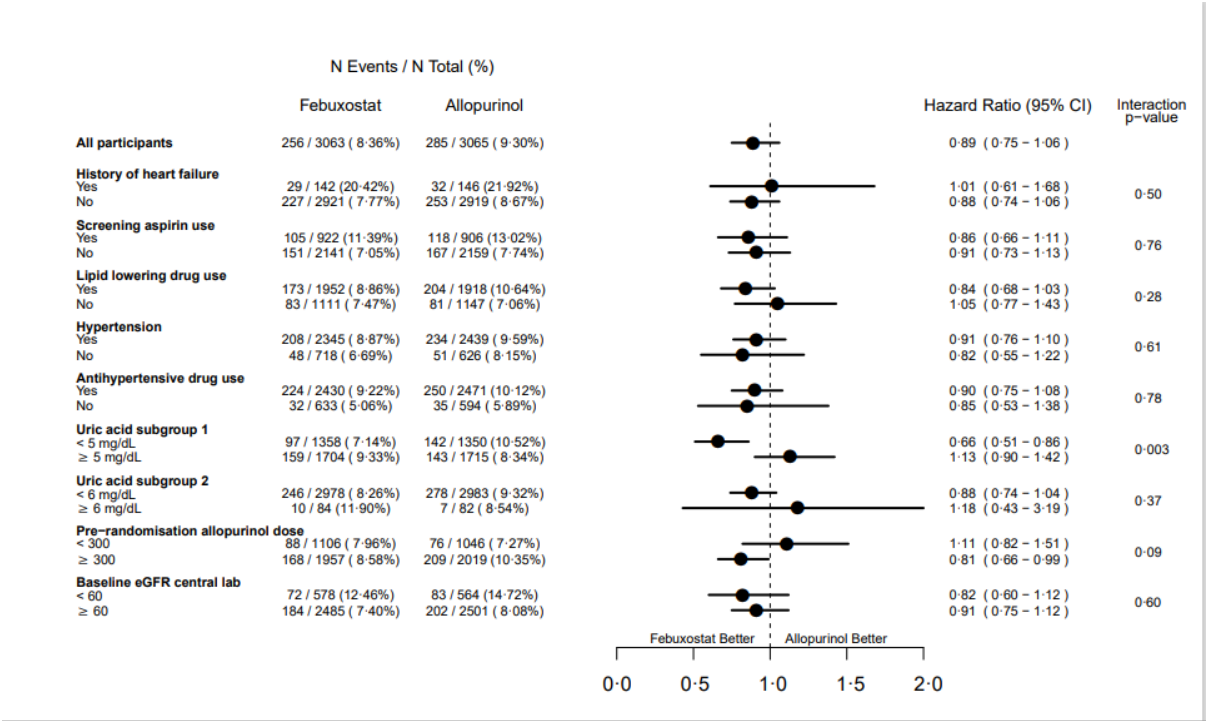
(a)



(b)

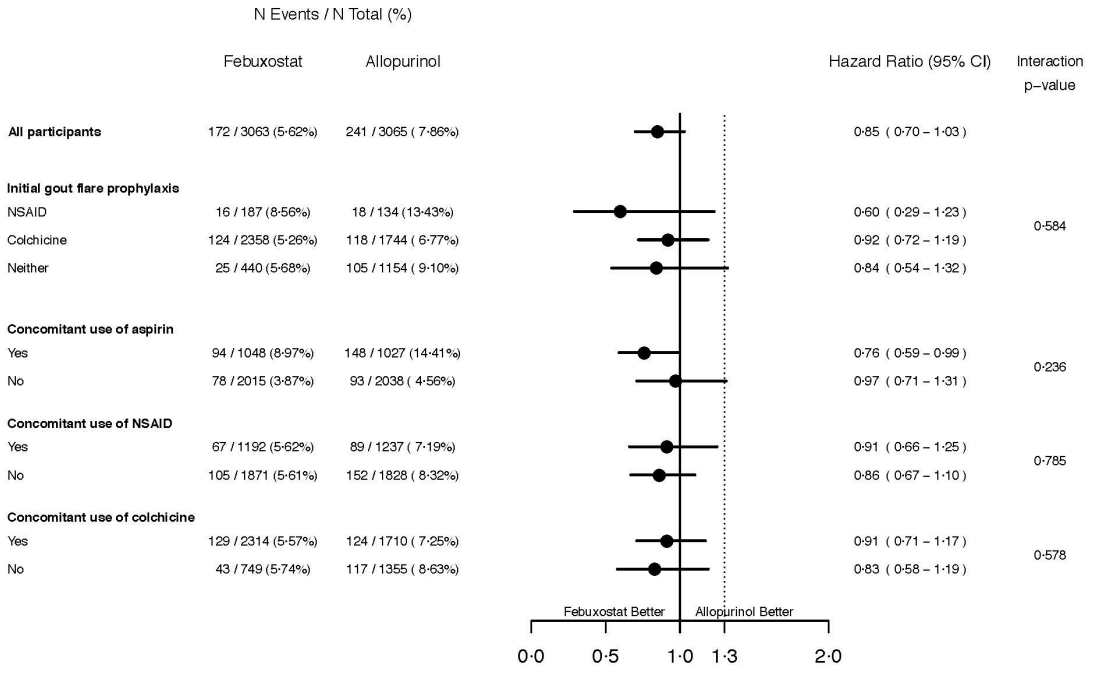


(c)

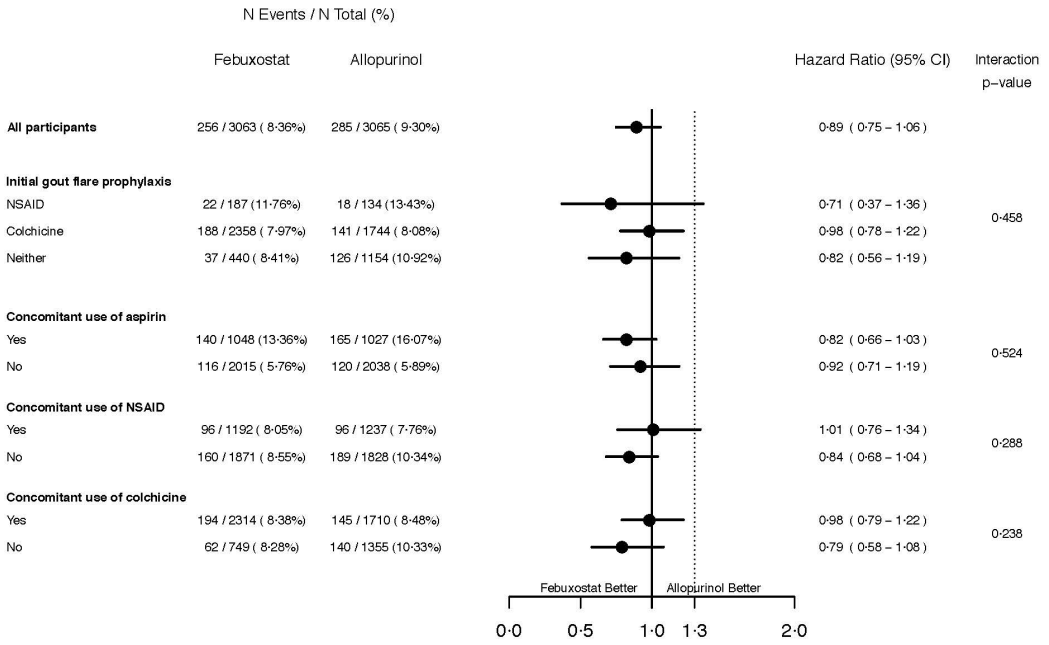

N Events / N Total (%)
Febuxostat
Allopurinol
Hazard Ratio (95% CI)
Interaction p−value
All participants
256 / 3063 (8·36%)
285 / 3065 (9·30%)
0·89 (0·75 − 1·06)
History of heart failure
Yes
29 / 142 (20·42%)
32 / 146 (21·92%)
1·01 (0·61 − 1·68)
No
227 / 2921 (7·77%)
253 / 2919 (8·67%)
0·88 (0·74 − 1·06)
0·50
Screening aspirin use
Yes
105 / 922 (11·39%)
118 / 906 (13·02%)
0·86 (0·66 − 1·11)
No
151 / 2141 (7·05%)
167 / 2159 (7·74%)
0·91 (0·73 − 1·13)
0·76
Lipid lowering drug use
Yes
173 / 1952 (8·86%)
204 / 1918 (10·64%)
0·84 (0·68 − 1·03)
No
83 / 1111 (7·47%)
81 / 1147 (7·06%)
1·05 (0·77 − 1·43)
0·28
Hypertension
Yes
208 / 2345 (8·87%)
234 / 2439 (9·59%)
0·91 (0·76 − 1·10)
No
48 / 718 (6·69%)
51 / 626 (8·15%)
0·82 (0·55 − 1·22)
0·61
Antihypertensive drug use
Yes
224 / 2430 (9·22%)
250 / 2471 (10·12%)
0·90 (0·75 − 1·08)
No
32 / 633 (5·06%)
35 / 594 (5·89%)
0·85 (0·53 − 1·38)
0·78
Uric acid subgroup 1
< 5 mg/dL
97 / 1358 (7·14%)
142 / 1350 (10·52%)
0·66 (0·51 − 0·86)
≥ 5 mg/dL
159 / 1704 (9·33%)
143 / 1715 (8·34%)
1·13 (0·90 − 1·42)
0·003
Uric acid subgroup 2
< 6 mg/dL
246 / 2978 (8·26%)
278 / 2983 (9·32%)
0·88 (0·74 − 1·04)
≥ 6 mg/dL
10 / 84 (11·90%)
7 / 82 (8·54%)
1·18 (0·43 − 3·19)
0·37
Pre−randomisation allopurinol dose
< 300
88 / 1106 (7·96%)
76 / 1046 (7·27%)
1·11 (0·82 − 1·51)
≥ 300
168 / 1957 (8·58%)
209 / 2019 (10·35%)
0·81 (0·66 − 0·99)
0·09
Baseline eGFR central lab
< 60
72 / 578 (12·46%)
83 / 564 (14·72%)
0·82 (0·60 − 1·12)
≥ 60
184 / 2485 (7·40%)
202 / 2501 (8·08%)
0·91 (0·75 − 1·12)
0·60
Febuxostat Better
Allopurinol Better
0·0
0·5
1·0
1·5
2·0

Supplementary Figure S5: Forest plots displaying hazard ratios (HR), 95% confidence intervals (CI) and p-values for a test for interaction, for sub-groups based on initial gout flare prophylaxis, and concomitant treatment with each of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine. Results are displayed for the primary endpoint (a) on-treatment and (b) by intention-to-treat. Randomised set (n=6128)

(a)



(b)


N Events / N Total (%)
Febuxostat
Allopurinol
Hazard Ratio (95% CI)
Interaction p–value
All participants
256 / 3063 (8·36%)
285 / 3065 (9·30%)
0·89 (0·75 – 1·06)
Initial gout flare prophylaxis
NSAID
22 / 187 (11·76%)
18 / 134 (13·43%)
0·71 (0·37 – 1·36)
0·458
Colchicine
188 / 2358 (7·97%)
141 / 1744 (8·08%)
0·98 (0·78 – 1·22)
Neither
37 / 440 (8·41%)
126 / 1154 (10·92%)
0·82 (0·56 – 1·19)
Concomitant use of aspirin
Yes
140 / 1048 (13·36%)
165 / 1027 (16·07%)
0·82 (0·66 – 1·03)
0·524
No
116 / 2015 (5·76%)
120 / 2038 (5·89%)
0·92 (0·71 – 1·19)
Concomitant use of NSAID
Yes
96 / 1192 (8·05%)
96 / 1237 (7·76%)
1·01 (0·76 – 1·34)
0·288
No
160 / 1871 (8·55%)
189 / 1828 (10·34%)
0·84 (0·68 – 1·04)
Concomitant use of colchicine
Yes
194 / 2314 (8·38%)
145 / 1710 (8·48%)
0·98 (0·79 – 1·22)
0·238
No
62 / 749 (8·28%)
140 / 1355 (10·33%)
0·79 (0·58 – 1·08)
Febuxostat Better
Allopurinol Better
0·0
0·5
1·0
1·3
2·0

Febuxostat versus Allopurinol Streamlined Trial

(FAST)

Clinical Endpoint Committee Charter

Version: 2.0

Document Date 14th January 2013

Contents

1. Introduction

The primary objective of the FAST (Febuxostat versus Allopurinol Streamlined Trial) is to compare the cardiovascular (CV) safety profile of febuxostat versus allopurinol when taken for an average of 3 years in patients aged 60 years or older with chronic hyperuricaemia in conditions where urate deposition has already occurred.

The primary endpoint of the study is the first occurrence of hospitalisation for non-fatal acute myocardial infarction, first occurrence of hospitalisation for biomarker positive acute coronary syndrome, first occurrence of stroke (with or without hospitalisation) or cardiovascular death.

The secondary study objectives are to evaluate other cardiovascular adverse events for both products.

Pre-specified cardiovascular events (see section 3) will be classified independently by the Clinical Endpoint Committee (CEC) utilising a consistent and unbiased classification system via an endpoint adjudication web portal.

The CEC will be blinded regarding any information relating to the randomisation group.

2 Composition and responsibilities of the CEC

2.1 CEC members and responsibilities

The CEC consists of 4 cardiologists and a vascular surgeon:

CEC Member	Affiliation
Professor John McMurray (Consultant Cardiologist), Chairman	University of Glasgow and Western Infirmary, Glasgow, Scotland.
Dr Mark Petrie (Consultant Cardiologist and Honorary Reader in Cardiology)	Golden Jubilee National Hospital, Clydebank and University of Glasgow, Scotland.
Dr Pardeep Jhund (Clinical Lecturer in Cardiology)	University of Glasgow and Western Infirmary, Glasgow, Scotland.
Dr Michael MacDonald (Specialist Registrar in Cardiology)	Golden Jubilee National Hospital, Clydebank.
Mr Douglas Orr (Consultant Vascular Surgeon)*	Western Infirmary, Glasgow, Scotland

* Specialist to be involved in adjudication of cases of limb ischaemia only

In the event that a CEC member is unable to continue participation, the CEC chairman will recommend a replacement to the Sponsor. The Sponsor has the final decision as to the replacement. CEC members may not participate in the study as principal or co-investigators, nor can they participate in the medical care of a patient in the study.

The CEC Chairman will

- Serve as a member of the FAST Steering Committee.
- Act as the primary liaison between the CEC and the Sponsor.
- Supervise the CEC coordination staff.
- Be responsible for the overall conduct of the CEC.

CEC members will be responsible for:

- Participating in training on the adjudication process and trial-specific events and definitions.
- Reviewing the relevant clinical data about a subject identified as having experienced a suspected event requiring adjudication.
- Adjudicating pre-specified clinical events (see section 3) according to the definitions outlined in section 5 of this charter.
- Timely submission of event adjudication decisions.
- Communicating with the CEC coordinator about needs when necessary.
- Attending scheduled CEC meetings throughout the study.

2.2 CEC coordination staff and responsibilities

The CEC is assisted by a CEC coordinator (Sr Barbara Meyer, BHF Cardiovascular Research Centre, University of Glasgow) who is a registered research nurse based in Professor McMurray's unit and who has considerable previous experience in the conduct of cardiovascular clinic trial activity. The CEC coordinator will work under the supervision of a CEC coordinating physician (Dr Eugene Connolly, Western Infirmary, Glasgow) who has extensive experience as a CEC coordinator and adjudicator for cardiovascular trial programmes.

The CEC coordinating staff will be responsible for coordinating the day- to- day operations of the CEC. This includes:

- Assisting in developing trial-specific adjudication documents and forms.
- Reviewing event data for those reported cardiovascular and non-cardiovascular events that require adjudication by the CEC (see section 3) to ensure that the information provided is adequate/complete.
- Reviewing other reported cardiovascular and non-cardiovascular events (i.e. those not appearing to constitute event types requiring CEC adjudication) to ensure that potential endpoint events that would require CEC adjudication have not been missed.
- Communicating promptly with the Robertson Centre for Biostatistics (RCB), Glasgow, and, if necessary, with study sites to resolve any data queries.
- Liaising with the CEC members to arrange regular, scheduled CEC meetings.
- Ensuring that final event classification decisions reached as a result of CEC meetings are delivered promptly to the RCB for entry onto the endpoint adjudication web portal.

3 Events to be reviewed

3.1 Deaths

The CEC will review all reported deaths and classify the cause of death according to the following schema:

- Non-cardiovascular

  A definite non-cardiovascular cause of death must be identified.

- Cardiovascular (CV)

    - Death due to acute myocardial infarction
    - Death due to stroke
    - Sudden cardiac death
    - Death due to heart failure
    - Cardiovascular procedure-related death
    - Other cardiovascular death (e.g. pulmonary embolism, ruptured aortic aneurysm)

- Undetermined cause of death (i.e. cause of death unknown)

Note on the classification of haemorrhagic deaths

Deaths due to gastrointestinal haemorrhage (e.g. from a peptic ulcer) will be classified as non-cardiovascular deaths.

Deaths due to vascular disease leading to fatal haemorrhage (e.g. ruptured aortic aneurysm) will be classified as "other cardiovascular" deaths (see above).

Deaths due to vascular trauma leading to fatal haemorrhage (e.g. stabbing) will be categorized as death due to trauma.

Similarly, deaths due to other types of secondary haemorrhage will be ascribed to the primary aetiology (e.g warfarin overdose, coagulopathy, etc).

3.2 Non-fatal events

The CEC will review the following reported non-fatal cardiovascular events:

- Acute myocardial infarction/biomarker positive acute coronary syndrome (reported to have been a reason for hospitalisation or to have occurred *during* a hospitalisation)

- Hospitalisation for angina*/other chest pain* (whether the angina/chest pain event was reported to have been the primary, or a contributing, reason for hospitalisation)

- Stroke/TIA** (whether reported to have been hospitalised or non-hospitalised or to have occurred *during* a hospitalisation)

- Hospitalisation for heart failure (whether the heart failure event was reported to have been the primary, or a contributing, reason for hospitalisation)

- Hospitalisation with arrhythmia (all arrhythmias reported to have been present on hospitalisation will be reviewed)

- Hospitalisation for resuscitated cardiac arrest (whether the resuscitatated cardiac arrest event was reported to have been the primary, or a contributing, reason for hospitalisation)

- Hospitalisation for venous thromboembolism (i.e. deep venous thrombosis, pulmonary embolism) whether the venous thromboembolic event was reported to have been the primary, or a contributing, reason for hospitalisation

- Hospitalisation for acute or chronic critical limb ischaemia (whether the acute or chronic critical limb ischaemia event was reported to have been the primary, or a contributing, reason for hospitalisation)

NB: Coronary/cerebral revascularisation procedures done over the course of the study will not be adjudicated by the CEC. These will be collected and collated by the sponsor during the course of the study (and will be reviewed by the CEC coordination staff to ensure that potential endpoint events (e.g. acute myocardial infarction, stroke) have not been missed)

*Reported hospitalisation for angina/other chest pain events are not study endpoints but such events will be reviewed by the CEC to ensure that acute myocardial infarction/biomarker positive ACS events have not been missed.

**While TIAs will reviewed by the CEC to ensure that stroke events have not been missed, the CEC will not attempt to validate a diagnosis of TIA because of the difficulties (including the transience of the symptoms and the lack of a definitive test) involved in doing this reliably. Thus, reported TIA events will just be classified as ‘stroke’ or ‘not a stroke’.

NB All hospitalised TIA events that are identified (e.g. from hospitalisation codes or by study site investigators) will be collected by the Sponsor during the course of the study.

Other non-fatal cardiovascular events will not routinely be reviewed by the CEC. However, these events will be reviewed by the CEC coordinating physician to ensure that potential endpoint events which would require adjudication by the CEC are not missed. If the CEC coordinating physician identifies a potential endpoint event, further information will be requested, as required and, if necessary, the event will be allocated to the CEC for adjudication.

Note on non-fatal *non-cardiovascular* events

Non-fatal non-cardiovascular events will not routinely be reviewed by the CEC. However, the first 100 non-cardiovascular hospitalisations will be reviewed by the CEC coordinating physician to ensure that potential endpoint events which would require adjudication by the CEC are not missed. Following this review, if analysis suggests that events of interest to the CEC would be likely to be missed because of a strategy of not reviewing non-cardiovascular events, the Chairman and the Steering Committee will discuss the steps necessary to ensure resolution of this issue.

4 Adjudication process

A flowchart of the overall CEC adjudication process is shown in Appendix A.

NB: For the first 20 reported events requiring adjudication, the events will be reviewed at a CEC meeting with all 4 cardiology members, and the CEC coordination staff, present. If there are any limb ischaemia events to be reviewed, then the vascular surgery specialist will also attend and these events will be classified on the basis of CEC consensus. Classification of the other cardiovascular event types will not involve the vascular surgery specialist. These events will be classified on the basis of consensus among the cardiology CEC members.

It is expected that this will be a face-to-face meeting, however, if for some reason a face- to-face meeting is not possible, a meeting by by means of remote communication (teleconference) may substitute. The purpose of this committee review will be to ensure that all committee members are aligned with regard to the application of the event definitions described in this charter

4.1 Identification and reporting of events

All deaths and hospitalisations occurring within Scotland will be retrieved regularly from the General Register Office (GRO) database and the Scottish Morbidity Record One (SMR1) database, respectively.

Hospitalisations and deaths occurring in England and Denmark will also be retrieved regularly.

Potential endpoints will be identified when specific ICD and OPCS codes are detected electronically, using software created by the RCB (see Appendix C).

Deaths and hospitalisations that occur outside the Scottish, English, and Danish record-linkage framework will be identified by the study site investigators (i.e. a primary care physician or a designee). Patients will be instructed to report all such hospitalisations to study site investigators or research nurses as soon as possible after the event. These events will be ICD coded and identified as potential endpoints using the same method described above.

When potential endpoint events are identified, trained nurses will scrutinise primary and secondary care records as well as death certification data, where appropriate. The data reviewed will be summarised onto *event pages* that have been specially designed to ensure that the information required for adjudication is captured. Where possible, the data will be supplemented by scanned images of relevant supportive source documentation (see section 4.7). Supportive source documents will be scrutinised to ensure that all data is blinded to both patient identity and randomised drug exposure before review by the CEC. The event data will be posted on the endpoint adjudication portal by the Robertson Centre, Glasgow for review by the CEC coordination staff.

4.2 CEC coordination staff review

Having been posted on the website, the CEC coordinator will review the *event packet* containing the relevant data for a reported event and check it for completeness. If required data is missing or incomplete, the process outlined in section 4.4 will be followed.

With the exception of potential limb ischaemia events (see note below), *event packets* for those events that require review by the CEC (see sections 3.1 and 3.2) will be allocated on a regular basis to a pair of CEC cardiology members (which will not include the Chairman) and the pair will receive electronic notification that they have events ready for adjudication. The pairs will be rotated automatically in a manner that ensures that events are distributed to the members on an even basis. A full tracking system and audit including details of the date of dispatch to the CEC members will be stored.

Those reported events *not* requiring adjudication by the CEC will be screened by the CEC coordinating physician to ensure that potential endpoint events have not been missed. If the coordinating physician is satisfied that a potential endpoint event requiring CEC adjudication has not been missed, the event will be signed-off electronically as “not a potential endpoint event”. If the CEC coordinating physician considers that a potential endpoint event may have been missed, further information will be requested, as required, by the CEC coordinator and, if necessary, the event will be forwarded to the CEC for adjudication.

Note: All potential limb ischaemia events will be classified by consensus at a CEC meeting with all members (including the vascular surgery specialist) present.

4.3 Phase 1 CEC review

Upon receipt of a batch of *event packets* containing the relevant event data for suspected events, the adjudicating pair of cardiology CEC physicians will review each one independently and will enter their adjudication decisions onto the web portal. This is the Phase 1 review. For each event where the two reviewers have agreed on a classification, the event is deemed classified.

If the classification decision of the two reviewers is not unanimous, classification of the event will be deferred pending its discussion by at least 3 cardiology CEC members (one of whom should be the Chairman) at a scheduled CEC meeting/teleconference ("Phase 2 CEC review" - see section 4.5).

Insufficient information to classify an event

If, at any time, a CEC member decides that a classification verdict is not obtainable because of incomplete/insufficient data, the process outlined in section 4.4 will be followed.

4.4 Incomplete event data

If, having reviewed the event data pertaining to an event, the CEC coordination staff, or a CEC member, deem that the information therein is insufficient for the purposes of event adjudication, an electronic request for further information will be made directly to the regional or study site, via the study web portal. This will be done by the CEC coordinator/CEC member who will detail the specific information required. If the requested information is made available to the CEC coordinator and is deemed sufficient for the purpose of adjudication, the new *event packet* (including the new, or updated, event data*)* will be distributed to the relevant pair of CEC members. This will then be reviewed independently by the pair of CEC members following the procedure outlined in section 4.3.

Alternatively, if the CEC coordinator deems that the further information obtained is insufficient for the purpose of adjudicating an event, a new request for further information will be generated using the process described above.

In instances where it is confirmed that efforts to obtain requested information have been unsuccessful (e.g. because the study site has indicated that the information is not available despite best efforts to obtain it), classification of the event will be deferred pending its discussion at a scheduled CEC meeting (see section 4.5).

4.5 Phase 2 CEC review

The full CEC and the CEC coordinating staff will convene at regular intervals throughout the study. In general, it is expected that that these will be face-to-face meetings, however, if for some reason a face- to- face meeting is not possible, a meeting by teleconference may substitute.

The primary objective of CEC meetings is the "Phase 2 review" and classification of those events for which a final classification decision has not been achieved by the Phase 1 review process already outlined above (section 4.3) and to review and classify potential limb

ischaemia events that have been reported. Phase 2 review of an event constitutes the discussion and adjudication of the event by the CEC as a group.

For the classification of potential limb ischaemia events, the vascular surgery specialist must be present and these events will be classified on the basis of CEC consensus. Classification of the other cardiovascular event types will not involve the vascular surgery specialist. These events will be classified on the basis of consensus among the cardiology CEC members. In general, it is expected that all 4 cardiologists will be present at meeting. However, if, due to exceptional circumstances, it is not possible to assemble all 4 cardiology members within a required timeframe, events may be classified on the basis of consensus among 3 cardiology members – one of whom must be the Chairman.

The final classification decision will be entered onto the web portal by the CEC coordination staff or the RCB. If the CEC are unable to arrive at a classification verdict for an event because of incomplete or inadequate information and it is felt that such information may be obtainable (e.g.. the study site has *not* indicated that the information required is *not* available), the Chairman will detail the precise information/documentation that is needed to achieve classification and the CEC coordinator will request this data using the process described in section 4.4. The event will be tabled and placed on the agenda for review at a subsequent scheduled CEC meeting when either the further information requested has been provided or when confirmation has been received that efforts to obtain the information have been unsuccessful. With respect to a death event; if, despite discussion, the cause of death remains unclear (and the study site has indicated that further information is *not* available despite best efforts to obtain it), the classification category “undetermined cause of death” will be used (see section 5.3.3 below).

4.6 Adjudication timelines

The CEC members will expect events to be allocated as they become available on the FAST web portal and will make every effort to enter their classification decisions onto the web-portal within 2 to 4 weeks from the time that the event data is received, although this may vary slightly. The prompt review/adjudication of events will be dependent on the CEC coordinator receiving the required event data (see 4.7) in a timely fashion and on study sites/regional centres dealing with data-queries as promptly as possible.

For events requiring discussion at a CEC meeting, every effort will be made to ensure that such meetings take place regularly and that any final classification decisions reached are delivered to the RCB for entry onto the web portal within 2 to 4 weeks of the meeting. The frequency of CEC meetings is outlined in the contract. If required, additional meetings can be arranged, provided that there is mutual agreement between the Sponsor and the CEC before any change is made.

If required, the above timelines may be amended as the study progresses, if the CEC and the other relevant parties agree on a new schedule of event turn-around time.

4.7 Clinical data to be provided

Event data for each potential endpoint event will be posted on a website portal by the RCB and will include:

a) A cover page that will identify the patient (by a unique patient identification number), specify the event(s) to be adjudicated and provide a checklist of the eCRF sections and any supportive source documentation [see d) below] provided.

b) The relevant completed *event page(s*) [each with a unique identifying event number] with the narrative (clinical summary) section (s).

c) Any other relevant eCRF sections (e.g concomitant medication section, cardiovascular/medical history section).

d) The appropriate supportive source documentation* for each event with an associated Essential Document Checklist (Appendix B)

*Where applicable and available, copies of the following source documentation should be provided for the following events:

<u>Death event:</u>

- Death certificate
- Autopsy report
- Hospitalisation records (see “hospitalisation event”, directly below)

<u>Hospitalisation event:</u>

Hospitalisation records, which will include:

- Hospital death/discharge summary
- Medical clerking records and relevant medical progress notes/continuation sheets
- Prescription charts

<u>Potential myocardial infarction/biomarker positive ACS/angina/other chest pain event:</u>

- ECGs: a baseline (e.g study-entry) ECG, ECGs pertaining to the event and, if applicable, an ECG recorded between baseline and the event
- Cardiac enzyme/marker laboratory reports
- Other cardiovascular investigation reports as requested on the MI event page (e.g. exercise-ECG, echocardiography, myocardial perfusion scan)
- Cardiovascular operation/procedure reports (e.g coronary angiography)

Potential stroke/TIA event:

- Neuroimaging (CT brain, MRI brain, cerebral angiography) reports
- Lumbar puncture report

Potential heart failure event

- ECGs: a baseline (e.g study-entry) ECG, ECGs pertaining to the event and, if applicable, an ECG recorded between baseline and the event
- Chest x-ray report
- Cardiac enzyme/marker laboratory report
- BNP/NT-proBNP report
- Other cardiovascular investigation reports (e.g. echocardiography, radionuclide ventriculography)
- Cardiovascular operation/procedure reports

Potential arrhythmia event:

- ECGs/rhythm strips pertaining to the event as well as (if available) ECGs/rhythm strips recorded at baseline and recorded between baseline and the event
- Cardiac enzyme/marker laboratory report
- Echocardiography report
- Cardiovascular operation/procedure reports (e.g. EP [electrophysiology] study, pacemaker/defibrillator implantation, coronary angiography)
- Other investigation reports as requested on the arrhythmia event page

Potential resuscitated cardiac arrest event:

- ECGs/rhythm strips pertaining to the event as well as (if available) ECGs/rhythm strips recorded at baseline and recorded between baseline and the event
- Resuscitation report/records
- Cardiac enzyme/marker laboratory reports
- Cardiovascular operation/procedure reports (e.g. EP [electrophysiology] study, pacemaker/defibrillator implantation, coronary angiography)

Potential DVT/pulmonary embolism event:

- D-dimer report
- Arterial blood gas measurements
- Limb ultrasonography report
- Venography report
- Chest x-ray report
- Ventilation-perfusion scan report
- CT chest/CT pulmonary angiography report
- Invasive pulmonary angiogram report
- ECGs: a baseline (e.g study-entry) ECG, ECGs pertaining to the event and, if applicable, an ECG recorded between baseline and the event

- Cardiac enzyme/marker laboratory report
- BNP/NT-proBNP report
- Echocardiography report
- Cardiovascular operation/procedure reports (e.g. coronary angiography)
- Other operation/procedure report (e.g. thrombectomy/embolectomy)
- Other investigation reports as requested on the DVT/pulmonary embolism event page

Potential limb ischaemia event

- Haemodynamic/physiological tests (e.g. arterial Doppler signalsankle systolic blood pressure, ankle-brachial index)
- Peripheral artery (invasive) angiography report
- Other peripheral artery imaging reports (e.g. CT angiography, duplex ultrasonography)
- Other imaging reports (e.g. echocardiography)
- ECGs: a baseline (e.g study-entry) ECG, ECGs pertaining to the event and, if applicable, an ECG recorded between baseline and the event
- Vascular operation or procedure reports (e.g. limb revascularisation, amputation)
- Other investigation reports as requested on the limb ischaemia event page

4.8 Quality assurance

For the purposes of quality assurance, the RCB will conduct regular interobservability studies by recirculating approximately 5% of all events previously allocated to the CEC coordinator. These will have new (dummy) identifying information assigned to them and will not be recognisable to the CEC coordination staff or to the CEC as being any different to new events requiring review/adjudication.

If there are any discrepancies between the initial and the subsequent review/adjudication decisions, the Chairman and the Steering Committee will discuss the steps necessary to ensure reconciliation and resolution of the issue.

5 Clinical Event definitions

5.1 Hospitalisation

Hospitalisation is defined as an emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

5.3 Non-fatal events

Date of onset

For purposes of classification, when classifying events that are a cause of hospitalisation, the date of admission will be used as the onset date. In cases where the stated date of admission differs from the date the patient first presented to hospital with the event (e.g. because of a period of observation in an emergency department, medical assessment unit or equivalent), the date of intial presentation to hospital will be used (provided that the patient had not been discharged from hospital in the interim). For events where an admission date is not applicable (e.g. events occuring *during* an ongoing hospitalisation), the date of onset as reported by the treating physician will be used.

5.2.1 Acute myocardial infarction

Note on biomarker elevations:

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL.

Spontaneous acute myocardial infarction:

A rise and/or fall of cardiac biomarkers (troponin or CK-MB) should usually be detected (see note below) with at least one value above the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischaemia (as outlined in Table 1, below) or new left bundle branch block (LBBB).
- Development of pathological Q waves on the ECG (see Table 2, below)
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute myocardial infarction

If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as:

a. One of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia (as outlined in Table 1, below) or new left bundle branch block. [The events committee will adjudicate in the context of the sequential ECG changes that are commonly seen in acute ST elevation/acute non-ST elevation myocardial infarction.]
- New pathological Q waves (see Table 2, below). [The events committee will adjudicate in the context of the sequential ECG changes that are commonly seen in acute ST elevation/acute non-ST elevation myocardial infarction.]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute myocardial infarction

AND

b. Both of the following:

- Evidence that cardiac biomarker values were decreasing (e.g. two samples 3-6 hours apart) prior to the suspected acute myocardial infarction*

- ≥ 20% increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation with the suspected recurrent myocardial infarction and a further sample taken 3-6 hours later

*If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent myocardial infarction is generally not possible.

Percutaneous coronary intervention-related acute myocardial infarction

Peri-percutaneous coronary intervention (PCI) acute myocardial infarction is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

4. Biomarker elevations within 48 hours of PCI:

   • Troponin or CK-MB (preferred) > 3 x URL ***and***

   • No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

Both of the following must be true:

- ≥ 50% increase in the cardiac biomarker result
- Evidence that cardiac biomarker values were decreasing (e.g. two samples 3-6 hours apart) prior to the suspected acute myocardial infarction

5. New pathological Q waves or new left bundle branch block (LBBB).
   [If the PCI was undertaken in the context of an acute myocardial infarction, the events committee will adjudicate in the context of the sequential ECG changes that are commonly seen in acute ST elevation/acute non-ST elevation myocardial infarction.]

6. Autopsy evidence of acute myocardial infarction

Coronary artery bypass grafting-related acute myocardial infarction

Peri-coronary artery bypass graft surgery (CABG) acute myocardial infarction is defined by the following criteria. Symptoms of cardiac ischemia are not required.

4. Biomarker elevations within 72 hours of CABG:
   - Troponin or CK-MB (preferred) > 5 x URL **and**
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

   OR

   • Both of the following must be true:

   - ≥ 50% increase in the cardiac biomarker result
   - Evidence that cardiac biomarker values were decreasing (e.g. two samples 3-6 hours apart) prior to the suspected acute myocardial infarction

   AND

5. One of the following:

   - New pathological Q-waves (preferably with evidence of persistence)
   - New LBBB (preferably with evidence of persistence)
   - Angiographically documented new graft or native coronary artery occlusion
   - Imaging evidence of new loss of viable myocardium

OR

6. Autopsy evidence of acute myocardial infarction

Note: For a diagnosis of acute myocardial infarction, elevation of cardiac biomarkers above the upper reference limit (or, if an URL is not available, above the local MI decision limit) should usually be present. If biomarkers are detectable but do not exceed the URL or the local MI decision limit, the classification "biomarker positive acute coronary syndrome" will be used, providing that the definition of this particular event-type (see below) is met.

However, myocardial infarction may be adjudicated for an event that has characteristics which are very suggestive of acute infarction but which does not meet the strict definition because biomarkers are not available (e.g. not measured) or are non-contributory (e.g. may have normalized).

Suggestive characteristics are:

- Typical cardiac ischemic-type pain/discomfort
  (except for suspected acute myocardial infarction occurring in the context of PCI or CABG where this requirement need not apply)

AND

- New ECG changes* or other evidence to support a diagnosis of acute myocardial infarction (e.g. imaging evidence of new loss of viable myocardium/new regional all motion abnormality or angiography demonstrating occlusive coronary thrombus)

*If ECG tracings are not available for review, the CEC may adjudicate on the basis of reported ECG changes that have been clearly documented in the case records or in the case report form.

Clinical classification of different types of myocardial infarction

Myocardial infarctions will be clinically classified as:

Type 1
Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.

Type 2
Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

Type 3

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or

new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a
Myocardial infarction associated with PCI.

Type 4b
Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy.

Type 5
Myocardial infarction associated with CABG.

Myocardial infarctions will be further sub-classified as:

4. ST segment elevation myocardial infarction (STEMI).

or

5. Non-ST segment elevation myocardial infarction (NSTEMI).

or

6. Myocardial infarction, type (i.e. STEMI or NSTEMI) unknown.

Table 1: ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy and left bundle branch block)

ST elevation
New ST elevation at the J-point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
ST depression and T wave changes
New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T wave inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

Table 2: Pathological Q waves:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF) a

A The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

5.2.2 Biomarker positive acute coronary syndrome (ACS)

Note: This does not include acute myocardial infarction which will be classified separately (see above).

For the diagnosis of biomarker positive ACS, the following criteria should be fulfilled:

There should be:

2 Clinical presentation consistent with ischaemia (e.g. typical cardiac ischaemic-type pain or discomfort).

and

2 Detectable cardiac biomarkers but without the fullfilment of the biomarker criteria outlined above for acute myocardial infarction.

[i.e. not exceeding the upper reference limit or, if an upper reference limit is not available, not exceeding the MI decision limit for the particular laboratory.]

and

3 The need for treatment with parenteral (intravenous, intra-arterial, buccal, transcutaneous or subcutaneous) anti-ischaemic/antithrombotic therapy and/or coronary revascularisation.

Note: The following are considered supportive of the diagnosis and, in general, at least one of these [(a), (b) or (c)] is expected to be present. However, this is not mandatory if the criteria 1 to 3 (above) are met and provided that the adjudicator is satisfied that the totality of the information is consistent with the diagnosis.

(a) New and/or reversible ST segment or T wave changes on the ECG.

(b) Investigations undertaken in view of the event (e.g. exercise ECG or stress myocardial perfusion scan) showing evidence of reversible myocardial ischaemia,

(c) Coronary angiography showing angiographically significant coronary disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take precedence.]

5.2.3 Hospitalisation for angina*

For the diagnosis of hospitalisation for angina, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfillment of the following criteria:

There should be:

2 Clinical presentation consistent with ischaemia (e.g. typical cardiac ischaemic-type pain or discomfort) but without the fulfilment of the above diagnostic criteria for acute myocardial infarction or biomarker positive acute coronary syndrome.

and

2 The need for treatment with new or increased anti-anginal therapy (excluding sublingual nitrate therapy) and/or coronary revascularisation

and

3 (a) New and/or reversible ST segment or T wave changes on the ECG.

Or

3 (b) Investigations undertaken in view of the event (e.g. exercise ECG or stress myocardial perfusion scan) showing evidence of reversible myocardial ischaemia,

Or

3 (c). Coronary angiography showing angiographically significant coronary disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take precedence.]

and

4 The CV-CEC should be satisified that angina was the primary reason for hospitalisation.

5.2.4 Hospitalisation for other chest pain*

There should be:

- Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay i.e. a date change) due to chest pain but where the definitions (above) of acute myocardial infarction, biomarker positive ACS or angina are not met.
- The CV-CEC should be satisfied that chest pain was the primary reason for hospitalisation.

*These events are not study endpoints but the definitions provided for these events will be used by the CEC to categorise reported myocardial infarction, biomarker positive ACS, angina and chest pain events that do not meet the study definitions of acute myocardial infarction or biomarker positive acute coronary syndrome.

5.2.5 Stroke

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

For the diagnosis of for stroke, the following 4 criteria should usually be fulfilled:

1. **Rapid onset* of a focal/global neurological deficit with at least one of the following:**

   - Change in level of consciousness
   - Hemiplegia
   - Hemiparesis
   - Numbness or sensory loss affecting one side of the body
   - Dysphasia/aphasia
   - Hemianopia (loss of half of the field of vision of one or both eyes)
   - Complete/partial loss of vision of one eye
   - Other new neurological sign(s)/symptom(s) consistent with stroke

   *If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation.

2. **Duration of a focal/global neurological deficit ≥ 24 hours**

   or

   < 24 hours if

   (i) this is because of at least one of the following therapeutic interventions:

   (a) pharmacologic i.e. thrombolytic drug administration.

   (b) non-pharmacologic i.e. neurointerventional procedure (e.g. intracranial angioplasty).

   or

   (ii) brain imaging available clearly documenting a new haemorrhage or infarct.

   or

   (iii) the neurological deficit results in death

3. **No other readily identifiable non-stroke cause for the clinical presentation** (e.g. brain tumour, hypoglycaemia, peripheral lesion).

4. **Confirmation of the diagnosis by at least one of the following****:

   d) neurology or neurosurgical specialist.
   e) brain imaging procedure (at least one of the following):
      (i) CT scan.
      (ii) MRI scan.
      (iii) cerebral vessel angiography.

f) lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial haemorrhage).

**If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone but *full CEC consensus will be mandatory.*

Strokes will be further sub-classified as:

- Ischaemic (non-hemorrhagic) stroke
  (ie caused by an infarction of central nervous system tissue)

or

- Hemorrhagic stroke
  (ie caused by nontraumatic intraparenchymal, intraventricular or subarachnoid hemorrhage)

or

- Stroke type (i.e. hemorrhagic or ischaemic) unknown (i.e when imaging/other investigations are unavailable or inconclusive).

5.2.6 Hospitalisation for heart failure

For the diagnosis of hospitalisation for heart failure, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfillment of the following criteria:

There should be:

5. clinical manifestations of new or worsening heart failure including at least one of the following:
   - New or worsening dyspnoea on exertion
   - New or worsening dyspnoea at rest
   - New or worsening fatigue/decreased exercise tolerance
   - New or worsening orthopnoea
   - New or worsening PND (paroxysmal nocturnal dyspnoea)

- New or worsening lower limb or sacral edema
- New or worsening pulmonary crackles/crepitations
- New or worsening elevation of JVP (jugular venous pressure)
- New or worsening third heart sound or gallop rhythm

And

6. Investigative evidence of structural or functional heart disease (<u>if available</u>) with at least *one* of the following:

    - Radiological evidence of pulmonary edema/congestion or cardiomegaly.
    - Imaging (e.g. echocardiography, cardiac magnetic resonance imaging, radionuclide ventriculography) evidence of an abnormality (e.g. left ventricular systolic dysfunction, significant valvular heart disease, left ventricular hypertrophy).
    - Elevation of BNP or NT-proBNP levels.
    - Other investigative evidence of structural or functional heart disease (e.g evidence obtained from pulmonary artery catheterisation).

    And

7. Need for new/increased therapy***** *specifically <u>for the treatment of heart failure</u>* including at least one of the following:

    - New or increased oral therapy for the treatment of heart failure
    - (See note on oral therapy, below)
    - Initiation of intravenous diuretic, inotrope, vasodilator or other recognised intravenous heart failure treatment or uptitration of such intravenous therapy if already receiving it
    - Mechanical or surgical intervention (e.g. mechanical or non-invasive ventilation, mechanical circulatory support, heart transplantation, ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, dialysis or other mechanical or surgical intervention that is specifically directed at treatment of heart failure.

*****If time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the CEC will adjudicate on clinical presentation and, if available, investigative evidence.

<u>Note on oral therapy</u>: In general, for an event to qualify as *heart failure requiring hospitalisation* on the basis of *oral* heart failure therapy (i.e. in cases where none of the intravenous or non-pharmacological therapies listed above have been utilised), the new or increased oral therapy should include oral diuretics. However, in special cases, other new or increased oral therapy (e.g. hydralazine/long acting nitrate, aldosterone antagonist) may be accepted provided that the adjudication committee is satisfied that:

c) the new or increased oral therapy was primarily directed at treating clinical manifestations of new or worsening heart failure (rather than, for example, initiation

or uptitration of heart failure therapy as part of the routine optimisation of medical therapy)

and

d) the totality of the evidence indicates that heart failure, rather than any other disease process, was the primary cause of the clinical presentation.

And

8. The CEC should be satisfied that heart failure was the primary disease process accounting for the clinical presentation.

5.2.7 Hospitalisation with arrhythmia

[Excluding hospitalisation for resuscitated cardiac arrest which is a separate endpoint – see note below]

For this diagnosis, there should be:

3. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

4. Documented ECG evidence of the arrhythmia/conduction disturbance.
[If ECG tracings are not available for review, the CEC may adjudicate on the basis of a reported arrhythmia/conduction disturbance that has been clearly documented in the case records.]

Arrhythmias will be categorised by the CEC as follows:

4) The primary reason for hospitalisation
(arrhythmias deemed to be secondary to acute myocardial infarction/biomarker positive ACS will not be included in this category)

5) A contributing reason for hospitalisation

(includes arrhythmias deemed to be secondary to acute myocardial infarction/biomarker positive ACS if the arrhythmia is adjudged to have contributed to the hospitalisation)

6) Other (i.e. arrhythmia present on admission but whether or not it contributed to the hospitalisation is uncertain).

Arrhythmias will be further subclassified as follows:

- Atrial fibrillation/flutter
- Atrial tachycardia
- Other supraventricular tachycardia
- Ventricular tachycardia
    - Non-sustained
    - Sustained
    - VT type (i.e. non-sustained or sustained) unknown
- Ventricular fibrillation
- Bradycardia/heart block
- Other arrhythmia/conduction disturbance

NOTE: If an arrhythmia event is deemed to meet the definition of hospitalisation for resuscitated cardiac arrest (see below), then “hospitalisation due to resuscitated cardiac arrest” will be the classification verdict recorded (i.e. to avoid “double counting”, the event will not also be classified as “hospitalisation with arrhythmia”).

5.2.8 Hospitalisation* for resuscitated cardiac arrest

For this diagnosis, there should be:

5. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

6. Sudden cardiac arrest or sudden cardiac death (see definition of sudden cardiac death, below) from which the patient is successfully resuscitated by cardiopulmonary resuscitation, cardioversion, defibrillation or other advanced

cardiac life support measures (e.g. emergency cardiac pacing) with recovery of consciousness and survival for more than 72 hours post resuscitation.

And

7. The cause of the cardiac arrest should not be due to another adjudicated cause (e.g. acute myocardial infarction).

And

8. The CEC should be satisfied that the event was the primary reason for hospitalisation.

Identified causes of transient loss of consciousness, such as seizures or vasovagal episodes that do not reflect significant cardiac dysfunction, are excluded.

*Should any “non-hospitalised” resuscitated cardiac arrest events occur (i.e. events of sudden cardiac arrest [with successful resuscitation] that do not result in a hospitalisation), these will also be adjudicated by the CEC according to criteria 2 and 3, above.

5.2.9 Hospitalisation for deep venous thrombosis (DVT)

For this diagnosis, there should be:

5. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

6. Documented confirmatory evidence of DVT e.g. imaging (such as ultrasonography, venography, etc.).

And

7. The need for pharmacological therapy (e.g. anticoagulation) or mechanical/surgical intervention (e.g. placement of a vena cava filter, percutaneous/surgical thrombectomy) directed at venous thromboembolism.

And

8. The CEC should be satisfied that DVT was the primary reason for hospitalisation. [In cases of hospitalisation due to venous thromboembolism where there is documented evidence of both deep venous thrombosis and pulmonary embolism, the CEC will decide which was the primary reason for hospitalisation and classify the hospitalisation accordingly.]

5.2.10 Hospitalisation for pulmonary embolism

For this diagnosis, there should be:

5. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

6. Documented confirmatory evidence of pulmonary embolism e.g. imaging (such as computed tomographic pulmonary angiography, conventional (invasive) pulmonary angiography, ventilation-perfusion scanning, etc.) or autopsy evidence.

And

7. The need for pharmacological therapy (e.g. anticoagulation, thrombolysis) or mechanical/surgical intervention (e.g. placement of a vena cava filter, percutaneous/surgical embolectomy) directed at venous thromboembolism.

And

8. The CEC should be satisfied that pulmonary embolism was the primary reason for hospitalisation. [In cases of hospitalisation due to venous thromboembolism where there is documented evidence of both deep venous thrombosis and pulmonary embolism, the CEC will decide which was the primary reason for hospitalisation and classify the hospitalisation accordingly.]

5.2.11 Hospitalisation for chronic critical lower limb ischaemia (due to obstructive atherosclerotic arterial disease)

Note that the term *chronic* critical limb ischaemia implies that the clinical manifestations *usually* have been present for greater than 2 weeks as opposed to *acute* critical limb ischaemia where there is a sudden, catastrophic change in a previously adequately perfused limb (see definition of acute critical limb ischaemia below).

For the diagnosis of chronic critical limb ischaemia, there should be:

6. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

And

7. Chronic (*usually* > 2 weeks) history of lower limb rest pain or non-healing ulcers or gangrene.

And

8. Documented confirmatory evidence of lower limb arterial occlusive disease e.g. haemodynamic/physiological (such as ankle systolic blood pressure, ankle-brachial index, toe pressure, transcutaneous oxygen tension ($tcPO_2$) or imaging (such as duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, conventional (invasive) angiography) that is considered to be responsible for the clinical presentation.

And

9. The need for treatment directed specifically at chronic critical limb ischaemia such as revascularisation (endovascular or surgical), pharmacological therapy (e.g. prostanoids), amputation or other recognised therapy directed at this diagnosis.

And

10. The CEC should be satisfied that chronic critical limb ischaemia was the primary reason for hospitalisation.

5.2.12 Hospitalisation for acute critical limb ischaemia (due to arterial embolism or thrombosis)

Note that the term acute critical limb ischaemia refers to a sudden decrease in limb perfusion that could threaten limb viability and where the presentation is *usually* within 2 weeks of the acute event (as opposed to chronic critical limb ischaemia – see definition above).

For this diagnosis, there should be:

6. Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change).

7. New or worsening (*usually* within 2 weeks of presentation) clinical manifestations of significant limb ischaemia (e.g. pain, pulselessness, pallor, paraesthesia, paralysis).

And

8. Either

a) Documented confirmatory evidence of an arterial occlusion such as haemodynamic/physiological (e.g. doppler signals) or imaging (e.g. duplex ultrasonography, computed tomographic angiography, magnetic resonance angiography, conventional [invasive] angiography) that is considered to be responsible for the clinical presentation.

Or

b) Clinical history consistent with an acute loss of blood flow to a peripheral artery with documented evidence supporting a likely embolic source e.g. documented atrial fibrillation (including paroxysmal), imaging evidence of a potential cardioembolic source (e.g. mural thrombus), documented arterial aneurysm, etc. or other evidence supportive of the diagnosis of acute critical limb ischaemia (e.g. findings in theatre if the patient is taken straight to theatre).

And

9. The need for treatment specifically directed at acute critical limb ischaemia such as intravenous anticoagulation (e.g. continuous intravenous heparin infusion), catheter-directed thrombolytic therapy, percutaneous thrombectomy/embolectomy, surgical revascularisation procedure or amputation.

And

10. The CEC should be satisfied that acute critical limb ischaemia was the primary reason for hospitalisation.

Note: Acute critical limb ischaemia events will be further subclassified as:

- Embolic

or

- Thrombotic

or

- Acute critical limb ischaemia, type (i.e. embolic or thrombotic) unknown (e.g. when imaging/other investigations are unavailable or inconclusive).

5.2.13 Other cardiovascular event

This category includes any cardiovascular event that does not fit any of the above definitions (e.g. cardiovascular operation/procedure, ruptured aortic aneurysm, endocarditis).

Such events will not be adjudicated by the CEC but will be reviewed by the CEC coordinating physician to ensure that potential endpoint events that would require CEC adjudication have not been missed.

5.3 Fatal events

In cases where a patient experiences an event and later dies due to that event, the event causing death and the death will be considered as separate events *only* if they are separated by a change in calendar day. If the event causing death and the death occur on the same calendar day, death will be the only event classified.

5.3.4 Cardiovascular deaths

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke and death due to other cardiovascular causes as follows:

Death due to Acute Myocardial Infarction refers to a death usually occurring up to 30 days after a documented acute myocardial infarction (verified either by the diagnostic criteria outlined above for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus) due to the myocardial infarction or its immediate consequences (e.g. progressive heart failure) and where there is no conclusive evidence of another cause of death.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and other (e.g. ECG, angiographic, autopsy) evidence.

NOTE: This category will include sudden cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation*, or left new left bundle branch block*, or evidence of fresh thrombus in a coronary artery by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood (i.e. acute myocardial infarction Type 3 – see section 5.2, above).

*If ECG tracings are not available for review, the CEC may adjudicate on the basis of reported new ECG changes that have been clearly documented in the case records or in the case report form.

Death resulting from a procedure to treat an acute myocardial infarction [percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)], or to treat a complication resulting from acute myocardial infarction, should also be considered death due to acute myocardial infarction.

Death resulting from a procedure to treat myocardial ischemia (angina) or death due to an acute myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation that was not undertaken to treat an

acute myocardial infarction or its complications should be considered as a death due to other cardiovascular causes.

Sudden Cardiac Death refers to a death that occurs unexpectedly in a previously stable patient. The cause of death should not be due to another adjudicated cause (e.g. acute myocardial infarction Type 3 – see section 5.2 above).

The following deaths should be included.

a. Death witnessed and instantaneous without new or worsening symptoms

b. Death witnessed within 60 minutes of the onset of new or worsening symptoms unless a cause other than cardiac is obvious.

c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor), or unwitnessed but found on implantable cardioverter-defibrillator review.

d. Death in patients resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, including acute myocardial infarction, and who die (without identification of a non-cardiac aetiology) within 72 hours or without gaining consciousness; similar patients who died during an attempted resuscitation.

e. Unwitnessed death without any other cause of death identified (information regarding the patient's clinical status in the 24 hours preceding death should be provided, if available)

Sudden cardiac death events will be further subclassifed by the CEC as:

3) Sudden cardiac death due to a documented arrhythmia
   (i.e. arrhythmia adjudged to be the primary terminal event ***and*** documented evidence of the arrhythmia)

4) "Other" sudden cardiac death (i.e. not classifiable as being due to a documented arrhythmia)
   [e.g. insufficient evidence to suggest that an arrhythmia was the primary terminal event and/or no documented evidence of an arrhythmia]

Death due to Heart Failure refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death (e.g. acute myocardial infarction).

Death due to heart failure should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of heart failure include any of the following:

a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure

Note: If time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the CEC will adjudicate on clinical presentation and, if available, investigative evidence.

b. Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema.

c. Confinement to bed predominantly due to heart failure symptoms.

d. Pulmonary edema sufficient to cause tachypnea and distress **not** occurring in the context of an acute myocardial infarction, worsening renal function (that is not wholly explained by worsening heart failure/cardiac function) or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

e. Cardiogenic shock **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

Death due to Stroke refers to death after a documented stroke (verified by the diagnostic criteria outlined above for stroke or by typical post mortem findings) that is either a direct consequence of the stroke or a complication of the stroke and where there is no conclusive evidence of another cause of death.

NOTE : In cases of early death where confirmation of the diagnosis cannot be obtained, the CEC may adjudicate based on clinical presentation alone.

Death due to a stroke reported to occur as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories [e.g. pulmonary embolism, cardiovascular intervention (other than one performed to treat an acute myocardial infarction or a complication of an acute myocardial infarction – see definition of death due to myocardial infarction, above), aortic aneurysm rupture, or peripheral arterial disease]. Mortal complications of cardiac surgery or non-surgical revascularisation should be classified as cardiovascular deaths.

5.3.5 Non-cardiovascular deaths

A non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. There should be unequivocal and documented evidence of a non-cardiovascular cause of death.

Further subclassification of non-cardiovascular death will be as follows:

- Pulmonary
- Renal
- Gastrointestinal
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Malignancy
- Hemorrhage, not intracranial
- Accidental/Trauma
- Suicide
- Non-cardiovascular surgery
- Other non-cardiovascular, specify

5.3.6 Undertermined cause of death

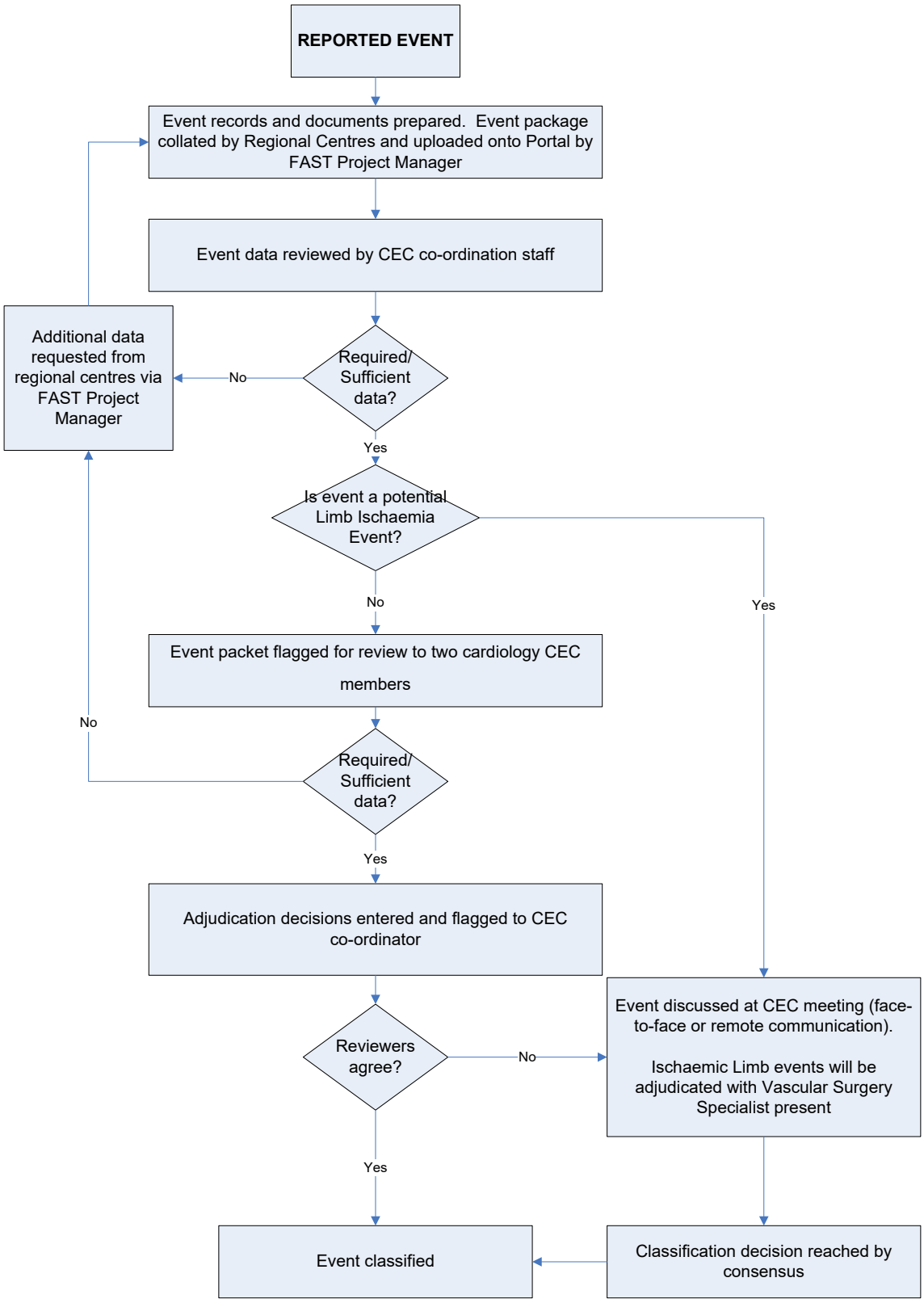
This refers to any death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause (e.g. due to lack of information such as a case where the only information available is “patient died”). It is expected that every effort will be made to provide the adjudicating committee with enough information to attribute deaths to either a cardiovascular or non-cardiovascular cause so that the use of this category is kept to a minimal number of patients.

6 Approvals

The following CEC and Sponsor representatives have approved this Charter.

Signature	**Date**
Prof. John McMurray CEC Chair	
Dr. Eugene Connolly CEC Coordinating Physician	
Professor Tom MacDonald CI FAST Trial	

Appendix A. Adjudication process flowchart



Appendix B. Essential Documentation Checklist

Type of Document	Included (√/X)	Page(s) in PDF
Clinical notes		
Referral letter		
Clinical written in-patient notes		
In-patient prescription charts		
Correspondence/letters		
Discharge letters Immediate discharge letter		
Other discharge letter (or letter to GP after death in hospital)		
Resuscitation report/records		
Post mortem report (if applicable)		
Death certificate (if applicable)		
Investigation Results		
Biochemistry Individual results forms		
Haematology Individual results forms		
Other lab results (specify e.g. Microbiol, Pathol)		
ECGs Pre-admission		
During admission		
Post-admission		
ECG rhythm strips if available (specify before, during, after event)		
CXRs Pre-admission		
During admission		
Post-admission		
Echocardiogram report		
Type of Document	**Included (√/X)**	**Page(s) in PDF**

Cardiac enzymes/markers CKMB		
Troponin I		
Troponin T		
BNP or TN- proBNP		
Exercise ECG/ETT report		
Myocardial perfusion scan report		
Radionuclide ventriculogram/MUGA scan report		
Cardiovascular procedure reports for cardiac vessels e.g. coronary angiogram, angioplasty, coronary artery bypass grafting, etc (specify)		
Cardiovascular procedure reports for rhythm problem e.g. electrophysiology (EP) study, pacemaker/defibrillator implantation.		
CT brain report		
MRI brain report		
Cerebral angiogram report		
Lumbar puncture report		
Carotid ultrasound report		
D-dimer result		
Arterial blood gas measurements		
Ultrasound of limb report e.g. Doppler of leg		
Venography of limb report		
Ventilation-perfusion (VQ) scan report		
CT pulmonary angiogram (CTPA) report		
Invasive pulmonary angiogram report		
Other operation / procedure report e.g. thrombectomy / embolectomy		
Haemodynamic / physiological tests e.g. arterial Doppler, ankle systolic blood pressure, ankle-brachial pressure index (ABPI)		
Invasive peripheral artery angiography report		
Other peripheral artery imaging reports e.g. CT angiography, MR angiography, duplex US.		
Vascular operation or procedure reports e.g. limb revascularization, amputation.		
Other significant reports (please specify)		

Appendix C. ICD and OPCS CODES

Potential endpoints of interest to the CEC will be identified by searching electronically for the following codes:

CODE type	Code	Description
DISEASE CODES		
CHEST PAINS		
ICD10	R07.0	Pain in throat
ICD10	R07.1	Chest pain on breathing/painful respiration
ICD10	R07.2	Precordial pain
ICD10	R07.3	Other chest pain/anterior chest wall pain
ICD10	R07.4	Chest pain unspecified
CORONARY HEART DISEASE		
STABLE ANGINA		
ICD10	I20	Angina pectoris
ICD10	I25	Chronic ischaemic heart disease
ICD10	I250	Atherosclerotic cardiovascular disease, so described
ICD10	I251	Atherosclerotic heart disease
ICD10	I209	Angina pectoris, unspecified
ICD10	I201	Angina pectoris with documented spasm
ICD10	I258	Other forms of chronic ischaemic heart disease
ICD10	I259	Chronic ischaemic heart disease, unspecified
ICD10	I208	Other forms of angina pectoris

ACUTE CORONARY SYNDROMES

ICD10	I200	Unstable angina
ICD10	I21	Acute myocardial infarction
ICD10	I210	Acute transmural myocardial infarction of anterior wall
ICD10	I211	Acute transmural myocardial infarction of inferior wall
ICD10	I212	Acute transmural myocardial infarction of other sites
ICD10	I213	Acute transmural myocardial infarction of unspecified site
ICD10	I214	Acute subendocardial myocardial infarction
ICD10	I219	Acute myocardial infarction, unspecified
ICD10	I22	Subsequent myocardial infarction
ICD10	I220	Subsequent myocardial infarction of anterior wall
ICD10	I221	Subsequent myocardial infarction of inferior wall
ICD10	I248	Other forms of acute ischaemic heart disease
ICD10	I249	Acute ischaemic heart disease, unspecified
ICD10	I24	Other acute ischaemic heart diseases
ICD10	I240	Coronary thrombosis not resulting in myocardial infarction
ICD10	I228	Subsequent myocardial infarction of other sites
ICD10	I229	Subsequent myocardial infarction of unspecified site

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

ICD10	I23	Certain current complication follow acute myocardial infarct
ICD10	I230	Haemopericardium as curr comp folow acut myocard infarct
ICD10	I231	Atral sept defect as curr comp folow acut myocardal infarct
ICD10	I232	Ventric sep defect as curr comp fol acut myocardal infarc
ICD10	I233	Rup cardac wal withou haemopercard as cur comp fol ac MI
ICD10	I234	Rup chordae tendinae as curr comp fol acut myocard infarct
ICD10	I235	Rup papilary muscle as curr comp fol acute myocard infarct
ICD10	I236	Thromb atrium/auric append/vent as curr comp foll acute MI
ICD10	I238	Oth current comp following acute myocardial infarction
ICD10	I241	Dressler's syndrome
ICD10	I253	Aneurysm of heart

ICD10	I510	Cardiac septal defect, acquired
ICD10	I511	Rupture of chordae tendineae, not elsewhere classified
ICD10	I512	Rupture of papillary muscle, not elsewhere classified
ICD10	I513	Intracardiac thrombosis, not elsewhere classified
PREVIOUS MYOCARDIAL INFARCTION		
ICD10	I252	Old myocardial infarction
OTHER CORONARY HEART DISEASE		
ICD10	I254	Coronary artery aneurysm
ICD10	I256	Silent myocardial ischaemia

CEREBROVASCULAR DISEASES		
ICD10	I60	Subarachnoid haemorrhage
ICD10	I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
ICD10	I601	Subarachnoid haemorrhage from middle cerebral artery
ICD10	I602	Subarachnoid haemorrhage from anterior communicating artery
ICD10	I603	Subarachnoid haemorrhage from posterior communicating artery
ICD10	I604	Subarachnoid haemorrhage from basilar artery
ICD10	I605	Subarachnoid haemorrhage from vertebral artery
ICD10	I606	Subarachnoid haemorrhage from other intracranial arteries
ICD10	I607	Subarachnoid haemorrhage from intracranial artery, unspec
ICD10	I608	Other subarachnoid haemorrhage
ICD10	I609	Subarachnoid haemorrhage, unspecified
ICD10	I61	Intracerebral haemorrhage
ICD10	I610	Intracerebral haemorrhage in hemisphere, subcortical
ICD10	I611	Intracerebral haemorrhage in hemisphere, cortical
ICD10	I612	Intracerebral haemorrhage in hemisphere, unspecified
ICD10	I613	Intracerebral haemorrhage in brain stem
ICD10	I614	Intracerebral haemorrhage in cerebellum
ICD10	I615	Intracerebral haemorrhage, intraventricular
ICD10	I616	Intracerebral haemorrhage, multiple localized
ICD10	I618	Other intracerebral haemorrhage

ICD10	I619	Intracerebral haemorrhage, unspecified
ICD10	I62	Other nontraumatic intracranial haemorrhage
ICD10	I620	Subdural haemorrhage (acute)(nontraumatic)
ICD10	I621	Nontraumatic extradural haemorrhage
ICD10	I629	Intracranial haemorrhage (nontraumatic), unspecified
ICD10	I63	Cerebral infarction
ICD10	I630	Cerebral infarct due to thrombosis of precerebral arteries
ICD10	I631	Cerebral infarction due to embolism of precerebral arteries
ICD10	I632	Cereb infarct due unsp occlusion or stenos precerebrl arts
ICD10	I633	Cerebral infarction due to thrombosis of cerebral arteries
ICD10	I634	Cerebral infarction due to embolism of cerebral arteries
ICD10	I635	Cerebrl infarct due unspec occlusion or stenos cerebrl arts
ICD10	I636	Cereb infarct due cerebral venous thrombosis, nonpyogenic
ICD10	I638	Other cerebral infarction
ICD10	I639	Cerebral infarction, unspecified
ICD10	I64X	Stroke, not specified as haemorrhage or infarction
ICD10	I65	Occlusion/stenos precerebral arts not result cerebrl infarct
ICD10	I650	Occlusion and stenosis of vertebral artery
ICD10	I651	Occlusion and stenosis of basilar artery
ICD10	I652	Occlusion and stenosis of carotid artery
ICD10	I653	Occlusion and stenosis of multip and bilat precerebrl arts
ICD10	I658	Occlusion and stenosis of other precerebral artery
ICD10	I659	Occlusion and stenosis of unspecified precerebral artery
ICD10	G45	Transient ischaemic attack/transient cerebral ischaemia
ICD10	I66	Occlusion/stenosis cerebral arts not result cerebral infarct
ICD10	I660	Occlusion and stenosis of middle cerebral artery
ICD10	I661	Occlusion and stenosis of anterior cerebral artery
ICD10	I662	Occlusion and stenosis of posterior cerebral artery
ICD10	I663	Occlusion and stenosis of cerebellar arteries
ICD10	I664	Occlusion and stenosis of multiple and bilat cerebrl arts
ICD10	I668	Occlusion and stenosis of other cerebral artery
ICD10	I669	Occlusion and stenosis of unspecified cerebral artery
ICD10	I67	Other cerebrovascular diseases

ICD10	I670	Dissection of cerebral arteries, nonruptured
ICD10	I671	Cerebral aneurysm, nonruptured
ICD10	I672	Cerebral atherosclerosis
ICD10	I673	Progressive vascular leukoencephalopathy
ICD10	I674	Hypertensive encephalopathy
ICD10	I675	Moyamoya disease
ICD10	I676	Nonpyogenic thrombosis of intracranial venous system
ICD10	I677	Cerebral arteritis, not elsewhere classified
ICD10	I678	Other specified cerebrovascular diseases
ICD10	I679	Cerebrovascular disease, unspecified
ICD10	I68	Cerebrovascular disorders in diseases classified elsewhere
ICD10	I680A	Cerebral amyloid angiopathy
ICD10	I681A	Cerebral arteritis in infect & parasit dis classif elsewh
ICD10	I682A	Cerebral arteritis in other diseases classified elsewhere
ICD10	I688A	Other cerebrovascular disorders in diseases EC
ICD10	I69	Sequelae of cerebrovascular disease
ICD10	I690	Sequelae of subarachnoid haemorrhage
ICD10	I691	Sequelae of intracerebral haemorrhage
ICD10	I692	Sequelae of other nontraumatic intracranial haemorrhage
ICD10	I693	Sequelae of cerebral infarction
ICD10	I694	Sequelae of stroke, not spec as haemorrhage or infarction
ICD10	I698	Sequelae of other and unspecified cerebrovascular diseases
ICD10	I70	Atherosclerosis
ICD10	G45	Transient cerebral ischaemic attacks and related syndromes
ICD10	G450	Vertebro-basilar artery syndrome
ICD10	G451	Carotid artery syndrome (hemispheric)
ICD10	G452	Multiple and bilateral precerebral artery syndromes
ICD10	G453	Amaurosis fugax
ICD10	G454	Transient global amnesia
ICD10	G458	Other transient cerebral ischaemic attacks and related synd
ICD10	G459	Transient cerebral ischaemic attack, unspecified

ICD10	G46	Vascular syndromes of brain in cerebrovascular diseases
ICD10	G460	Middle cerebral artery syndrome
ICD10	G461A	Anterior cerebral artery syndrome
ICD10	G462A	Posterior cerebral artery syndrome
ICD10	G463A	Brain stem stroke syndrome
ICD10	G464A	Cerebellar stroke syndrome
ICD10	G465A	Pure motor lacunar syndrome
ICD10	G466A	Pure sensory lacunar syndrome
ICD10	G467A	Other lacunar syndromes
ICD10	G468A	Oth vascular syndromes of brain in cerebrovascular dis

HEART FAILURE SYNDROMES

ICD10	I50	Heart failure
ICD10	I500	Congestive heart failure
ICD10	I501	Left ventricular failure
ICD10	I509	Heart failure, unspecified
ICD10	J81	Pulmonary oedema

CARDIOMYOPATHIES

ICD10	I42	Cardiomyopathy
ICD10	I420	Dilated cardiomyopathy
ICD10	I255	Ischaemic cardiomyopathy
ICD10	I421	Obstructive hypertrophic cardiomyopathy
ICD10	I422	Other hypertrophic cardiomyopathy
ICD10	I423	Endomyocardial (eosinophilic) disease
ICD10	I424	Endocardial fibroelastosis
ICD10	I425	Other restrictive cardiomyopathy
ICD10	I426	Alcoholic cardiomyopathy
ICD10	I427	Cardiomyopathy due to drugs and other external agents
ICD10	I428	Other cardiomyopathies
ICD10	I429	Cardiomyopathy, unspecified
ICD10	I43	Cardiomyopathy in diseases classified elsewhere
ICD10	I430A	Cardiomyopathy in infectious & parasitic diseases CE
ICD10	I431A	Cardiomyopathy in metabolic diseases

ICD10	I432A	Cardiomyopathy in nutritional diseases
ICD10	I438A	Cardiomyopathy in other diseases classified elsewhere

SHOCK (NOT ELSEWHERE CLASSFIED)

ICD10	R57	Shock, not elsewhere classified
ICD10	R570	Cardiogenic shock
ICD10	R571	Hypovolaemic shock
ICD10	R578	Other shock
ICD10	R579	Shock, unspecified

HYPERTENSION AND RELATED CONDITIONS

ICD10	I11	Hypertensive heart disease
ICD10	I110	Hypertensive heart disease with (congestive) heart failure
ICD10	I119	Hypertensive heart disease without (conges) heart failure
ICD10	I12	Hypertensive renal disease
ICD10	I120	Hypertensive renal disease with renal failure
ICD10	I129	Hypertensive renal disease without renal failure
ICD10	I13	Hypertensive heart and renal disease
ICD10	I130	Hypertens heart and renal dis with (conges) heart failure
ICD10	I131	Hypertensive heart and renal disease with renal failure
ICD10	I132	Hyper heart and renal dis both (cong) heart and renal fail
ICD10	I139	Hypertensive heart and renal disease, unspecified
ICD10	I15	Secondary hypertension
ICD10	I150	Renovascular hypertension
ICD10	I151	Hypertension secondary to other renal disorders
ICD10	I152	Hypertension secondary to endocrine disorders
ICD10	I158	Other secondary hypertension
ICD10	I674	Hypertensive encephalopathy
ICD10	I159	Secondary hypertension, unspecified

HEART VALVE DISORERS AND RELATED CONDITIONS

ICD10	I00X	Rheumatic fever without mention of heart involvement
ICD10	I01	Rheumatic fever with heart involvement
ICD10	I010	Acute rheumatic pericarditis

ICD10	I011	Acute rheumatic endocarditis
ICD10	I012	Acute rheumatic myocarditis
ICD10	I018	Other acute rheumatic heart disease
ICD10	I019	Acute rheumatic heart disease, unspecified
ICD10	I02	Rheumatic chorea
ICD10	I020	Rheumatic chorea with heart involvement
ICD10	I029	Rheumatic chorea without heart involvement
ICD10	I05	Rheumatic mitral valve diseases
ICD10	I050	Mitral stenosis
ICD10	I051	Rheumatic mitral insufficiency
ICD10	I052	Mitral stenosis with insufficiency
ICD10	I058	Other mitral valve diseases
ICD10	I059	Mitral valve disease, unspecified
ICD10	I34	Nonrheumatic mitral valve disorders
ICD10	I340	Mitral (valve) insufficiency
ICD10	I341	Mitral (valve) prolapse
ICD10	I342	Nonrheumatic mitral (valve) stenosis
ICD10	I348	Other nonrheumatic mitral valve disorders
ICD10	I349	Nonrheumatic mitral valve disorder, unspecified
ICD10	I35	Nonrheumatic aortic valve disorders
ICD10	I350	Aortic (valve) stenosis
ICD10	I351	Aortic (valve) insufficiency
ICD10	I352	Aortic (valve) stenosis with insufficiency
ICD10	I358	Other aortic valve disorders
ICD10	I359	Aortic valve disorder, unspecified
ICD10	I06	Rheumatic aortic valve diseases
ICD10	I060	Rheumatic aortic stenosis
ICD10	I061	Rheumatic aortic insufficiency
ICD10	I062	Rheumatic aortic stenosis with insufficiency
ICD10	I068	Other rheumatic aortic valve diseases
ICD10	I069	Rheumatic aortic valve disease, unspecified
ICD10	I07	Rheumatic tricuspid valve diseases
ICD10	I070	Tricuspid stenosis
ICD10	I071	Tricuspid insufficiency

ICD10	I072	Tricuspid stenosis with insufficiency
ICD10	I078	Other tricuspid valve diseases
ICD10	I079	Tricuspid valve disease, unspecified
ICD10	I36	Nonrheumatic tricuspid valve disorders
ICD10	I360	Nonrheumatic tricuspid (valve) stenosis
ICD10	I361	Nonrheumatic tricuspid (valve) insufficiency
ICD10	I362	Nonrheumatic tricuspid (valve) stenosis with insufficiency
ICD10	I368	Other nonrheumatic tricuspid valve disorders
ICD10	I369	Nonrheumatic tricuspid valve disorder, unspecified
ICD10	I08	Multiple valve diseases
ICD10	I080	Disorders of both mitral and aortic valves
ICD10	I081	Disorders of both mitral and tricuspid valves
ICD10	I082	Disorders of both aortic and tricuspid valves
ICD10	I083	Combined disorders of mitral, aortic and tricuspid valves
ICD10	I088	Other multiple valve diseases
ICD10	I089	Multiple valve disease, unspecified
ICD10	I09	Other rheumatic heart diseases
ICD10	I090	Rheumatic myocarditis
ICD10	I091	Rheumatic diseases of endocardium, valve unspecified
ICD10	I092	Chronic rheumatic pericarditis
ICD10	I098	Other specified rheumatic heart diseases
ICD10	I099	Rheumatic heart disease, unspecified
ICD10	I37	Pulmonary valve disorders
ICD10	I370	Pulmonary valve stenosis
ICD10	I371	Pulmonary valve insufficiency
ICD10	I372	Pulmonary valve stenosis with insufficiency
ICD10	I378	Other pulmonary valve disorders
ICD10	I379	Pulmonary valve disorder, unspecified
ICD10	I390A	Mitral valve disorders in diseases classified elsewhere
ICD10	I391A	Aortic valve disorders in diseases classified elsewhere
ICD10	I392A	Tricuspid valve disorders in diseases classified elsewhere
ICD10	I393A	Pulmonary valve disorders in diseases classified elsewhere
ICD10	I394A	Multiple valve disorders in diseases classified elsewhere

PULMONARY CIRCULATORY DISEASE

ICD10	I26	Pulmonary embolism
ICD10	I260	Pulmonary embolism with mention of acute cor pulmonale
ICD10	I269	Pulmonary embolism without mention of acute cor pulmonale
ICD10	I27	Other pulmonary heart diseases
ICD10	I270	Primary pulmonary hypertension
ICD10	I271	Kyphoscoliotic heart disease
ICD10	I278	Other specified pulmonary heart diseases
ICD10	I279	Pulmonary heart disease, unspecified
ICD10	I28	Other diseases of pulmonary vessels
ICD10	I280	Arteriovenous fistula of pulmonary vessels
ICD10	I281	Aneurysm of pulmonary artery
ICD10	I288	Other specified diseases of pulmonary vessels
ICD10	I289	Disease of pulmonary vessels, unspecified

PERICARDIAL DISEASES

ICD10	I30	Acute pericarditis
ICD10	I300	Acute nonspecific idiopathic pericarditis
ICD10	I301	Infective pericarditis
ICD10	I308	Other forms of acute pericarditis
ICD10	I309	Acute pericarditis, unspecified
ICD10	I31	Other diseases of pericardium
ICD10	I310	Chronic adhesive pericarditis
ICD10	I311	Chronic constrictive pericarditis
ICD10	I312	Haemopericardium, not elsewhere classified
ICD10	I313	Pericardial effusion (noninflammatory)
ICD10	I318	Other specified diseases of pericardium
ICD10	I319	Disease of pericardium, unspecified
ICD10	I32	Pericarditis in diseases classified elsewhere
ICD10	I320A	Pericarditis in bacterial diseases classified elsewhere
ICD10	I321A	Pericarditis in other infectious and parasitic diseases EC
ICD10	I328A	Pericarditis in other diseases classified elsewhere

ENDOCARDITIS AND CARDIAC INFECTIONS

ICD10	I33	Acute and subacute endocarditis
ICD10	I330	Acute and subacute infective endocarditis
ICD10	I398A	Endocarditis, valve unspec, in diseases class elsewhere
ICD10	I339	Acute endocarditis, unspecified
ICD10	I38X	Endocarditis, valve unspecified
ICD10	I39	Endocarditis and heart valve disorders in diseases EC
ICD10	I520A	Other heart disorders in bacterial diseases EC
ICD10	I521A	Oth heart disorders in oth infectious and parasitic dis EC
ICD10	I980A	Cardiovascular syphilis
ICD10	I981A	Cardiovascular disorder other infectious and parasitic dis

MYOCARDITIS

ICD10	I40	Acute myocarditis
ICD10	I400	Infective myocarditis
ICD10	I401	Isolated myocarditis
ICD10	I408	Other acute myocarditis
ICD10	I409	Acute myocarditis, unspecified
ICD10	I41	Myocarditis in diseases classified elsewhere
ICD10	I410A	Myocarditis in bacterial diseases classified elsewhere
ICD10	I411A	Myocarditis in viral diseases classified elsewhere
ICD10	I412A	Myocarditis in other infectious and parasitic diseases EC
ICD10	I514	Myocarditis, unspecified
ICD10	I418A	Myocarditis in other diseases classified elsewhere

CARDIAC CONDUCTING SYSTEM DISEASE		SE
ICD10	I441	Atrioventricular block, second degree
ICD10	I442	Atrioventricular block, complete

CARDIAC ARREST

ICD10	I46	Cardiac arrest
ICD10	I460	Cardiac arrest with successful resuscitation
ICD10	I461	Sudden cardiac death, so described

ICD10	I469	Cardiac arrest, unspecified

CARDIAC ARRYTHMIAS

ICD10	I47	Paroxysmal tachycardia
ICD10	I470	Re-entry ventricular arrhythmia
ICD10	I471	Supraventricular tachycardia
ICD10	I472	Ventricular tachycardia
ICD10	I479	Paroxysmal tachycardia, unspecified
ICD10	I48X	Atrial fibrillation and flutter
ICD10	I49	Other cardiac arrhythmias
ICD10	I490	Ventricular fibrillation and flutter
ICD10	I495	Sick sinus syndrome
ICD10	I498	Other specified cardiac arrhythmias
ICD10	I499	Cardiac arrhythmia, unspecified

DISEASES OF THE AORTA

ICD10	I71	Aortic aneurysm and dissection
ICD10	I710	Dissection of aorta [any part]
ICD10	I711	Thoracic aortic aneurysm, ruptured
ICD10	I712	Thoracic aortic aneurysm, without mention of rupture
ICD10	I713	Abdominal aortic aneurysm, ruptured
ICD10	I714	Abdominal aortic aneurysm, without mention of rupture
ICD10	I715	Thoracoabdominal aortic aneurysm, ruptured
ICD10	I716	Thoracoabdominal aortic aneurysm, without mention of rupture
ICD10	I718	Aortic aneurysm of unspecified site, ruptured
ICD10	I719	Aortic aneurysm of unspec site, without mention of rupture
ICD10	I72	Other aneurysm
ICD10	I790A	Aneurysm of aorta in diseases classified elsewhere
ICD10	I791A	Aortitis in diseases classified elsewhere

PERIPHERAL ARTERIAL AND VENOUS DISEASES

ICD10	I702	Atherosclerosis of arteries of extremities

ICD10	I708	Atherosclerosis of other arteries
ICD10	I720	Aneurysm of carotid artery
ICD10	I721	Aneurysm of artery of upper extremity
ICD10	I722	Aneurysm of renal artery
ICD10	I723	Aneurysm of iliac artery
ICD10	I724	Aneurysm of artery of lower extremity
ICD10	I728	Aneurysm of other specified arteries
ICD10	I729	Aneurysm of unspecified site
ICD10	I730	Raynaud's syndrome
ICD10	I731	Thromboangiitis obliterans [Buerger]
ICD10	I738	Other specified peripheral vascular diseases
ICD10	I739	Peripheral vascular disease, unspecified
ICD10	I74	Arterial embolism and thrombosis
ICD10	I740	Embolism and thrombosis of abdominal aorta
ICD10	I741	Embolism and thrombosis of other and unspec parts of aorta
ICD10	I742	Embolism and thrombosis of arteries of upper extremities
ICD10	I743	Embolism and thrombosis of arteries of lower extremities
ICD10	I744	Embolism and thrombosis of arteries of extremities, unspec
ICD10	I745	Embolism and thrombosis of iliac artery
ICD10	I748	Embolism and thrombosis of other arteries
ICD10	I749	Embolism and thrombosis of unspecified artery
ICD10	I77	Other disorders of arteries and arterioles
ICD10	I770	Arteriovenous fistula, acquired
ICD10	I771	Stricture of artery
ICD10	I772	Rupture of artery
ICD10	I776	Arteritis, unspecified
ICD10	I778	Other specified disorders of arteries and arterioles
ICD10	I80	Phlebitis and thrombophlebitis
ICD10	I800	Phlebitis/thrombophlebitis superfic vessels low extremties
ICD10	I801	Phlebitis and thrombophlebitis of femoral vein
ICD10	I802	Phlebitis/thrombophlebitis oth deep vessels low extremties
ICD10	I803	Phlebitis and thrombophlebitis of lower extremities, unspec

ICD10	I808	Phlebitis and thrombophlebitis of other sites
ICD10	I809	Phlebitis and thrombophlebitis of unspecified site
ICD10	I82	Other venous embolism and thrombosis
ICD10	I821	Thrombophlebitis migrans
ICD10	I822	Embolism and thrombosis of vena cava
ICD10	I823	Embolism and thrombosis of renal vein
ICD10	I828	Embolism and thrombosis of other specified veins
ICD10	I829	Embolism and thrombosis of unspecified vein

VARIOUS NON SPECIFIC CODES

ICD10	I515	Myocardial degeneration
ICD10	I516	Cardiovascular disease, unspecified
ICD10	I517	Cardiomegaly
ICD10	I518	Other ill-defined heart diseases
ICD10	I519	Heart disease, unspecified
ICD10	I52	Other heart disorders in diseases classified elsewhere
ICD10	I51	Complications and ill-defined descriptions of heart disease
ICD10	I528A	Other heart disorders in other diseases classified elsewhere
ICD10	I97	Postprocedural disorders of circulatory system NEC
ICD10	I970	Postcardiotomy syndrome
ICD10	I971	Other functional disturbances following cardiac surgery
ICD10	I978	Other postprocedural disorders of circulatory system NEC
ICD10	I979	Postprocedural disorder of circulatory system, unspecified
ICD10	I98	Other disorders of circulatory system in diseases EC
ICD10	I988A	Other specified disorders of circulatory system in dis EC
ICD10	I99X	Other and unspecified disorders of circulatory system

PROCEDURE CODES

CARDIAC SURGICAL PROCEDURES

CORONARY ARTERY SURGERY

OPCS4.4	K40.1	Saphenous vein graft replacement of one coronary artery
OPCS4.4	K40.2	Saphenous vein graft replacement of two coronary arteries

OPCS4.4	K40.3	Saphenous vein graft replacement of three coronary arteries
OPCS4.4	K40.4	Saphenous vein graft replacement of four or more coronary arteries
OPCS4.4	K40.8	Other specified saphenous vein graft replacement of coronary artery
OPCS4.4	K40.9	Unspecified saphenous vein graft replacement of coronary artery
OPCS4.4	K41.1	Autograft replacement of one coronary artery NEC
OPCS4.4	K41.2	Autograft replacement of two coronary arteries NEC
OPCS4.4	K41.3	Autograft replacement of three coronary arteries NEC
OPCS4.4	K41.4	Autograft replacement of four or more coronary arteries NEC
OPCS4.4	K41.8	Other specified other autograft replacement of coronary artery
OPCS4.4	K41.9	Unspecified other autograft replacement of coronary artery
OPCS4.4	K42.1	Allograft replacement of one coronary artery
OPCS4.4	K42.2	Allograft replacement of two coronary arteries
OPCS4.4	K42.3	Allograft replacement of three coronary arteries
OPCS4.4	K42.4	Allograft replacement of four or more coronary arteries
OPCS4.4	K42.8	Other specified allograft replacement of coronary artery
OPCS4.4	K42.9	Unspecified allograft replacement of coronary artery
OPCS4.4	K43.1	Prosthetic replacement of one coronary artery
OPCS4.4	K43.2	Prosthetic replacement of two coronary arteries
OPCS4.4	K43.3	Prosthetic replacement of three coronary arteries
OPCS4.4	K43.4	Prosthetic replacement of four or more coronary arteries
OPCS4.4	K43.8	Other specified prosthetic replacement of coronary artery
OPCS4.4	K43.9	Unspecified prosthetic replacement of coronary artery
OPCS4.4	K44.1	Replacement of coronary arteries using multiple methods
OPCS4.4	K44.2	Revision of replacement of coronary artery
OPCS4.4	K44.8	Other specified other replacement of coronary artery
OPCS4.4	K44.9	Unspecified other replacement of coronary artery
OPCS4.4	K45.1	Double anastomosis of mammary arteries to coronary arteries
OPCS4.4	K45.2	Double anastomosis of thoracic arteries to coronary arteries NEC

OPCS4.4	K45.3	Anastomosis of mammary artery to left anterior descending coronary artery
OPCS4.4	K45.4	Anastomosis of mammary artery to coronary artery NEC
OPCS4.4	K45.5	Anastomosis of thoracic artery to coronary artery NEC
OPCS4.4	K45.6	Revision of connection of thoracic artery to coronary artery
OPCS4.4	K45.8	Other specified connection of thoracic artery to coronary artery
OPCS4.4	K45.9	Unspecified connection of thoracic artery to coronary artery
OPCS4.4	K46.1	Double implantation of mammary arteries into heart
OPCS4.4	K46.2	Double implantation of thoracic arteries into heart NEC
OPCS4.4	K46.3	Implantation of mammary artery into heart NEC
OPCS4.4	K46.4	Implantation of thoracic artery into heart NEC
OPCS4.4	K46.5	Revision of implantation of thoracic artery into heart
OPCS4.4	K46.8	Other specified other bypass of coronary artery
OPCS4.4	K46.9	Unspecified other bypass of coronary artery
OPCS4.4	K47.1	Endarterectomy of coronary artery
OPCS4.4	K47.2	Repair of arteriovenous fistula of coronary a
OPCS4.4	K47.3	Repair of aneurysm of coronary artery
OPCS4.4	K47.4	Repair of rupture of coronary artery
OPCS4.4	K47.5	Repair of arteriovenous malformation of coronary artery
OPCS4.4	K47.8	Other specified repair of coronary artery
OPCS4.4	K47.9	Unspecified repair of coronary artery
OPCS4.4	K48.1	Transection of muscle-bridge of coronary artery
OPCS4.4	K48.2	Transposition of coronary artery NEC
OPCS4.4	K48.3	Open angioplasty of coronary artery
OPCS4.4	K48.4	Exploration of coronary artery
OPCS4.4	K48.8	Other specified other open operations on coronary artery
OPCS4.4	K48.9	Unspecified other open operations on coronary artery

TRANSPLANTATION PROCEDURES

OPCS4.4	K01.1	Allotransplantation of heart and lung
OPCS4.4	K01.2	Revision of transplantation of heart and lung
OPCS4.4	K01.8	Other specified transplantation of heart and lung
OPCS4.4	K01.9	Unspecified transplantation of heart and lung

OPCS4.4	K02.1	Allotransplantation of heart NEC
OPCS4.4	K02.2	Xenotransplantation of heart
OPCS4.4	K02.3	Implantation of prosthetic heart
OPCS4.4	K02.4	Piggy back transplantation of heart
OPCS4.4	K02.5	Revision of implantation of prosthetic heart
OPCS4.4	K02.6	Revision of transplantation of heart NEC
OPCS4.4	K02.8	Other specified other transplantation of heart
OPCS4.4	K02.9	Unspecified other transplantation of heart

VALVE CARDIAC SURGERY

OPCS4.4	K25.1	Allograft replacement of mitral valve
OPCS4.4	K25.2	Xenograft replacement of mitral valve
OPCS4.4	K25.3	Prosthetic replacement of mitral valve
OPCS4.4	K25.4	Replacement of mitral valve NEC
OPCS4.4	K25.5	Mitral valve repair NEC
OPCS4.4	K25.8	Other specified plastic repair of mitral valve
OPCS4.4	K25.9	Unspecified plastic repair of mitral valve
OPCS4.4	K26.1	Allograft replacement of aortic valve
OPCS4.4	K26.2	Xenograft replacement of aortic valve
OPCS4.4	K26.3	Prosthetic replacement of aortic valve
OPCS4.4	K26.4	Replacement of aortic valve NEC
OPCS4.4	K26.5	Aortic valve repair NEC
OPCS4.4	K26.8	Other specified plastic repair of aortic valve
OPCS4.4	K26.9	Unspecified plastic repair of aortic valve
OPCS4.4	K27.1	Allograft replacement of tricuspid valve
OPCS4.4	K27.2	Xenograft replacement of tricuspid valve
OPCS4.4	K27.3	Prosthetic replacement of tricuspid valve
OPCS4.4	K27.4	Replacement of tricuspid valve NEC
OPCS4.4	K27.5	Repositioning of tricuspid valve
OPCS4.4	K27.6	Tricuspid valve repair NEC
OPCS4.4	K27.8	Other specified plastic repair of tricuspid valve
OPCS4.4	K27.9	Unspecified plastic repair of tricuspid valve
OPCS4.4	K28.1	Allograft replacement of pulmonary valve
OPCS4.4	K28.2	Xenograft replacement of pulmonary valve

OPCS4.4	K28.3	Prosthetic replacement of pulmonary valve
OPCS4.4	K28.4	Replacement of pulmonary valve NEC
OPCS4.4	K28.5	Pulmonary valve repair NEC
OPCS4.4	K28.8	Other specified plastic repair of pulmonary valve
OPCS4.4	K28.9	Unspecified plastic repair of pulmonary valve
OPCS4.4	K29.1	Allograft replacement of valve of heart NEC
OPCS4.4	K29.2	Xenograft replacement of valve of heart NEC
OPCS4.4	K29.3	Prosthetic replacement of valve of heart NEC
OPCS4.4	K29.4	Replacement of valve of heart NEC
OPCS4.4	K29.5	Repair of valve of heart NEC
OPCS4.4	K29.6	Truncal valve repair
OPCS4.4	K29.7	Replacement of truncal valve
OPCS4.4	K29.8	Other specified plastic repair of unspecified valve of heart
OPCS4.4	K29.9	Unspecified plastic repair of unspecified valve of heart
OPCS4.4	K30.1	Revision of plastic repair of mitral valve
OPCS4.4	K30.2	Revision of plastic repair of aortic valve
OPCS4.4	K30.3	Revision of plastic repair of tricuspid valve
OPCS4.4	K30.4	Revision of plastic repair of pulmonary valve
OPCS4.4	K30.5	Revision of plastic repair of truncal valve
OPCS4.4	K30.8	Other specified revision of plastic repair of valve of heart
OPCS4.4	K30.9	Unspecified revision of plastic repair of valve of heart
OPCS4.4	K31.1	Open mitral valvotomy
OPCS4.4	K31.2	Open aortic valvotomy
OPCS4.4	K31.3	Open tricuspid valvotomy
OPCS4.4	K31.4	Open pulmonary valvotomy
OPCS4.4	K31.5	Open truncal valvotomy
OPCS4.4	K31.8	Other specified open incision of valve of heart
OPCS4.4	K31.9	Unspecified open incision of valve of heart
OPCS4.4	K32.1	Closed mitral valvotomy
OPCS4.4	K32.2	Closed aortic valvotomy
OPCS4.4	K32.3	Closed tricuspid valvotomy
OPCS4.4	K32.4	Closed pulmonary valvotomy
OPCS4.4	K32.8	Other specified closed incision of valve of heart
OPCS4.4	K32.9	Unspecified closed incision of valve of heart

OPCS4.4	K33.1	Aortic root replacement using pulmonary valve autograft with right ventricle to pulmonary artery valved conduit
OPCS4.4	K33.2	Aortic root replacement using pulmonary valve autograft with right ventricle to pulmonary artery valved conduit and aortoventriculoplasty
OPCS4.4	K33.3	Aortic root replacement using homograft
OPCS4.4	K33.4	Aortic root replacement using mechanical prosthesis
OPCS4.4	K33.5	Aortic root replacement
OPCS4.4	K33.6	Aortoventriculoplasty with pulmonary valve autograft
OPCS4.4	K33.8	Other specified operations on aortic root
OPCS4.4	K33.9	Unspecified operations on aortic root
OPCS4.4	K34.1	Annuloplasty of mitral valve
OPCS4.4	K34.2	Annuloplasty of tricuspid valve
OPCS4.4	K34.3	Annuloplasty of valve of heart NEC
OPCS4.4	K34.4	Excision of vegetations of valve of heart
OPCS4.4	K34.5	Closure of tricuspid valve
OPCS4.4	K34.6	Closure of pulmonary valve
OPCS4.4	K34.8	Other specified other open operations on valve of heart
OPCS4.4	K34.9	Unspecified other open operations on valve of heart

PERCUTANEOUS CLOSURE OF SEPTAL DEFECTS

OPCS4.4	K13.1	Percutaneous transluminal repair of defect of interventricular septum using prosthesis
OPCS4.4	K13.2	Percutaneous transluminal repair of defect of interventricular septum NEC
OPCS4.4	K13.3	Percutaneous transluminal repair of defect of interatrial septum using prosthesis
OPCS4.4	K13.4	Percutaneous transluminal repair of defect of interatrial septum NEC
OPCS4.4	K13.5	Percutaneous transluminal repair of defect of unspecified septum using prosthesis
OPCS4.4	K13.8	Other specified transluminal repair of defect of septum
OPCS4.4	K13.9	Unspecified transluminal repair of defect of septum
OPCS4.4	K16.1	Percutaneous transluminal balloon atrial septostomy
OPCS4.4	K16.2	Percutaneous transluminal atrial septostomy NEC
OPCS4.4	K16.3	Percutaneous transluminal atrial septum fenestration closure with prosthesis

OPCS4.4	K16.4	Percutaneous transluminal atrial septum fenestration
OPCS4.4	K16.5	Percutaneous transluminal closure of patent oval foramen with prosthesis
OPCS4.4	K16.6	Percutaneous transluminal chemical mediated septal ablation
OPCS4.4	K16.8	Other specified other therapeutic transluminal operations on septum of heart
OPCS4.4	K16.9	Unspecified other therapeutic transluminal operations on septum of heart

CARDIAC SURGERY ON CONDUCTING SYSTEM OF HEART

OPCS4.4	K52.1	Open ablation of atrioventricular node
OPCS4.4	K52.2	Epicardial excision of rhythmogenic focus
OPCS4.4	K52.3	Endocardial excision of rhythmogenic focus
OPCS4.4	K52.4	Open division of accessory pathway within heart
OPCS4.4	K52.5	Open division of conducting system of heart NEC
OPCS4.4	K52.6	Incision of tissue in atria
OPCS4.4	K52.8	Other specified open operations on conducting system of heart
OPCS4.4	K52.9	Unspecified open operations on conducting system of heart

INSERTION OF CIRCULATORY SUPPORT DEVICES

OPCS4.4	K54.1	Open implantation of ventricular assist device
OPCS4.4	K54.2	Open removal of ventricular assist device
OPCS4.4	K54.8	Other specifed open heart assist operations
OPCS4.4	K54.9	Unspecified open heart assist operations
OPCS4.4	K56.1	Transluminal insertion of pulsation balloon into aorta
OPCS4.4	K56.2	Transluminal insertion of heart assist system NEC
OPCS4.4	K56.3	Transluminal maintenance of heart assist system
OPCS4.4	K56.4	Transluminal removal of heart assist system
OPCS4.4	K56.8	Other specified transluminal heart assist operations
OPCS4.4	K56.9	Unspecified transluminal heart assist operations

PERCUTANEOUS VALVE PROCEDURES

OPCS4.4	K35.1	Percutaneous transluminal mitral valvotomy
OPCS4.4	K35.2	Percutaneous transluminal aortic valvotomy
OPCS4.4	K35.3	Percutaneous transluminal tricuspid valvotomy
OPCS4.4	K35.4	Percutaneous transluminal pulmonary valvotomy
OPCS4.4	K35.5	Percutaneous transluminal valvuloplasty
OPCS4.4	K35.6	Percutaneous transluminal pulmonary valve perforation and dilation
OPCS4.4	K35.7	Percutaneous transluminal pulmonary valve replacement
OPCS4.4	K35.8	Other specified therapeutic transluminal operations on valve of heart
OPCS4.4	K35.9	Unspecified therapeutic transluminal operations on valve of heart

ELECTROPHYSIOLOGY PROCEDURES

OPCS4.4	K57.1	Percutaneous transluminal ablation of atrioventricular node
OPCS4.4	K57.2	Percutaneous transluminal ablation of conducting system of heart NEC
OPCS4.4	K57.3	Percutaneous transluminal removal of foreign body from heart
OPCS4.4	K57.4	Percutaneous transluminal ablation of accessory pathway
OPCS4.4	K57.5	Percutaneous transluminal ablation of atrial wall
OPCS4.4	K57.6	Percutaneous transluminal ablation of ventricular wall
OPCS4.4	K57.7	Percutaneous transluminal ablation for congenital heart malformation
OPCS4.4	K57.8	Other specified other therapeutic transluminal operations on heart
OPCS4.4	K57.9	Unspecified other therapeutic transluminal operations on heart
OPCS4.4	K58.1	Percutaneous transluminal mapping of conducting system of heart
OPCS4.4	K58.2	Percutaneous transluminal electrophysiological studies on conducting system of heart
OPCS4.4	K58.3	Percutaneous transluminal right ventricular biopsy
OPCS4.4	K58.4	Percutaneous transluminal left ventricular biopsy
OPCS4.4	K58.5	Transluminal intracardiac echocardiography
OPCS4.4	K58.8	Other specified diagnostic transluminal operations on heart

OPCS4.4	K58.9	Unspecified diagnostic transluminal operations on heart

PACEMAKERS AND DEFIBRILLATORS

OPCS4.4	K59.1	Implantation of cardioverter defibrillator using one electrode lead
OPCS4.4	K59.2	Implantation of cardioverter defibrillator using two electrode leads
OPCS4.4	K59.3	Resiting of lead of cardioverter defibrillator
OPCS4.4	K59.4	Renewal of cardioverter defibrillator
OPCS4.4	K59.5	Removal of cardioverter defibrillator
OPCS4.4	K59.8	Other specified cardioverter defibrillator introduced through the vein
OPCS4.4	K59.9	Unspecified cardioverter defibrillator introduced through the vein
OPCS4.4	K60.1	Implantation of intravenous cardiac pacemaker system
OPCS4.4	K60.2	Resiting of lead of intravenous cardiac pacemaker system
OPCS4.4	K60.3	Renewal of intravenous cardiac pacemaker system
OPCS4.4	K60.4	Removal of intravenous cardiac pacemaker system
OPCS4.4	K60.5	Implantation of intravenous single chamber cardiac pacemaker system
OPCS4.4	K60.6	Implantation of intravenous dual chamber cardiac pacemaker system
OPCS4.4	K60.7	Implantation of intravenous biventricular cardiac pacemaker system
OPCS4.4	K60.8	Other specified cardiac pacemaker system introduced through vein
OPCS4.4	K60.9	Unspecified cardiac pacemaker system introduced through vein
OPCS4.4	K61.1	Implantation of cardiac pacemaker system NEC
OPCS4.4	K61.2	Resiting of lead of cardiac pacemaker system NEC
OPCS4.4	K61.3	Renewal of cardiac pacemaker system NEC
OPCS4.4	K61.4	Removal of cardiac pacemaker system NEC
OPCS4.4	K61.5	Implantation of single chamber cardiac pacemaker system
OPCS4.4	K61.6	Implantation of dual chamber cardiac pacemaker system
OPCS4.4	K61.7	Implantation of biventricular cardiac pacemaker system
OPCS4.4	K61.8	Other specified other cardiac pacemaker system
OPCS4.4	K61.9	Unspecified other cardiac pacemaker system

RIGHT AND LEFT HEART CATHETER PROCEDURES

OPCS4.4	K63.1	Angiocardiography of combination of right and left side of heart
OPCS4.4	K63.2	Angiocardiography of right side of heart NEC
OPCS4.4	K63.3	Angiocardiography of left side of heart NEC
OPCS4.4	K63.4	Coronary arteriography using two catheters
OPCS4.4	K63.5	Coronary arteriography using single catheter
OPCS4.4	K63.6	Coronary arteriography NEC
OPCS4.4	K63.8	Other specified contrast radiology of heart
OPCS4.4	K63.9	Unspecified contrast radiology of heart
OPCS4.4	K65.1	Catheterisation of combination of right and left side of heart NEC
OPCS4.4	K65.2	Catheterisation of right side of heart NEC
OPCS4.4	K65.3	Catheterisation of left side of heart NEC
OPCS4.4	K65.4	Catheterisation of left side of heart via atrial transeptal puncture
OPCS4.4	K65.8	Other specified catheterisation of heart
OPCS4.4	K65.9	Unspecified catheterisation of heart

PERICARDIAL PROCEDURES

OPCS4.4	K67.1	Excision of lesion of pericardium
OPCS4.4	K67.8	Other specified excision of pericardium
OPCS4.4	K67.9	Unspecified excision of pericardium
OPCS4.4	K68.1	Decompression of cardiac tamponade
OPCS4.4	K68.2	Pericardiocentesis NEC
OPCS4.4	K68.8	Other specified drainage of pericardium
OPCS4.4	K68.9	Unspecified drainage of pericardium
OPCS4.4	K69.1	Freeing of adhesions of pericardium
OPCS4.4	K69.2	Fenestration of pericardium
OPCS4.4	K69.8	Other specified incision of pericardium
OPCS4.4	K69.9	Unspecified incision of pericardium
OPCS4.4	K71.1	Biopsy of lesion of pericardium
OPCS4.4	K71.2	Repair of pericardium
OPCS4.4	K71.3	Injection of therapeutic substance into pericardium

OPCS4.4	K71.4	Exploration of pericardium
OPCS4.4	K71.8	Other specified other operations on pericardium
OPCS4.4	K77.1	Percutaneous transluminal pericardiocentesis
OPCS4.4	K77.8	Other specified transluminal drainage of pericardium
OPCS4.4	K77.9	Unspecified transluminal drainage of pericardium
OPCS4.4	K71.9	Unspecified other operations on pericardium

CORONARY ANGIOPLASTY PROCEDURES

OPCS4.4	K75.1	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery
OPCS4.4	K75.2	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery
OPCS4.4	K75.3	Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery
OPCS4.4	K75.4	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC
OPCS4.4	K75.8	Other specified percutaneous transluminal balloon angioplasty and stenting of coronary artery
OPCS4.4	K75.9	Unspecified percutaneous transluminal balloon angioplasty and stenting of coronary artery
OPCS4.4	K76.1	Percutaneous transluminal balloon dilation of cardiac conduit
OPCS4.4	K76.8	Other specified transluminal operations on cardiac conduit
OPCS4.4	K76.9	Unspecified transluminal operations on cardiac conduit
OPCS4.4	K78.1	Transluminal occlusion of left internal mammary artery side branch
OPCS4.4	K78.8	Other specified transluminal operations on internal mammary artery side branch
OPCS4.4	K78.9	Unspecified ?? transluminal operations on internal mammary artery side branch
OPCS4.4	K49.1	Percutaneous transluminal balloon angioplasty of one coronary artery
OPCS4.4	K49.2	Percutaneous transluminal balloon angioplasty of multiple coronary arteries
OPCS4.4	K49.3	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery
OPCS4.4	K49.4	Percutaneous transluminal cutting balloon angioplasty of coronary artery

OPCS4.4	K49.8	Other specified transluminal balloon angioplasty of coronary artery
OPCS4.4	K49.9	Unspecified transluminal balloon angioplasty of coronary artery
OPCS4.4	K50.1	Percutaneous transluminal laser coronary angioplasty
OPCS4.4	K50.2	Percutaneous transluminal coronary thrombolysis using streptokinase
OPCS4.4	K50.3	Percutaneous transluminal injection of therapeutic substance into coronary artery NEC
OPCS4.4	K50.4	Percutaneous transluminal atherectomy of coronary artery
OPCS4.4	K50.8	Other specified other therapeutic transluminal operations on coronary artery
OPCS4.4	K50.9	Unspecified other therapeutic transluminal operations on coronary artery
OPCS4.4	K51.1	Percutaneous transluminal angioscopy
OPCS4.4	K51.2	Intravascular ultrasound of coronary artery
OPCS4.4	K51.8	Other specified diagnostic transluminal operations on coronary artery
OPCS4.4	K51.9	Unspecified diagnostic transluminal operations on coronary artery

VARIOUS NON-SPECIFIC CARDIAC PROCEDURE CODES

OPCS4.4	K53.1	Inspection of valve of heart
OPCS4.4	K53.2	Exploration of heart NEC
OPCS4.4	K53.8	Other specified other incision of heart
OPCS4.4	K53.9	Unspecified other incision of heart
OPCS4.4	K55.1	Ligation of sinus of valsalva
OPCS4.4	K55.2	Open chest massage of heart
OPCS4.4	K55.3	Open removal of cardiac thrombus
OPCS4.4	K55.4	Open removal of cardiac vegetations NEC
OPCS4.4	K66.8	Other specified other operations of heart
OPCS4.4	K66.9	Unspecified other operations on heart

CEREBR0VASCULAR PROCEDURES

CAROTID ARTERY PROCEDURES

OPCS4.4	L29.1	Replacement of carotid artery using graft

OPCS4.4	L29.2	Intracranial bypass to carotid artery NEC
OPCS4.4	L29.3	Bypass to carotid artery NEC
OPCS4.4	L29.4	Endarterectomy of carotid artery and patch repair of carotid artery
OPCS4.4	L29.5	Endarterectomy of carotid artery NEC
OPCS4.4	L29.6	High-flow interposition extracranial to intracranial bypass from external carotid artery to middle cerebral artery
OPCS4.4	L29.7	Bypass of carotid artery by anastomosis of superficial temporal artery to middle cerebral artery
OPCS4.4	L29.8	Other specified reconstruction of carotid artery
OPCS4.4	L29.9	Unspecified reconstruction of carotid artery
OPCS4.4	L30.1	Repair of carotid artery NEC
OPCS4.4	L30.2	Ligation of carotid artery
OPCS4.4	L30.3	Open embolectomy of carotid artery
OPCS4.4	L30.4	Operations on aneurysm of carotid artery
OPCS4.4	L30.5	Operations on carotid body
OPCS4.4	L30.8	Other specified other open operations on carotid artery
OPCS4.4	L30.9	Unspecified other open operations on carotid artery
OPCS4.4	L31.1	Percutaneous transluminal angioplasty of carotid artery
OPCS4.4	L31.2	Arteriography of carotid artery
OPCS4.4	L31.3	Endovascular repair of carotid artery
OPCS4.4	L31.4	Percutaneous transluminal insertion of stent into carotid artery
OPCS4.4	L31.8	Other specified transluminal operations on carotid artery
OPCS4.4	L31.9	Unspecified transluminal operations on carotid artery

CEREBRAL ARTERY PROCEDURES

OPCS4.4	L33.1	Excision of aneurysm of cerebral artery
OPCS4.4	L33.2	Clipping of aneurysm of cerebral artery
OPCS4.4	L33.3	Ligation of aneurysm of cerebral artery NEC
OPCS4.4	L33.4	Obliteration of aneurysm of cerebral artery NEC
OPCS4.4	L33.8	Other specified operations on aneurysm of cerebral artery
OPCS4.4	L33.9	Unspecified operations on aneurysm of cerebral artery
OPCS4.4	L34.1	Reconstruction of cerebral artery
OPCS4.4	L34.2	Anastomosis of cerebral artery

OPCS4.4	L34.3	Open embolectomy of cerebral artery
OPCS4.4	L34.4	Open embolisation of cerebral artery
OPCS4.4	L34.8	Other specified other open operations on cerebral artery
OPCS4.4	L34.9	Unspecified other open operations on cerebral artery
OPCS4.4	L35.1	Percutaneous transluminal embolisation of cerebral artery
OPCS4.4	L35.2	Arteriography of cerebral artery
OPCS4.4	L35.3	Percutaneous transluminal insertion of stent into cerebral artery
OPCS4.4	L35.8	Other specified transluminal operations on cerebral artery
OPCS4.4	L35.9	Unspecified transluminal operations on cerebral artery

SUBCLAVIAN/VERTEBRAL ARTERY PROCEDURES

OPCS4.4	L37.1	Bypass of subclavian artery NEC
OPCS4.4	L37.2	Endarterectomy of vertebral artery
OPCS4.4	L37.3	Endarterectomy of subclavian artery and patch repair of subclavian artery
OPCS4.4	L37.4	Endarterectomy of subclavian artery NEC
OPCS4.4	L37.8	Other specified reconstruction of subclavian artery
OPCS4.4	L37.9	Unspecified reconstruction of subclavian artery
OPCS4.4	L38.1	Repair of subclavian artery NEC
OPCS4.4	L38.2	Ligation of subclavian artery
OPCS4.4	L38.3	Open embolectomy of subclavian artery
OPCS4.4	L38.4	Operations on aneurysm of subclavian artery
OPCS4.4	L38.8	Other specified other open operations on subclavian artery
OPCS4.4	L38.9	Unspecified other open operations on subclavian artery
OPCS4.4	L39.1	Percutaneous transluminal angioplasty of subclavian artery
OPCS4.4	L39.2	Percutaneous transluminal embolectomy of subclavian artery
OPCS4.4	L39.3	Percutaneous transluminal embolisation of subclavian artery
OPCS4.4	L39.4	Arteriography of subclavian artery
OPCS4.4	L39.5	Percutaneous transluminal insertion of stent into subclavian artery
OPCS4.4	L39.8	Other specified transluminal operations on subclavian artery

OPCS4.4	L39.9	Unspecified transluminal operations on subclavian artery
EVACUATION OF INTRACEREBRAL HAEMORRHAGE		
OPCS4.4	A05.2	Evacuation of haematoma from temporal lobe of brain
OPCS4.4	A05.3	Evacuation of haematoma from cerebellum
OPCS4.4	A05.4	Evacuation of intracerebral haematoma NEC
OTHER PROCEDURES (includes arterial, venous and amputation procedures)		
OPCS4.4	L12.4	Open embolectomy of pulmonary artery
OPCS4.4	L13.1	Percutaneous transluminal embolectomy of pulmonary artery
OPCS4.4	L13.3	Arteriography of pulmonary artery
OPCS4.4	L48	Emergency replacement of aneurysmal iliac artery
OPCS4.4	L48.1	Emergency replacement of aneurysmal common iliac artery by anastomosis of aorta to common iliac artery
OPCS4.4	L48.2	Emergency replacement of aneurysmal iliac artery by anastomosis of aorta to external iliac artery
OPCS4.4	L48.3	Emergency replacement of aneurysmal artery of leg by anastomosis of aorta to common femoral artery
OPCS4.4	L48.4	Emergency replacement of aneurysmal artery of leg by anastomosis of aorta to superficial femoral artery
OPCS4.4	L48.5	Emergency replacement of aneurysmal iliac artery by anastomosis of iliac artery to iliac artery
OPCS4.4	L48.6	Emergency replacement of aneurysmal artery of leg by anastomosis of iliac artery to femoral artery
OPCS4.4	L48.8	Other specified emergency replacement of aneurysmal iliac artery
OPCS4.4	L48.9	Unspecified emergency replacement of aneurysmal iliac artery
OPCS4.4	L49	Other replacement of aneurysmal iliac artery

OPCS4.4	L49.1	Replacement of aneurysmal common iliac artery by anastomosis of aorta to common iliac artery NEC
OPCS4.4	L49.2	Replacement of aneurysmal iliac artery by anastomosis of aorta to external iliac artery NEC
OPCS4.4	L49.3	Replacement of aneurysmal artery of leg by anastomosis of aorta to common femoral artery NEC
OPCS4.4	L49.4	Replacement of aneurysmal artery of leg by anastomosis of aorta to superficial femoral artery NEC
OPCS4.4	L49.5	Replacement of aneurysmal iliac artery by anastomosis of iliac artery to iliac artery NEC
OPCS4.4	L49.6	Replacement of aneurysmal artery of leg by anastomosis of iliac artery to femoral artery NEC
OPCS4.4	L49.8	Other specified other replacement of aneurysmal iliac artery
OPCS4.4	L49.9	Unspecified other replacement of aneurysmal iliac artery
OPCS4.4	L50	Other emergency bypass of iliac artery
OPCS4.4	L50.1	Emergency bypass of common iliac artery by anastomosis of aorta to common iliac artery NEC
OPCS4.4	L50.2	Emergency bypass of iliac artery by anastomosis of aorta to external iliac artery NEC
OPCS4.4	L50.3	Emergency bypass of artery of leg by anastomosis of aorta to common femoral artery NEC
OPCS4.4	L50.4	Emergency bypass of artery of leg by anastomosis of aorta to deep femoral artery NEC
OPCS4.4	L50.5	Emergency bypass of iliac artery by anastomosis of iliac artery to iliac artery NEC
OPCS4.4	L50.6	Emergency bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC
OPCS4.4	L50.8	Other specified other emergency bypass of iliac artery
OPCS4.4	L50.9	Unspecified other emergency bypass of iliac artery
OPCS4.4	L51	Other bypass of iliac artery
OPCS4.4	L51.1	Bypass of common iliac artery by anastomosis of aorta to common iliac artery NEC
OPCS4.4	L51.2	Bypass of iliac artery by anastomosis of aorta to external iliac artery NEC
OPCS4.4	L51.3	Bypass of artery of leg by anastomosis of aorta to common femoral artery NEC
OPCS4.4	L51.4	Bypass of artery of leg by anastomosis of aorta to deep femoral artery NEC
OPCS4.4	L51.5	Bypass of iliac artery by anastomosis of iliac artery to iliac artery NEC

OPCS4.4	L51.6	Bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC
OPCS4.4	L51.8	Other specified other bypass of iliac artery
OPCS4.4	L51.9	Unspecified other bypass of iliac artery
OPCS4.4	L52	Reconstruction of iliac artery
OPCS4.4	L52.1	Endarterectomy of iliac artery and patch repair of iliac artery
OPCS4.4	L52.2	Endarterectomy of iliac artery NEC
OPCS4.4	L52.8	Other specified reconstruction of iliac artery
OPCS4.4	L52.9	Unspecified reconstruction of iliac artery
OPCS4.4	L53	Other open operations on iliac artery
OPCS4.4	L53.1	Repair of iliac artery NEC
OPCS4.4	L53.2	Open embolectomy of iliac artery
OPCS4.4	L53.3	Operations on aneurysm of iliac artery NEC
OPCS4.4	L53.8	Other specified other open operations on iliac artery
OPCS4.4	L53.9	Unspecified other open operations on iliac artery
OPCS4.4	L54	Transluminal operations on iliac artery
OPCS4.4	L54.1	Percutaneous transluminal angioplasty of iliac artery
OPCS4.4	L54.2	Percutaneous transluminal embolectomy of iliac artery
OPCS4.4	L54.3	Arteriography of iliac artery
OPCS4.4	L54.4	Percutaneous transluminal insertion of stent into iliac artery
OPCS4.4	L54.8	Other specified transluminal operations on iliac artery
OPCS4.4	L54.9	Unspecified transluminal operations on iliac artery
OPCS4.4	L56	Emergency replacement of aneurysmal femoral artery
OPCS4.4	L56.1	Emergency replacement of aneurysmal femoral artery by anastomosis of femoral artery to femoral artery
OPCS4.4	L56.2	Emergency replacement of aneurysmal femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis
OPCS4.4	L56.3	Emergency replacement of aneurysmal femoral artery by anastomosis of femoral artery to popliteal artery using vein graft
OPCS4.4	L56.4	Emergency replacement of aneurysmal femoral artery by anastomosis of femoral artery to tibial artery using prosthesis

OPCS4.4	L56.5	Emergency replacement of aneurysmal femoral artery by anastomosis of femoral artery to tibial artery using vein graft
OPCS4.4	L56.6	Emergency replacement of aneurysmal femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis
OPCS4.4	L56.7	Emergency replacement of aneurysmal femoral artery by anastomosis of femoral artery to peroneal artery using vein graft
OPCS4.4	L56.8	Other specified emergency replacement of aneurysmal femoral artery
OPCS4.4	L56.9	Unspecified emergency replacement of aneurysmal femoral artery
OPCS4.4	L57	Other replacement of aneurysmal femoral artery
OPCS4.4	L57.1	Replacement of aneurysmal femoral artery by anastomosis of femoral artery to femoral artery NEC
OPCS4.4	L57.2	Replacement of aneurysmal femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC
OPCS4.4	L57.3	Replacement of aneurysmal femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC
OPCS4.4	L57.4	Replacement of aneurysmal femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC
OPCS4.4	L57.5	Replacement of aneurysmal femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC
OPCS4.4	L57.6	Replacement of aneurysmal femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC
OPCS4.4	L57.7	Replacement of aneurysmal femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC
OPCS4.4	L57.8	Other specified other replacement of aneurysmal femoral artery
OPCS4.4	L57.9	Unspecified other replacement of aneurysmal femoral artery
OPCS4.4	L58	Other emergency bypass of femoral artery
OPCS4.4	L58.1	Emergency bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC
OPCS4.4	L58.2	Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC

OPCS4.4	L58.3	Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC
OPCS4.4	L58.4	Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC
OPCS4.4	L58.5	Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC
OPCS4.4	L58.6	Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC
OPCS4.4	L58.7	Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC
OPCS4.4	L58.8	Other specified other emergency bypass of femoral artery
OPCS4.4	L58.9	Unspecified other emergency bypass of femoral artery
OPCS4.4	L59	Other bypass of femoral artery
OPCS4.4	L59.1	Bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC
OPCS4.4	L59.2	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC
OPCS4.4	L59.3	Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC
OPCS4.4	L59.4	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC
OPCS4.4	L59.5	Bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC
OPCS4.4	L59.6	Bypass of femoral artery by anastomosis of femoral artery to peronealartery using prosthesis NEC
OPCS4.4	L59.7	Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC
OPCS4.4	L59.8	Other specified other bypass of femoral artery
OPCS4.4	L59.9	Unspecified other bypass of femoral artery
OPCS4.4	L60	Reconstruction of femoral artery
OPCS4.4	L60.1	Endarterectomy of femoral artery and patch repair of femoral artery
OPCS4.4	L60.2	Endarterectomy of femoral artery NEC
OPCS4.4	L60.3	Profundoplasty of femoral artery and patch repair of deep femoral artery
OPCS4.4	L60.4	Profundoplasty of femoral artery NEC
OPCS4.4	L60.8	Other specified reconstruction of femoral artery
OPCS4.4	L60.9	Unspecified reconstruction of femoral artery
OPCS4.4	L62	Other open operations on femoral artery

OPCS4.4	L62.1	Repair of femoral artery NEC
OPCS4.4	L62.2	Open embolectomy of femoral artery
OPCS4.4	L62.3	Ligation of aneurysm of popliteal artery
OPCS4.4	L62.4	Operations on aneurysm of femoral artery NEC
OPCS4.4	L62.8	Other specified other open operations on femoral artery
OPCS4.4	L62.9	Unspecified other open operations on femoral artery
OPCS4.4	L63	Transluminal operations on femoral artery
OPCS4.4	L63.1	Percutaneous transluminal angioplasty of femoral artery
OPCS4.4	L63.2	Percutaneous transluminal embolectomy of femoral artery
OPCS4.4	L63.3	Percutaneous transluminal embolisation of femoral artery
OPCS4.4	L63.4	Arteriography of femoral artery
OPCS4.4	L63.5	Percutaneous transluminal insertion of stent into femoral artery
OPCS4.4	L63.8	Other specified transluminal operations on femoral artery
OPCS4.4	L63.9	Unspecified transluminal operations on femoral artery
OPCS4.4	L65	Revision of reconstruction of artery
OPCS4.4	L65.1	Revision of reconstruction involving aorta
OPCS4.4	L65.2	Revision of reconstruction involving iliac artery
OPCS4.4	L65.3	Revision of reconstruction involving femoral artery
OPCS4.4	L65.8	Other specified revision of reconstruction of artery
OPCS4.4	L65.9	Unspecified revision of reconstruction of artery
OPCS4.4	L66	Other therapeutic transluminal operations on artery
OPCS4.4	L66.1	Percutaneous transluminal arterial thrombolysis and reconstruction
OPCS4.4	L66.2	Percutaneous transluminal stent reconstruction of artery
OPCS4.4	L66.3	Percutaneous transluminal occlusion of artery
OPCS4.4	L66.4	Percutaneous transluminal balloon test occlusion of artery
OPCS4.4	L66.5	Percutaneous transluminal balloon angioplasty of artery
OPCS4.4	L66.7	Percutaneous transluminal placement of peripheral stent in artery
OPCS4.4	L66.8	Other specified other therapeutic transluminal operations on artery
OPCS4.4	L66.9	Unspecified other therapeutic transluminal operations on artery
OPCS4.4	L67	Excision of other artery
OPCS4.4	L67.1	Biopsy of artery NEC

OPCS4.4	L67.8	Other specified excision of other artery
OPCS4.4	L67.9	Unspecified excision of other artery
OPCS4.4	L68	Repair of other artery
OPCS4.4	L68.1	Endarterectomy and patch repair of artery NEC
OPCS4.4	L68.2	Endarterectomy NEC
OPCS4.4	L68.3	Repair of artery using prosthesis NEC
OPCS4.4	L68.4	Repair of artery using vein graft NEC
OPCS4.4	L68.8	Other specified repair of other artery
OPCS4.4	L68.9	Unspecified repair of other artery
OPCS4.4	L70	Other open operations on other artery
OPCS4.4	L70.1	Open embolectomy of artery NEC
OPCS4.4	L70.2	Open embolisation of artery NEC
OPCS4.4	L70.3	Ligation of artery NEC
OPCS4.4	L70.4	Open cannulation of artery
OPCS4.4	L70.5	Operations on aneurysm of artery NEC
OPCS4.4	L70.8	Other specified other open operations on other artery
OPCS4.4	L70.9	Unspecified other open operations on other artery
OPCS4.4	L71	Therapeutic transluminal operations on other artery
OPCS4.4	L71.1	Percutaneous transluminal angioplasty of artery
OPCS4.4	L71.2	Percutaneous transluminal embolectomy of artery
OPCS4.4	L71.3	Percutaneous transluminal embolisation of artery
OPCS4.4	L71.4	Percutaneous transluminal cannulation of artery
OPCS4.4	L71.5	Percutaneous transluminal dilation of artery
OPCS4.4	L71.6	Percutaneous transluminal thrombolysis of artery
OPCS4.4	L71.7	Percutaneous transluminal atherectomy
OPCS4.4	L71.8	Other specified therapeutic transluminal operations on other artery
OPCS4.4	L71.9	Unspecified therapeutic transluminal operations on other artery
OPCS4.4	L72	Diagnostic transluminal operations on other artery
OPCS4.4	L72.1	Arteriography NEC
OPCS4.4		
OPCS4.4	L72.3	Percutaneous transluminal angioscopy NEC

OPCS4.4	L72.6	Intravascular ultrasound of artery NEC
OPCS4.4	L72.8	Other specified diagnostic transluminal operations on other artery
OPCS4.4	L72.9	Unspecified diagnostic transluminal operations on other artery
OPCS4.4	L73	Mechanical embolic protection of blood vessel
OPCS4.4	L73.1	Mechanical embolic protection NEC
OPCS4.4	L73.2	Mechanical embolic protection of artery
OPCS4.4	L73.3	Mechanical embolic protection of vein
OPCS4.4	L73.8	Other specified mechanical embolic protection of blood vessel
OPCS4.4	L73.9	Unspecified mechanical embolic protection of blood vessel
OPCS4.4	L76	Endovascular placement of stent
OPCS4.4	L76.1	Endovascular placement of one metallic stent
OPCS4.4	L76.2	Endovascular placement of one plastic stent
OPCS4.4	L76.3	Endovascular placement of two metallic stents
OPCS4.4	L76.4	Endovascular placement of two plastic stents
OPCS4.4	L76.5	Endovascular placement of three or more metallic stents
OPCS4.4	L76.6	Endovascular placement of three or more plastic stents
OPCS4.4	L76.7	Endovascular placement of metallic stent with mechanical embolic protection
OPCS4.4	L76.8	Other specified endovascular placement of stent
OPCS4.4	L76.9	Unspecified endovascular placement of stent
OPCS4.4	L79	Other operations on vena cava
OPCS4.4	L79.1	Insertion of filter into vena cava
OPCS4.4	L79.2	Plication of vena cava
OPCS4.4	L79.3	Stenting of vena cava NEC
OPCS4.4	L79.4	Attention to filter into vena cava NEC
OPCS4.4	L79.5	Removal of filter in vena cava
OPCS4.4		
OPCS4.4	L89	Other endovascular placement of stent
OPCS4.4	L89.1	Endovascular placement of two drug-eluting stents
OPCS4.4	L89.2	Endovascular placement of two coated stents
OPCS4.4	L89.3	Endovascular placement of three or more drug-eluting stents
OPCS4.4	L89.4	Endovascular placement of three or more coated stents

OPCS4.4	L89.5	Endovascular placement of one drug-eluting stent
OPCS4.4	L89.6	Endovascular placement of one coated stent
OPCS4.4	L89.8	Other specified other endovascular placement of stent
OPCS4.4	L89.9	Unspecified other endovascular placement of stent
OPCS4.4	L90	Open removal of thrombus from vein
OPCS4.4	L90.1	Open thrombectomy of vein of upper limb
OPCS4.4	L90.2	Open thrombectomy of vein of lower limb
OPCS4.4	L90.3	Open thrombectomy of renal vein
OPCS4.4	L90.8	Other specified open removal of thrombus from vein
OPCS4.4	L90.9	Unspecified open removal of thrombus from vein
OPCS4.4		
OPCS4.4	L96	Percutaneous removal of thrombus from vein
OPCS4.4	L96.1	Percutaneous mechanical thromboembolectomy
OPCS4.4	L96.2	Percutaneous aspiration thromboembolectomy
OPCS4.4	L96.8	Other specified percutaneous removal of thrombus from vein
OPCS4.4	L96.9	Unspecified percutaneous removal of thrombus from vein
OPCS4.4	L97	Other operations on blood vessel
OPCS4.4	X07	Amputation of arm
OPCS4.4	X07.1	Forequarter amputation
OPCS4.4	X07.2	Disarticulation of shoulder
OPCS4.4	X07.3	Amputation of arm above elbow
OPCS4.4	X07.4	Amputation of arm through elbow
OPCS4.4	X07.5	Amputation of arm through forearm
OPCS4.4	X07.8	Other specified amputation of arm
OPCS4.4	X07.9	Unspecified amputation of arm
OPCS4.4	X08	Amputation of hand
OPCS4.4	X08.1	Amputation of hand at wrist
OPCS4.4	X08.2	Amputation of thumb
OPCS4.4	X08.3	Amputation of phalanx of finger
OPCS4.4	X08.4	Amputation of finger NEC
OPCS4.4	X08.8	Other specified amputation of hand
OPCS4.4	X08.9	Unspecified amputation of hand

OPCS4.4	X09	Amputation of leg
OPCS4.4	X09.1	Hindquarter amputation
OPCS4.4	X09.2	Disarticulation of hip
OPCS4.4	X09.3	Amputation of leg above knee
OPCS4.4	X09.4	Amputation of leg through knee
OPCS4.4	X09.5	Amputation of leg below knee
OPCS4.4	X09.8	Other specified amputation of leg
OPCS4.4	X09.9	Unspecified amputation of leg
OPCS4.4	X10	Amputation of foot
OPCS4.4	X10.1	Amputation of foot through ankle
OPCS4.4	X10.2	Disarticulation of tarsal bones
OPCS4.4	X10.3	Disarticulation of metatarsal bones
OPCS4.4	X10.4	Amputation through metatarsal bones
OPCS4.4	X10.8	Other specified amputation of foot
OPCS4.4	X10.9	Unspecified amputation of foot
OPCS4.4	X11	Amputation of toe
OPCS4.4	X11.1	Amputation of great toe
OPCS4.4	X11.2	Amputation of phalanx of toe
OPCS4.4	X11.8	Other specified amputation of toe
OPCS4.4	X11.9	Unspecified amputation of toe

Febuxostat versus Allopurinol Streamlined Trial (FAST)

Independent Data Monitoring Committee Charter

Independent Data Monitoring Committee Roster:

IDMC Members

Professor Attilio Maseri (Chairperson)

Professor Gordon Murray, (University of Edinburgh)

Professor Howard Bird (University of Leeds) (Acting Chairperson March 2019 onwards)

Dr James Dear (University of Edinburgh) (Member from March 2019 onwards)

IDMC Contacts

Sponsor

The University of Dundee

Chief Investigator

Professor Tom MacDonald

IDMC Coordinator

Ms Wendy Saywood (FAST Project Manager)

Unblinded Statisticians

(Robertson Centre for Biostatistics, Glasgow)

Kirsty Wetherall

Alex McConnachie

Table of Contents

APPROVING OFFICIALS

Name	**Signature**	**Date**
Prof Howard Bird Acting IDMC Chairperson	_____	_____
Prof Gordon Murray IDMC Member	_____	_____
Prof James Dear IDMC Member	_____	_____
Prof Tom MacDonald Chief Investigator (Representative of the Sponsor (University of Dundee))	_____	_____

I. Scope of FAST STUDY IDMC Charter

The FAST STUDY Independent Data Monitoring Committee (IDMC) will independently monitor patient safety and efficacy information during this study.

The objective of the FAST STUDY IDMC Charter is to outline the specific purposes and functions of the IDMC, the procedures for data abstraction and data delivery conventions to and from the IDMC members for review purposes.

II. Composition of FAST STUDY IDMC

The IDMC will be composed of three (3) members: one Chairperson, and two (2) additional individuals. The IDMC members will include two physicians, one with cardiovascular specialty and one with vascular specialty, as well as a Biostatistician with clinical trial and prior IDMC experience. Prof Attilio Maseri will serve as Chairperson of the IDMC. In the event that the Chairperson is unable to fulfil their responsibilities Prof Howard Bird will take on this role and a replacement member will be sought and approved. Additional IDMC members are named on the IDMC roster. The Sponsor, University of Dundee, will approve all IDMC members.

IDMC members will not be involved as investigators in the FAST study protocol. In addition, IDMC members must not have a conflict of interest that would bias their review of trial data (e.g. IDMC members must not have a financial interest that could be substantially affected by the outcome of the study, strong views on the relative merits of the study drug, or relationships with individuals in trial leadership positions that could be considered reasonably likely to affect their objectivity).

All IDMC members are expected to serve from study start until the study is completed (at least until end of study final database lock). Should it be necessary for a member to resign, the member must submit the effective date of resignation in writing to University of Dundee and the IDMC Chairperson. In the event a member resigns, University of Dundee, in consultation with the IDMC Chairperson, will initiate the process to identify a replacement member.

III. IDMC Contacts and ad hoc Consultants

IDMC contacts and ad hoc consultants are not considered to be members of the IDMC. The official IDMC contacts are named on the IDMC roster and will be appointed as follows:

The University of Dundee will assign an IDMC Coordinator who will provide administrative, logistical, and coordinating services to the IDMC. The IDMC Coordinator will serve as the primary, central point of contact for communications with the IDMC members and IDMC-related issues and will interface with University of Dundee and the operational leads on the project team, as appropriate.

The Robertson Centre for Biostatistics, University of Glasgow will assign Unblinded Biostatisticians who will generate the IDMC Data Reports. In addition, these individuals will be available to the IDMC, to provide consultation regarding the information presented within the IDMC Data Reports.

From the Sponsor, University of Dundee, an identified representative will serve as a primary contact person for the IDMC and IDMC issues (refer to Appendix A for communication flow).

The IDMC may, with prior approval from University of Dundee, contact and involve selected expert consultants who may provide additional, relevant insight or expertise to the IDMC, regarding any specific issues that may arise.

As a rule, IDMC contacts and consultants must not attend closed sessions of IDMC Data Review Meetings.

The IDMC Chairperson will ensure that IDMC contacts and consultants are not inappropriately exposed to fully unblinded and/or unblinded data made available to the IDMC.

IV. FAST STUDY IDMC Responsibilities

The FAST study IDMC is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety, efficacy and other clinical trial data at regular intervals. As such, the primary objective of the IDMC is to monitor the safety of the subjects in the FAST study by reviewing the available clinical data at scheduled time points including twice yearly meetings (which may be face to face or via teleconference) and on an ad hoc basis as needed. After the review of each Data Report has been completed, the IDMC Chairperson or delegate will provide the official IDMC recommendation to the study sponsor (University of Dundee) via the IDMC Coordinator regarding the appropriateness of continuing the study, from a safety and efficacy perspective, as well as any other recommendations relevant to study conduct and/or patient safety.

The operating procedures of the IDMC are based on and are in compliance with the US Food and Drug Administration's draft "Guidance for Clinical Trial Sponsors on the Establishment of Clinical Trial Data Monitoring Committees."

Specifically, the IDMC members are authorised and charged to perform the following functions:

- Provide approval for and operate in accordance with the specifications outlined in this IDMC Charter.

- Monitor the safety of patients enrolled and to be enrolled in FAST STUDY, and the efficacy of the trial, through scheduled review of accumulating clinical data from the ongoing clinical trial.

- Review and evaluate the content of all Data Reports received.

- Participate in and vote on IDMC recommendations.

Throughout the trial, the IDMC Chairperson will serve in a leadership role and will be authorised and charged with the following additional responsibilities:

- Conduct all IDMC Data Review meetings

- Ensure that all relevant data have been reviewed by the IDMC members and that all issues have been addressed.

- Ensure that blinded individuals (i.e. the IDMC Coordinator, IDMC contacts, and IDMC consultants) are not inappropriately exposed to confidential and/or unblinded data.

- Ensure that only the members of the IDMC are present during IDMC deliberations, when IDMC recommendations are discussed and IDMC voting procedures are conducted.

- Generate confidential, written minutes of all closed and executive sessions of any IDMC Meetings and maintain these minutes as confidential to IDMC members and the unblinded statisticians from the Robertson Centre for Biostatistics, only, until the final (end of study) database lock is complete.

- Provide IDMC approval of records and minutes of open and final sessions of all IDMC meetings.

- Maintain a secure central file of all data outputs received for IDMC review and all minutes of all sessions of IDMC meetings. Provide a copy of this file to University of Dundee, once the final (end of study) database lock is complete.

- Communicate, author, sign, and provide the official, final recommendations of the IDMC within specified timelines and according to the specifications outlined in this charter. If the IDMC is divided in opinion on any major issue affecting the IDMC's recommendation to the Sponsor, the IDMC Chairperson is responsible for assembling and presenting the majority and dissenting opinions for all recommendations considered (refer to Appendix A for communication flow).

- Arrange for consultation(s) and/or request additional data, as deemed necessary.

V UNIVERSITY OF DUNDEE Sponsor Responsibilities

The Sponsor, University of Dundee, will have the following responsibilities with respect to the FAST STUDY IDMC:

- Provide final approval of the IDMC Chairperson and Members to serve on the IDMC.

- Ensure relevant clinical or other data available to University of Dundee on the safety of Febuxostat are provided for communication to the IDMC.

- Collaborate with the Chief Investigator to ensure that IDMC members are informed of trial progress and issues on a quarterly basis.

- In preparation for data review meetings, collaborate with the Chief Investigator and the Robertson Centre for Biostatistics to prepare and provide a general summary of the status of the trial and any relevant clinical issues.

- Provide Sponsor representation at all open sessions of IDMC meetings, as needed.

- Provide final approval, in conjunction with the IDMC Chairperson, of minutes of open sessions of IDMC meetings.

- Arrange for fair and reasonable reimbursement to IDMC members for their data monitoring activities (i.e., data monitoring services provided and any study-related travel costs, such as transportation, lodging, and meals).

- Provide a primary contact representative to receive recommendations from the IDMC.

- Maintain ultimate responsibility for safe study conduct.

VI. ROBERTSON CENTRE BIOSTATISTICS Responsibilities

The Robertson Centre for Biostatistics will provide Unblinded Biostatisticians in support of the IDMC process. The responsibilities of the Unblinded Biostatisticians are as follows:

- Provide approval for and operate in accordance with the specifications outlined in this IDMC Charter.

- Work with IDMC members to determine the data that are necessary for the IDMC Data Reports.

- Generate the IDMC Data Reports.

- Maintain an archive of electronic copies of datasets and programs used to generate the IDMC Data Reports.

- Provide access for the IDMC members to download copies of the confidential IDMC Data Reports.

- Provide consultation regarding the information presented in the IDMC Data Reports, as requested by the IDMC members.

VII. IDMC Coordinator Responsibilities

The University of Dundee will provide an IDMC Coordinator for the FAST STUDY. The IDMC Coordinator will provide full administrative, logistical and coordinating support to the IDMC members.

The IDMC Coordinator will be charged with the following responsibilities:

- Provide approval for and operate in accordance with the specifications outlined in this IDMC Charter.

- Serve as the primary, central point of contact for the IDMC members and as the main liaison between the FAST STUDY operations teams and the IDMC members.

- Coordinate the implementation of the schedule for preparation and distribution of Data Reports to IDMC members.

- Follow-up to verify that all data required by the IDMC are provided according to an agreed timeframe.

- Obtain IDMC recommendation letters and distribute them, as described in this IDMC Charter.

- Coordinate arrangements for all data review meetings and any IDMC ad hoc meetings, as outlined in this charter.

- Maintain a central file of all key IDMC-related correspondences. Provide this file to University of Dundee after the final (end of study) database lock is completed.

University of Dundee will process IDMC member invoices and expense reports.

VIII FAST STUDY IDMC Member Training

All IDMC members will receive protocol overview and IDMC process training. To this end, an IDMC Kick-off Meeting will be held. The objectives of the IDMC Kick-off meeting will be to orient the IDMC members to the relevant study protocol, familiarize them with the contents of the IDMC Charter, and provide them with operational instructions/training.

IX. Ongoing Communications & Notifications to FAST STUDY IDMC

The IDMC Coordinator will provide the IDMC Chairperson with copies of all IND Safety Letters related to the FAST STUDY.

X. FAST STUDY IDMC Data Reports

IDMC members will receive all IDMC Data Reports directly from the Unblinded Biostatisticians, via a secure password-protected download facility.

IDMC Data Reports will be provided to the IDMC members at least one week prior to scheduled data review meetings.

Data included in each IDMC Data Report will be cumulative-to-date at the time of the established data cut-off. The cut-off date for the data included in the Data Reports, as well as the current enrolment figures, will be stated in a cover letter.

The IDMC may request additional information on individual patients, as needed.

The IDMC may request additional tables and/or analyses to be included in the Data Reports, as needed.

Data Reports for review by the IDMC will be presented in an unblinded fashion for both safety and efficacy reviews.

XI.FAST STUDY IDMC Meetings

IDMC Data Review Meeting Frequency

Once all IDMC training is complete and the IDMC Charter has been finalised, it is anticipated that Nine IDMC data review meetings will be scheduled. The first meeting will take place in year one and meetings will be conducted twice yearly thereafter or more frequently if required.

A Haybittle-Peto-like [1, 2] boundary will be applied as a guideline (corresponding to nominal alpha = 0.001, 2-sided) for assessing data for the primary endpoint for overwhelming evidence of superiority of one treatment regime over the other.

The IDMC may formulate its own internal guidelines for monitoring other outcomes. These should be minuted.

In addition to these planned data review meetings, the IDMC will have the ability to hold ad hoc meetings, should they be deemed necessary.

IDMC Meeting Agendas

With input from the IDMC Chairperson, the IDMC Coordinator will establish the agenda for each planned data review meeting and for any ad hoc IDMC meetings.

IDMC Attendance

All three (3) IDMC members should be in attendance, in order for each IDMC data review meeting to be convened, and in order for voting procedures to be conducted. In exceptional circumstances two (2) IDMC members can review the IDMC Data Reports, but the third member MUST be consulted before the IDMC would make a recommendation for any significant change to the trial conduct.

IDMC Meeting Structure

It is anticipated that IDMC data review meetings will generally be teleconferences but face to face meetings may be necessary at times.

IDMC data review meetings will normally consist of two sessions: an open session, and a closed session. The Unblinded Biostatisticians will attend the closed session of the IDMC meeting, but do not have voting rights. When necessary, formal votes can be taken at an executive session only including the IDMC members.

During open sessions the IDMC members, as well as the IDMC Coordinator, the Sponsor, the Unblinded Biostatisticians and any other IDMC contacts and consultants may be present. During open sessions, the IDMC members will receive a project update and will have an opportunity to discuss the progress of the trial with the IDMC Coordinator.

During closed sessions, the IDMC members will confidentially review the IDMC Data Report.

The IDMC Chairperson or delegate will communicate the final recommendations directly to the IDMC Coordinator after the meeting with a written report. This will be forwarded to the Study Steering Committee and Sponsor.

IDMC Voting Procedures: Recommendation to Sponsor

After review and discussion of each Data Report, the IDMC members will vote to determine the final IDMC recommendation within one of the following four options:

- Continue the study without modification;
- Continue the study and amend the protocol, as specified;
- Pause enrolment, pending resolution of a specified issue;
- Terminate the study.

All IDMC members must participate in this voting procedure. The IDMC Chairperson will document the outcome of the vote. From review of the votes, the IDMC Chairperson will assess whether a consensus opinion has been achieved.

If IDMC consensus is not achieved, majority vote will determine the final decision of the IDMC, and the IDMC Chairperson or delegate will be responsible for assembling and presenting the majority and dissenting opinions to University of Dundee, for all recommendations considered.

If deemed necessary, the IDMC may elect to postpone the determination of an IDMC recommendation, pending external consultation(s) and/or receipt of additional data and a subsequent closed IDMC Data Review Meeting session.

The recommendations of the IDMC will be based on the members' clinical and biostatistical assessment of the cumulative safety data provided for review. As there will be interim analyses carried out, the IDMC members will be guided by formal statistical stopping guidelines. As part of the recommendation to the Sponsor, the IDMC may also make comments and suggestions that might enhance study performance, as deemed appropriate.

IDMC Meeting Minutes

IDMC Data Review meeting minutes will be divided by session and will reflect attendance, as well as whether each individual attended in person or via teleconference.

Since all details of IDMC deliberations must be kept strictly confidential among members of the IDMC, the closed and executive portions of the IDMC Data Review meeting minutes must remain confidential until after the study database is locked and the treatment groups for the entire study are unblinded. The IDMC Chairperson (or a designee selected among the IDMC members) will produce the minutes of the closed and executive sessions of IDMC meetings. These minutes will be distributed only to IDMC members and the unblinded statisticians, for the duration of the data collection until final database lock.

The IDMC Chairperson or delegate will file all minutes from all sessions, centrally. After the study database is locked and the treatment groups for the entire study are unblinded, the IDMC Chairperson will forward the central file of all IDMC minutes for all sessions to University of Dundee.

XII. FAST STUDY IDMC Communication of Recommendation

Once the IDMC recommendation is finalised by IDMC vote, the IDMC Chairperson will communicate the IDMC recommendation to University of Dundee, as follows:

- Formal, written communication of the IDMC recommendation will take the form of an IDMC recommendation letter from the IDMC Chairperson or delegate and should be provided to the IDMC Coordinator within 5 business days after the IDMC recommendation is finalised.

- Communications of IDMC recommendations will reflect the consensus opinion of the IDMC members. In the event that consensus cannot be reached, majority and dissenting opinions will be summarized and presented.

The IDMC Coordinator will receive the IDMC Recommendation Letter and distribute it to the Sponsor and the Chair of the Steering Committee, as well as to other individuals, as specified by University of Dundee.

The IDMC Coordinator will also provide copies of the IDMC Recommendation Letters to investigators for submission to Institutional Review Boards (IRBs), upon receipt of investigator requests for this information.

XIII Implementation of FAST STUDY IDMC Recommendations

Any recommendations provided to the Sponsor by the IDMC will be treated as such. University of Dundee after consultation with the study Steering Committee will hold the ultimate responsibility to implement the recommendations and take appropriate actions.

The University of Dundee will notify the IDMC Chairperson in writing of actions taken in response to a given IDMC recommendation, for cases in which Sponsor action other than to continue the study without modification was recommended

XIV. FAST STUDY IDMC Document Handling & Records Retention

Confidentiality

The IDMC will maintain a strictly confidential relationship to the FAST STUDY data. The IDMC will only reveal specific details and information associated with IDMC data review to appropriate parties, as specified by this IDMC Charter.

The materials provided to the IDMC should be considered and handled as strictly confidential in nature, as they have the potential to contain unblinded information regarding the trial, which cannot be communicated to non-IDMC members. As such, no member of the IDMC should release these data – or inappropriately disclose the contents – to unauthorised persons. If a situation occurs where confidential information is released inadvertently to someone outside of the IDMC, the IDMC Co-coordinator should be informed and she will follow up immediately to establish the best course of action to maintain study integrity.

With specific reference to the above instruction, IDMC members should take care to maintain the blind of the Sponsor and agents of the Sponsor (e.g., employees of University of Dundee) at all times for the duration of the trial.

In exceptional circumstances, and with prior written agreement from the Sponsor and Steering Committee Chair, the IDMC Chairperson might be authorised to disclose confidential information to representatives from a regulatory authority or other official body.

Data Handling

The IDMC Chairperson or delegate must retain a copy of all data reviewed by the IDMC in a central file.

Records Retention

The IDMC Chairperson or delegate should maintain a copy of the IDMC file (i.e., copies of all data reviewed by the IDMC and copies of final minutes of all sessions of any IDMC meeting) until two years after the end of the FAST study. After the two-year period, the IDMC Chairperson should contact the Sponsor, to determine if further retention and/or archiving are necessary.

XV. INDEMNIFICATION AND LIABILITY

Sponsor Indemnification

Sponsor shall indemnify, defend and hold harmless each IDMC member, from and against any and all losses, damages, liabilities, reasonable attorney fees, court costs, and expenses (collectively "Losses") resulting or arising from any third-party claims, actions, proceedings, investigations or litigation relating to or arising from or in connection with the performance of responsibilities by such IDMC member contemplated herein, except to the extent any such Losses have resulted from a breach of such IDMC member's obligations hereunder or from any wilful or intentional misconduct of the IDMC member seeking indemnity hereunder. This indemnification provision shall not extent to any claim brought against an IDMC member by Sponsor or their respective affiliates, its directors, officers, employees, agents and subcontractors.

IDMC Member Indemnification

Each IDMC member shall indemnify, defend and hold harmless Sponsor, its affiliates, directors, officers, employees, agents and subcontractors (hereinafter collectively "Sponsor"), from and against any and all losses, damages, liabilities, reasonable attorney fees, court costs, and expenses (collectively "Losses") resulting or arising from any third-party claims, actions, proceedings, investigations or litigation relating to or arising from or in connection with the study FAST STUDY, provided that such Losses have resulted from any material breach of such IDMC member's obligations hereunder or from a judicial finding of wilful or intentional misconduct of such IDMC member.

Indemnification Procedure

Each IDMC member seeking indemnification from Sponsor hereunder shall give Sponsor within seven (7) days written notice of any such claim or lawsuit (including a copy thereof) served upon it and shall fully cooperate with Sponsor and its legal representatives in the investigation of any matter the subject of indemnification. The IDMC member shall not unreasonably withhold its approval of the settlement of any claim, liability, or action covered by this indemnification provision.

Sponsor seeking indemnification from any IDMC member hereunder shall give such IDMC member(s) prompt notice of any such claim or lawsuit (including a copy thereof) served upon it and shall fully cooperate with IDMC member and its legal representatives in the investigation of any matter the subject of indemnification. Sponsor shall not unreasonably withhold its approval of the settlement of any claim, liability, or action covered by this indemnification provision.

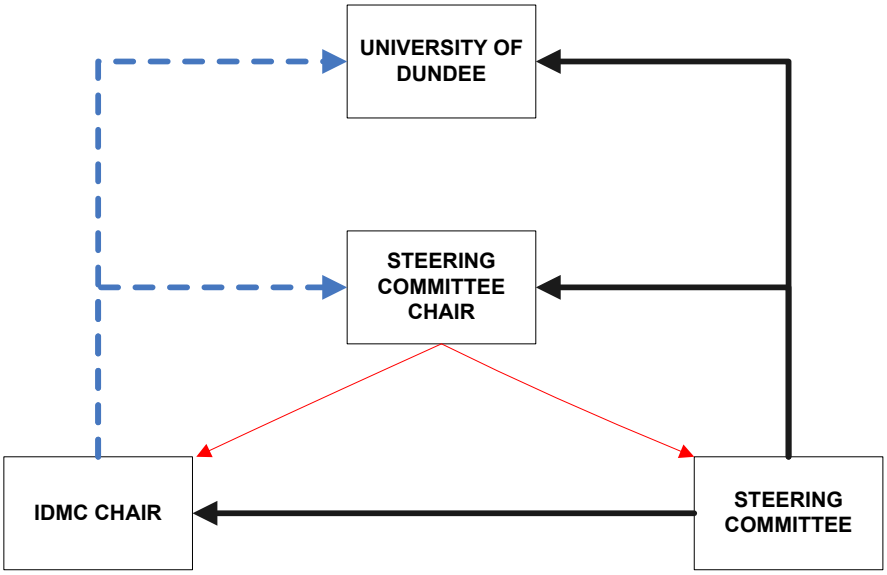
Limitation of Liability

Notwithstanding anything contained herein, neither any IDMC member nor Sponsor, nor any of its affiliates, directors, officers, employees, agents or subcontractors shall have any liability of any type (including, but not limited to, contract, negligence, and tort liability), for any loss of profits, opportunity or goodwill, or any type of special, incidental, indirect or consequential damage or loss in connection with or arising out of the obligations to be performed hereunder or otherwise in connection with the FAST study.

Other Remedies and Rights

The indemnification provided for herein shall be in addition, and not in limitation or in lieu of, any remedies or rights either party may have in law or equity or otherwise.

XVI. APPENDIX A: Communication flow between Committee Members



- Any communication (written or verbal) between committees should be conducted by chairpersons only.

- The sponsor should be copied on all written communications and involved in all discussions between committee chairpersons.

FAST Statistical Analysis Plan

FEBUXOSTAT VERSUS ALLOPURINOL

STREAMLINED TRIAL

(FAST)

FINAL ANALYSIS – STATISTICAL ANALYSIS PLAN

Study Title:	Febuxostat versus Allopurinol Streamlined Trial		
Short Title:	FAST		
IDs:	EUDRACT N°: 2011-001883-23		
Funded by:	MENARINI		
Protocol Version:	Version 20 (29th June 2018)		
SAP Version:	V1.0	Date:	24th August 2020

		Signature	Date
Prepared by:	Michele Robertson Assistant Director Commercial Biostatistics Robertson Centre for Biostatistics University of Glasgow		
Approved by:	Professor Ian Ford Senior Research Fellow Robertson Centre for Biostatistics University of Glasgow		
	Professor Alex McConnachie Professor of Clinical Trial Biostatistics Robertson Centre for Biostatistics University of Glasgow		
Principal Investigator	Professor Thomas M MacDonald Professor of Clinical Pharmacology and Pharmacoepidemiology Molecular and Clinical Medicine University of Dundee		

CONTENTS

1. INTRODUCTION

1.1. STUDY BACKGROUND

The European Union (EU) Risk Management Plan (RMP) for febuxostat (Version 2.0; 19 February 2008) indicates that a post marketing study to evaluate the cardiovascular (CV) effects of febuxostat is to be conducted as part of the Pharmacovigilance Plan.

FAST is a large safety study of febuxostat versus standard urate lowering therapy with allopurinol for chronic symptomatic hyperuricaemia. This study aims to compare the relative cardiovascular safety of the two treatment strategies.

The Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout (CARES) study[i] was published in 2018 and raised questions about the safety of febuxostat. This statistical analysis plan has been updated to include additional analyses of importance following the CARES study report.

1.2. STUDY OBJECTIVES

The primary study objective is to compare the cardiovascular safety profile (in terms of Anti-Platelet Trialists' Collaboration [APTC] events) of febuxostat versus allopurinol when taken for an average of three years in patients 60 years of age or older with chronic hyperuricaemia in conditions where urate deposition has already occurred.

The secondary study objectives are to evaluate other cardiovascular adverse events for both products.

1.3. STUDY DESIGN

Phase IV post authorisation safety study.

This randomised, parallel group clinical trial utilises the prospective, randomised, open, blinded endpoint (PROBE) design. Patients with clinically diagnosed symptomatic hyperuricaemia who are 60 years of age or older, with at least one additional CV risk factor, and who are currently prescribed allopurinol for chronic hyperuricaemia in conditions where urate deposition have already occurred are identified in the setting of either primary or secondary care.

Patients are followed up for an average of three years from randomisation by two-monthly (± one month) follow-up (by phone, letter or visit to the patient) and record-linkage with hospitalisations and deaths.

The study will terminate after patients have been followed-up for an average of at least three years and when it is predicted that at least 456 APTC subjects have experienced a first primary event on-treatment (OT).

Full details of the inclusion and exclusion criteria are noted in the protocol.

1.4. RANDOMISATION

After screening and consent, and before randomisation, all patients received allopurinol at a dose optimised according to clinical judgement, European League Against Rheumatism (EULAR) recommendations and the current SmPC with a goal to achieve either a serum uric acid (sUA) level of <6mg/dL or the maximum tolerated dose/maximum licensed dose (MTD/MLD) for that patient.

At the end of the allopurinol dose optimisation phase, eligible patients were randomised and were instructed not to take any ULT during the washout period. The randomisation was stratified according to whether or not the patients had a history of the following cardiovascular events: myocardial infarction (MI), stroke or of hospitalisation due to congestive heart failure (CHF) or peripheral vascular disease (PVD).

1.5. SAMPLE SIZE AND POWER

456 APTC events are required to show non-inferiority between the febuxostat and allopurinol treatment arms assuming a non-inferiority limit for the hazard ratio of 1.3, with 80% power and a one sided alpha of 0.025.

Non-inferiority will be claimed if the upper limit of the 95% CI for the hazard ratio is ≤1.3 for the per-protocol analysis. The non-inferiority margin has been selected as representing a minimal difference of clinical interest, which has been found useful in a number of cardiovascular risk contexts, including Food and Drug Administration's (FDA) guidance on cardiovascular risk in anti-diabetic compounds[ii].

Assuming a 12 month accrual period, an average of 36 month evaluation period after completion of accrual and an APTC cardiovascular event rate at 3 years in the allopurinol treatment arm conservatively estimated at 10%, then 2282 patients will be required in each treatment arm to detect the 456 events.

Since an on-treatment analysis will result in reduced follow-up that is difficult to predict a-priori, assuming a dropout rate of 20%, we intend to recruit 2853 patients in each treatment arm, 5706 patients overall and to continue follow-up for an average of at least 3 years and until it is predicted that at least 456 APTC events are identified in the OT analysis.

In the event that the target number of OT events is not achieved, the power will be recalculated based on the actual events achieved and the assumed non-inferiority limit of 1.3. In addition, the non-inferiority limit that would provide a power of 80% will be calculated. These will be calculated after database lock.

1.6. STATISTICAL ANALYSIS PLAN (SAP)

1.6.1. SAP OBJECTIVES

The objective of this SAP is to describe the statistical analyses to be carried out for the FAST final analysis.

1.6.2. General Principles

The final report will summarise data overall and by treatment group.

Continuous variables will be summarised by the number of observations, number of missing values, mean, standard deviation (SD), median, quartiles and range. Categorical variables will be summarised by the number of observations, number of missing values and the number and percentage of individuals in each category.

All analyses will be adjusted for the randomisation stratification variables and country (Scotland/England/Denmark/Sweden).

The study protocol refers to a Per-Protocol (PP) population. This terminology is misleading as the primary aim is to focus on the period of time individuals are on treatment rather than on a subset of the population. Hence, in this document we use the term On-treatment (OT) rather than PP. No specific PP population is analysed. The focus is on validly randomised participants analysed according to ITT and OT.

1.6.3. Current Protocol

The current version of the protocol at the time of writing is version 20 dated 29th June 2018. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. This will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.6.4. Deviations to those specified in the protocol

The analysis of subgroups differs from that specified in the protocol. The protocol approach does not meet the guidelines where valid subgroup should be based solely on baseline data.

The hs CRP values received were not believed to be reliable and were therefore omitted from this analysis.

1.6.5. Additional analyses to those specified in the protocol

As a result of the CARES study findings, additional analyses will be performed regarding baseline renal function and events occurring following the end of investigational medicinal product (IMP) exposure. In addition, due to new data on the possible cardiovascular benefits of colchicine, additional analyses are planned to assess the impact of colchicine use as prophylaxis in the FAST study on outcomes with a focus on coronary disease. We will also examine the impact of non-steroidal anti-inflammatory drugs (NSAID) use as prophylaxis in the FAST study on outcomes.

Additional subgroup analyses have been included in addition to those specified in the protocol.
hs TnI has been added as a baseline covariate.

1.6.6. Software

Analyses will be conducted using SAS for Windows v9.4, or higher.

2. ANALYSIS

2.1. STUDY POPULATIONS

The randomized population to be used for efficacy analyses will include all randomized participants excluding those where there are valid concerns regarding the validity of their data. The consort diagram will summarise the numbers of patients excluded from the analysis.

The number of subjects consented and screened, entering the allopurinol lead-in phase, excluded during the lead-in phase, randomised, withdrawn from randomised treatment and withdrawn from all study follow-up will be summarised. Time in the study (from randomisation) will be also be summarised.

The number of subjects recruited from each region will also be summarised.

The frequency of, and times to complete, withdrawal from follow-up (including record linkage) and withdrawal from randomised study drug (allopurinol or febuxostat) will be summarised by treatment group and depicted graphically using cumulative incidence plots. The reasons for complete withdrawal from follow-up and reasons for withdrawing from study drug (allopurinol or febuxostat) will be summarised.

The safety population is defined as the randomised population excluding those for whom we have clear evidence that no study drug was taken.

2.2. MAIN ANALYSIS END OF STUDY AND CENSORING PROCESS

The first analysis to be carried out will be a non-inferiority analysis of the primary outcome based on an OT analysis (covering the period patients remain on randomised therapy), with a supporting non-inferiority analysis using an intention-to-treat (ITT) analysis. If non-inferiority is demonstrated, a superiority analysis will be carried out based on ITT. If non-inferiority is not demonstrated, the results of the superiority analysis be will reported in the study report without a p-value.

The OT analysis will censor patients after permanent discontinuation from original randomised therapy, death from any cause not included in the endpoint being considered, date of withdrawal of all consent to participate further in the study, date of loss to follow-up or end of study, whichever occurs first.

The ITT analysis will censor patients after death from any cause not included in the endpoint being considered, date of withdrawal of all consent to participate further in the study, date of loss to follow-up or end of study, whichever occurs first.

Corresponding analyses will be reported on all secondary endpoints.

Patients will be censored in the survival analysis at the earliest of the following dates:

OT analysis:

- Date of withdrawal of consent to participate further in the study
- End of study date
- Date permanently discontinued from randomised treatment (date of last study drug intake recorded in the case report form or, if not known, 56 days after the last recorded supply of study medication)
- Date of death (if it is not part of the endpoint under consideration)

ITT analysis:

- Date of withdrawal of all consent to participate further in the study including withdrawal from record-linkage follow up.
- End of study date
- Date of death (if it is not part of the endpoint under consideration)

2.3. BASELINE CHARACTERISTICS

The following baseline information will be summarised for the randomised population, overall and by treatment group:

Demographic and lifestyle characteristics:

- Age, sex, ethnicity, smoking history, alcohol consumption, BMI, waist circumference, hip circumference, country

Vital signs data:

- Blood pressures, heart rate.

All laboratory parameters.

Cardiovascular, gastrointestinal (GI) and other medical histories:

- MI, cerebrovascular incident, transient ischaemic attack (TIA), established peripheral vascular disease, peripheral revascularisation, high blood pressure, other acute coronary syndrome, coronary revascularisation, angina pectoris requiring medical treatment, heart failure, raised cholesterol, evidence of CVD, peptic ulcer, GI bleeding, renal disease, asthma, chronic obstructive pulmonary disease (COPD), cancer (excluding minor skin cancers) in previous 5 years, diabetes, other significant chronic and ongoing diseases.

Cardiovascular risk factors:

- Age ≥70 years (male) or ≥75 years (female), smoking (current or within the last two years), diabetes mellitus, impaired glucose tolerance, hypertension, dyslipidaemia, chronic kidney disease stage 1-3, microalbuminuria or proteinuria, family history of CHD or stroke, inflammatory arthritis, chronic NSAID therapy, previous CV event (MI, CVA or TIA),

previous stroke, MI or other acute coronary syndrome, peripheral vascular disease, COPD, BMI > 30 kg/m^2

Gout measurements:

- Age when symptoms of gout/hyperuricaemia started, number of joints affected, gout attack affecting big toe (yes/no), crystals of gout under the skin (yes/no), any episode of acute painful gout in the past 12 months.

Allopurinol current dose and length of time on treatment (at screening).

Final dose of allopurinol at the end of the allopurinol lead-in phase.

All medications reported at the screening visit will be summarised to WHO (version Dec 1 2005 Format C) ATC levels 1 and 4. In addition the following prescribed medication groupings will also be summarised: thiazides diuretics; loop diuretics; ACEI; amoxicillin; ampicillin; capecitabine; azathioprine; mercaptopurine; didanosine; statins; antiplatelets; aspirin; NSAIDs; anticoagulants; proton pump inhibitors; corticosteroids; diabetes drugs; SGLT2 inhibitors; insulin; ibuprofen; and colchicine. Over-the-counter aspirin; ibuprofen and colchicine will be combined with the prescribed drugs in the summary tables.

All baseline characteristics are recorded at the screening visit with the exception of lab data. The lab data were recorded during the lead-in phase, where the last non-missing value is taken as the baseline value. The allopurinol doses were recorded at screening and during the lead-in phase. Both the screening dose and last pre-randomisation dose are summarised.

2.4. Efficacy Endpoints

2.4.1. Primary endpoint

The primary analysis will be the time from randomisation to first occurrence of any event included in the APTC composite endpoint of:

- Acute non-fatal MI/ biomarker positive acute coronary syndrome (ACS) (reported to have been a reason for hospitalisation)
- Stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation)
- Cardiovascular death (including undetermined deaths)

Cardiovascular events, other than revascularisations and TIAs, will be adjudicated by a blinded independent committee.

A time-to-event analysis will be carried out for the primary endpoint, using a Cox proportional hazards model including the randomised treatment group and randomisation stratification variable (whether or not the patient had a history of cardiovascular events (myocardial infarction, stroke or hospitalisation due to congestive heart failure or peripheral vascular disease)) and country as covariates. From this model, the estimated treatment effect, 95% confidence interval and p-value from the Wald statistic will be presented. A cumulative incidence plot of events by treatment group will be produced. The first analysis will be carried out OT with a follow-up ITT analysis. The numbers of participants with first events,

crude percentage of participants with events, rates of events /100 participant years of follow-up will be summarised by treatment group.

Note that for data protection legislation reasons, follow-up will be incomplete in participants who withdraw all consent to participate in the study. Note also that patients may now have the right to ask that all their data be deleted so it may be that some participants who are randomised may be deleted from the database. NHS-Digital in England have informed us that we cannot get any data via record linkage for participants who have withdrawn consent, even data up to the point of withdrawal if it has not previously been provided. We will still obtain investigator reported data from all regions and via record linkage from regions other than England up to the date of withdrawal. A technical problem in Denmark may result in a lack of record-linkage data in 2019. Sweden may not be able to provide record linkage data despite our best efforts to get this.

To adjust for the possibility of differential dropout in the OT analysis, a further analysis will be carried out adjusting for baseline age, sex, LDL- and HDL-cholesterol and hs TnI, systolic blood pressure (SBP), smoking status and histories of diabetes, hypertension and cardiovascular disease. Missing baseline data will be imputed using the other non-missing baseline covariates with a stochastic regression model using a single imputation.

2.4.2. SUBGROUP ANALYSES

Subgroup analyses will be carried out for the primary endpoint. For each of the baseline covariates noted below, p-values for the test of the interaction between the variable defining the subgroup and randomized treatment allocation will be derived using the Wald statistic.

1. History of myocardial infarction, stroke or other acute coronary syndrome (yes/no), individually and in combination.
2. Age (above/below median)
3. Sex (male/female)
4. Baseline CV risk factors (<3/ 3 or more)
5. Years since gout diagnosis (above/below median)
6. Ethnicity (white or non-white)
7. Family history of CHD or stroke (yes/no)
8. Baseline SBP (above/below median)
9. Baseline total cholesterol (above/below median)
10. Baseline HDL cholesterol (above/below median)
11. BMI (above/below median)
12. Smoking status (current/former/never)
13. Diabetes (yes/no)
14. Heart failure (yes/no)
15. Baseline (screening) Aspirin use (yes/no)
16. Baseline (screening) Lipid lowering therapy use (yes/no)
17. Hypertension (yes/no)
18. Baseline (screening) Antihypertensive drug use (yes/no)
19. Baseline (pre-randomisation) sUA (<6 mg/dL/>=6mg/dL)
20. Baseline (pre-randomisation) sUA (<5 mg/dL/>=5mg/dL)

21. Pre-randomisation allopurinol use (above/below median)
22. Baseline renal function (eGFR above/below median)
23. Pre-randomised dose of allopurinol

2.4.3. SECONDARY ENDPOINTS

Secondary endpoints will be:

- Hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS)
- Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation)
- Cardiovascular death (including undetermined deaths)
- All-cause mortality
- Hospitalisation for heart failure
- Hospitalisation for unstable, new or worsening angina
- Hospitalisation for coronary revascularisation*
- Hospitalisation for cerebral revascularisation*
- Hospitalisation for transient ischaemic attack (TIA)
- Hospitalisation for non-fatal cardiac arrest
- Hospitalisation for venous and peripheral arterial vascular thrombotic event
- Hospitalisation for arrhythmia with no evidence of ischaemia

* Not formally adjudicated

Note that the TIAs were clinically reviewed (blinded) centrally but not by the endpoint committee.

The secondary endpoints will be analysed for both ITT and OT in the same manner as the primary endpoint. Should the total number of events (for any secondary endpoint) be less than 10, the Cox regression analysis will be replaced by a Fishers' Exact test.

2.4.4. EXPLORATORY ANALYSES

The proportion of patients, split by randomised treatment group, whose serum uric acid (sUA) level is ≥6.0 mg/dL vs. <6.0 mg/dL and ≥5.0 mg/dL vs. <5.0 mg/dL after each year of treatment will be assessed using logistic regression analysis, adjusted for the stratification variable and country, with p-values, estimated odds ratios and 95% confidence intervals.

Incident cancers will be grouped by site of cancer.

2.4.5. ADDITIONAL ANALYSES

In addition to the main analysis noted above, a sensitivity analysis will extend the censoring dates for withdrawal from treatment in the OT analysis by 90 days or to the end of study date, whichever occurs soonest, to account for the fact that withdrawal or crossover may be

a presage of disease. This will be done for the primary outcome and all secondary outcomes on the OT analysis.

Additional analyses will be carried out for the primary endpoint, CV death and all-cause death. Comparing, groups defined by:

i) Initial gout flare prophylaxis (colchicine vs. NSAID vs. neither)
ii) Any concomitant use of aspirin (yes vs. no)
iii) Any concomitant use of an NSAID (yes vs. no)
iv) Any concomitant use of colchicine (yes vs. no)

All of these analyses will be adjusted for the stratification variable, country and randomized treatment group and the list of baseline covariates specified in 2.4.1.

2.4.6. Assumption Checking

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

2.5. Safety Outcomes

Safety outcomes post randomisation will be presented for the safety population, that is the randomised population excluding those where we have clear evidence that no study drug was taken. Subjects omitted from the safety analysis will have their adverse event (AE)/serious adverse event (SAE) data listed except for subjects who have withdrawn consent for all of their data to be used in the study.

2.5.1. Analysis Periods

The safety analyses for AEs, SAEs and Deaths will be carried out for each of the following follow-up dates: 1 – date of death/withdrawal of consent to record linkage or end of study plus 28 days (non-deaths/withdrawal of consent to record linkage) and 2 – date of death/withdrawal of consent to record linkage or end of study IMP plus 28 days (whichever date comes first).

All SAEs and non-serious adverse events considered related to study drug that occur prior to randomisation will be listed.

2.5.2. Treatment Exposure

The total dose dispensed for the randomised study treatment and in addition NSAIDs, colchicine and PPIs will be summarised.

2.5.3. Adverse Events, Serious Adverse Events and Deaths

AEs considered related to study treatment, SAEs and SAEs considered related to study drug and deaths will be summarised by treatment group, by system organ class and preferred term as classified by MedDRA (version 13_1). In addition an overall summary table will be provided for related AEs (all, severe, action taken of drug withdrawn, severe with action taken of drug withdrawn) and SAEs (all, action taken of drug withdrawn, severe, related SAE, related SAE with action taken of drug withdrawn). The total number of events, numbers of participants with first events, crude % of participants with events, rates of events /100 participant years of follow-up will be summarised by treatment group.

The distribution of the total number of events will be reported for each category of intensity (SAE related AE), action (SAE) and outcome (SAE).

The occurrence of gout flares during the lead-in phase will be summarised for those who have had allopurinol up-titrated during this phase. The post randomisation frequency of occurrence of gout flares will be analysed using a negative binomial regression model.

Cumulative incidence plots by treatment group will be produced separately for the time to first serious adverse event and time to death.

2.5.4. Laboratory Values

Laboratory values and changes from baseline will be summarised for the annual visits and for the final assessment using box and whisker plots and using means and 95% CIs, medians, lower and upper quartile and ranges. Results may be transformed as appropriate.

2.5.5. Concomitant medications

The number and percentage of patients reporting use of concomitant medication during the post-baseline period will be summarised overall and by Anatomical Therapeutic Chemical classification codes (WHO-DD). Tabulations will be sorted by ATC class (level 1 and level 4).

3. Tables and Figures

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

4. Listings

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

Any listings required for the regulatory submission will be produced in both Word and PDF format.

5. Document History

This is version 1.0 of this document, dated 24th August 2020, and is the original creation.

[i] White WB, Saag KG, Becker MA et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1201-1210.

ii Guidance for Industry: Diabetes Mellitus - Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes, FDA, December 2008.

Febuxostat versus Allopurinol Streamlined Trial (FAST)

A prospective, randomised, open-label, blinded endpoint (PROBE) clinical trial evaluating the long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia

EUDRACT No: 2011-001883-23

ISRCTN No: ISRCTN72443278

Date: **29/06/18**

Version: **20.0**

Professor Thomas M MacDonald

On behalf of the FAST investigators.

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Contents

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACS	Acute Coronary Syndrome
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
APTC	Anti-platelet Trialists' Collaboration
AST	Aspartate aminotransferase
BMI	Body mass index
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CKD	Chronic kidney disease
CoA	Certificate of analysis
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRO	Clinical trial organisation
CTSU	Clinical trial supplies unit
eCRF	Electronic case report form
CV	Cardiovascular
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
EU	European Union
EULAR	European League Against Rheumatism
FAST	Febuxostat versus Allopurinol Streamlined Trial
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good manufacturing process

GP	General Practitioner
GRO	General Registrar Office
HDL	High density lipoprotein
hsCRP	High sensitivity C-reactive protein
ICH	International Conference on Harmonisation
HRC	Hypertension Research Centre
IDMC	Independent data monitoring committee
IMP	Investigational Medicinal Product
ITT	Intention to treat
LDL	Low density lipoprotein
LTE	Long-term extension
MEMO	Medicines Monitoring Unit
MHRA	Medicines and Healthcare Product Regulatory Agency
MI	Myocardial infarction
MLD	Maximum licensed dose
MREC	Multi-Centre Research Ethics Committee
MSU	Monosodium urate
MTD	Maximum tolerated dose
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PICTF	Pharmaceutical Industry Competitive Task Force
PP	Per-protocol
PROBE	Prospective, randomised, open label, blinded endpoint
PVD	Peripheral vascular disease
RMP	Risk management plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SmPC	Summary of product characteristics
SMR1	Scottish Morbidity Record One
sUA	Serum uric acid

SUSARS	Suspected unexpected serious adverse drug reactions
TIA	Transient ischaemic attack
TSH	Thyroid stimulating hormone
UGT	Uridine diphosphate glycosyltransferase
ULT	Urate lowering therapy
UK	United Kingdom
WOSCOPS	West of Scotland Coronary Prevention Study
XO	Xanthine oxidase

1. Synopsis

Study Title:	Febuxostat versus Allopurinol Streamlined Trial (FAST) A prospective, randomised, open-label, blinded endpoint (PROBE) clinical trial evaluating the long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia Study EUDRACT n° 2011-001883-23
Study Objectives:	To compare the cardiovascular (CV) safety profile (in terms of Anti-Platelet Trialists' Collaboration [APTC] events) of febuxostat versus allopurinol when taken for an average of 3 years in patients aged 60 years or older with chronic hyperuricaemia in conditions where urate deposition has already occurred. The secondary study objectives are to evaluate other cardiovascular adverse events for both products.
Phase of Trial:	Phase IV post authorisation safety study.
Study Design:	This study is designed as a prospective, randomised, parallel group, open label, blinded endpoint (PROBE) study comparing febuxostat versus allopurinol in the clinical setting (General Practitioners and specialists) within specified European countries. Trial centres will be set up in Scotland, England and Denmark. Other European countries could be set up in case of slow rate recruitment, e.g. Sweden and the Netherlands. The study population will include patients with chronic hyperuricaemia (in conditions where urate deposition has already occurred) with cardiovascular risk factors (i.e. patients 60 years or older and with at least one other CV risk factor). The estimated ratio of male to female patients is 70% to 30% respectively. All consented and screened patients potentially eligible for the study will receive allopurinol treatment prior to randomisation (allopurinol lead-in phase) according to the European League Against Rheumatism (EULAR) recommendations and the current summary of product characteristics (SmPC). All patients will have their serum uric acid (sUA) levels determined. If the patient is below the target sUA level of 6 mg/dL, no dose escalation is required. Patients with a sUA level of ≥6 mg/dL will have their allopurinol dose optimised according to clinical judgement, EULAR recommendations and the current SmPC. This process will continue until the physician considers that the optimal allopurinol dose level has been reached for each patient, by achieving either a sUA level of <6 mg/dL, or reaching either the maximum tolerate dose (MTD) or the maximum licensed dose (MLD) with due regard to the patient's renal function.

	At the end of the allopurinol lead-in phase, patients with a sUA level of <6 mg/dL or receiving the MTD/MLD of allopurinol will be randomised in a 1:1 ratio to receive either febuxostat or allopurinol treatment. Randomisation will be stratified according to whether or not the patients had a history of the following cardiovascular events: myocardial infarction (MI), stroke or previous hospitalisation due to congestive heart failure (CHF) or peripheral vascular disease (PVD). After randomisation all patients will undergo a washout period of one week (window 7 to 21 days) prior to initiation of study treatment. During the washout period, they must not receive urate lowering therapy (ULT). Patients who require allopurinol dose titration should continue to receive gout flare prophylaxis during the washout period. Gout flare prophylaxis will not be given during the washout period to patients who do not require allopurinol dose titration. All patients randomised to allopurinol will receive allopurinol treatment at the dose determined before randomisation. During the course of the study, the dose can be adjusted according to clinical judgement as determined by EULAR recommendations and the current SmPC. All patients randomised to febuxostat will initially receive febuxostat 80 mg daily. Patients will have their sUA level determined after 2 weeks of febuxostat treatment (9 to 24 days), and patients with a sUA level of ≥6 mg/dL will have their febuxostat dose increased to 120 mg daily, followed by the determination of their sUA level 2 weeks later. Patients will then continue to receive treatment according to clinical judgement, EULAR recommendations and the current SmPC. Patients should receive prophylaxis for gout flare for 6 months from the start of the allopurinol lead-in phase, or for 6 months after starting randomised medication as appropriate, and for 6 months following any subsequent adjustment in ULT. Prescription of treatment medication for gout flares (preventive or curative) will be in accordance with EULAR recommendations and the current SmPC. Four gout flare prophylaxis regimens will be available to the trial investigator or designee: First line: colchicine 0.5 mg once or twice daily. Second line: naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily. Third line: meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily. Fourth line: diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

	Patients will be followed up for an average of 3 years from randomisation. Follow-up will be scheduled at two monthly (± one month) intervals by phone, letter or visit to the patient by the study nurses or medical staff. The follow-up of outcomes will be done by record-linkage, in countries where this is possible, to hospitalisations and deaths and by direct reporting by study site coordinators. Each patient's sUA, serum creatinine determinations, liver function tests and eGFR calculations will be monitored at a central laboratory annually (±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study. Additional laboratory assessments including sUA measurements may be undertaken at the discretion of the primary care physicians as part of the standard clinical care, EULAR recommendations and according to the current SmPC. The trial will be powered to demonstrate that febuxostat is not inferior to standard allopurinol therapy for the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular composite endpoint. The study will terminate after patients have been followed up for an average of at least 3 years and until at least 456 APTC events have been identified in the per-protocol (PP) population.
Study Population:	5706 patients in total (2853 in each treatment group) from more than one European country will be randomised in the study. The estimated ratio of male to female patients is 70% to 30% respectively. **Inclusion Criteria** 1. Male or female patients aged 60 years or older with at least one additional cardiovascular risk factor: • Age ≥70 years (male) or ≥75 years (female) • Smoking (current or within the last 2 years) • Diabetes mellitus • Impaired glucose tolerance • Hypertension (SBP >140 mmHg and/or DBP >90 mmHg) or receiving treatment to lower blood pressure • Dyslipidaemia (investigator assessment) • Chronic kidney disease (CKD) • Microalbuminuria or proteinuria • Family history of coronary heart disease or stroke in first degree relative at age <55 years • Inflammatory arthritis (investigator assessment – including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis) • Chronic NSAID therapy (investigator assessment)

	• Previous cardiovascular (CV) event (MI, cerebrovascular accident [CVA]-or transient ischaemic attack [TIA]) • Peripheral vascular disease (investigator / clinical assessment) • Chronic obstructive pulmonary disease (COPD) • Body mass index >30 kg/m^2 2. Patients who, in the opinion of the recruiting physician, require treatment for chronic hyperuricaemia where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis) fulfilling the recommendation for treatment with urate lowering therapy. 3. Patients who have received ≥60 days treatment with allopurinol, or ≥2 allopurinol prescriptions, within the previous 6 months. 4. Patients, who in the opinion of the recruiting physician or study site coordinator, are eligible for treatment (with reference to the summary of product characteristics) with either allopurinol or febuxostat. 5. Patients who are willing to give permission for their paper and electronic medical records, hospitalisation data, prescribing data, and (in the event of their death) their death certification data to be accessed and abstracted by trial investigators. 6. Patients who are willing to be contacted and interviewed by trial investigators or delegates (suitably trained research nurses), should the need arise (e.g., for adverse event [AE] assessment and to determine whether an episode of acute gout has occurred). **Exclusion Criteria** 1. Patients who have any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics) or any of the components of their formulations. 2. Patients who are not receiving allopurinol as ULT. 3. Patients with severe renal impairment (eGFR <30 mL/min as defined by the Cockroft-Gault formula (http://www.nephron.com/cgi-bin/CGSI.cgi) according to creatinine, age, sex and body weight). 4. Patients with moderate or severe hepatic impairment i.e. cirrhosis with clinical and/or biological decompensation (i.e. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x reference value, ascites, lower limb oedema, icterus or increased prothrombin time >2x reference value). 5. Patients with a life-threatening co-morbidity or with a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol.

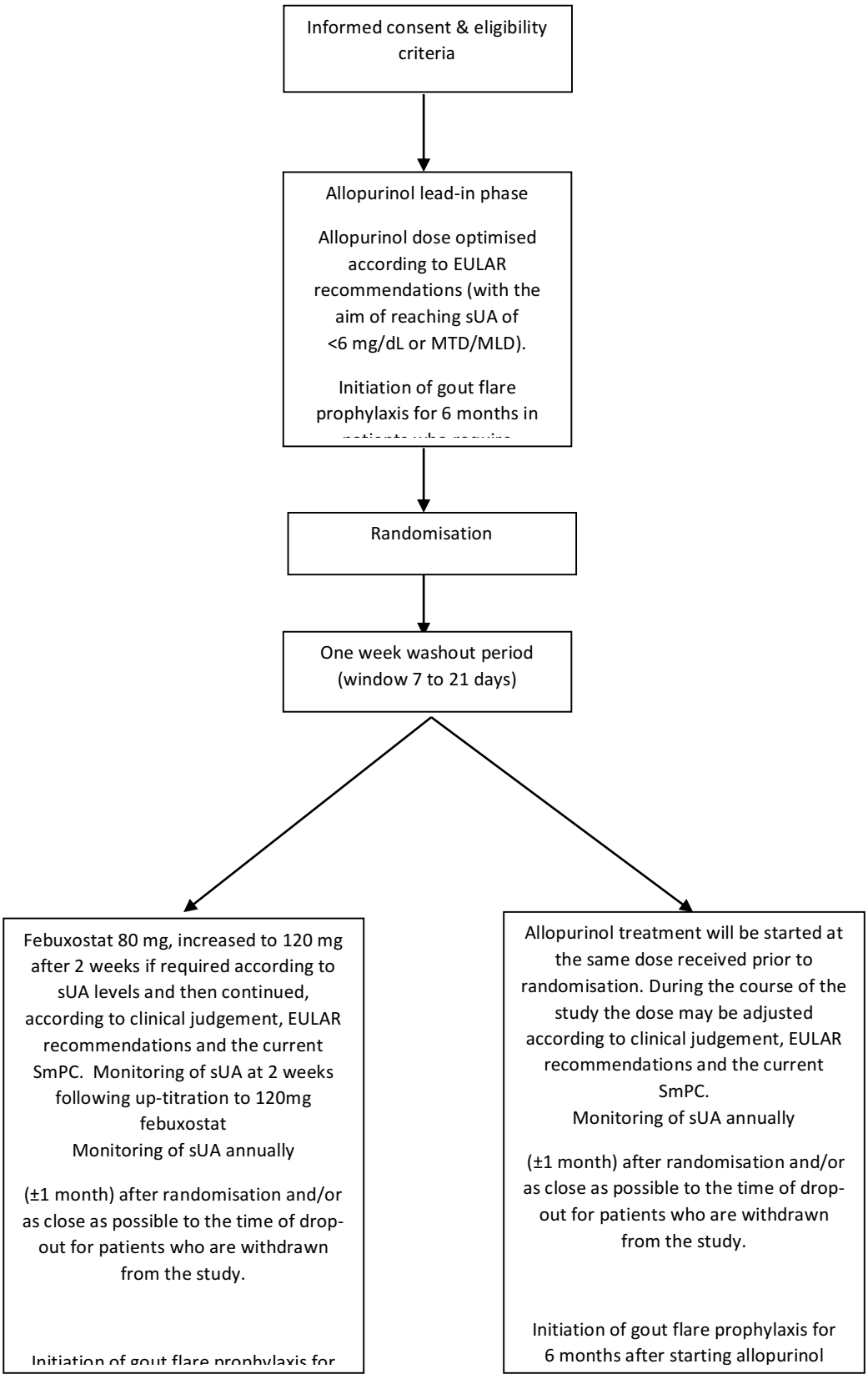
	6. Patients with a diagnosis of, or receiving treatment for malignancy (excluding minor skin cancer and indolent cancers that are not thought to be life threatening and require no treatment) in the previous 5 years. (Investigator opinion) 7. Patients who have experienced either a myocardial infarction or stroke within the 6 months prior to the screening visit. 8. Patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV. 9. Patients whose behaviour or lifestyle would render them less likely to comply with study medication (i.e., abuse of alcohol, substance misuse, debilitating psychiatric conditions or inability to provide informed consent). 10. Patients with a current acute gout flare or who are within 14 days of the resolution of a gout flare. 11. Patients currently participating in another clinical trial or who have participated in a non-interventional clinical trial in the previous 1 month or an interventional clinical trial in the previous 3 months..
Study Treatment:	**Investigational Medicinal Product (IMP):** **Febuxostat 80 or 120 mg:** one tablet daily. All patients randomised to febuxostat treatment will receive 80 mg initially, which may be increased to 120 mg daily at the discretion of the investigator, based on clinical judgement, EULAR recommendations and the current SmPC.
	Allopurinol: 100 or 300 mg tablets. After screening and consent, and before randomisation, all patients will receive allopurinol at a dose optimised according to clinical judgement, EULAR recommendations and the current SmPC with a goal to achieve either a sUA level of <6 mg/dL or the MTD/MLD for that patient. In accordance with the current SmPC, allopurinol dosing may be in the range of 100 to 900 mg per day. Patients will undergo a washout period of one week (window 7 to 21 days) after randomisation and prior to initiating study treatment. Patients randomised to allopurinol will receive allopurinol at the dose determined before randomisation. During the course of the study, the dose can be adjusted according to clinical judgement as determined by EULAR recommendations and the current SmPC. Every attempt should be made to maintain patients on randomised medication. Physicians may prescribe rescue gout prophylaxis (with the exception of the alternative study treatment) to patients randomised to either arm of the study in order to maintain them on randomised treatment. If a trial investigator (or designee) decides a change in treatment is necessary i.e. discontinues randomised medication in favour of an alternative ULT, the patient will be withdrawn from the per-protocol analysis. However, all patients will be followed up until the end of the trial for the intention to treat analysis (ITT) unless they withdraw consent for follow-up.

	In line with current clinical practice, patients will stay in the study even if they do not have a sUA level of <6 mg/dL at any dosage during the study, even after appropriate dose increases of febuxostat or allopurinol.
	Treatment of Gout Flares Prescription of treatment medication for gout flares (preventive or curative) will be in accordance with EULAR recommendations and the current SmPC. Four gout flare prophylaxis regimens will be available to the trial investigator or designee: First line: colchicine 0.5 mg once or twice daily. Second line: naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily. Third line: meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily. Fourth line: diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily. Patients should receive prophylaxis for gout flare for 6 months from the start of the allopurinol lead-in phase, or for 6 months after starting randomised medication as appropriate, and for 6 months following any subsequent increase in ULT. Training on the current recommendations for the management of gout (ULT and prevention of gout flares) will be given to the trial investigators before study initiation.
Study Evaluations:	Details of demography, lifestyle characteristics, medical history, co-morbidities and concomitant medications will be recorded at screening. sUA will be monitored at a central laboratory annually (±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study. Additional laboratory assessments including sUA measurements may be undertaken at the discretion of the primary care physicians as part of the standard clinical care, EULAR recommendations and according to the current SmPC. **Primary Endpoint(s) and Evaluation(s):** The primary analysis will be the time from randomisation to first occurrence of any event included in the APTC composite endpoint of: • Hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS) • Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation) • Death due to a cardiovascular event

	Cardiovascular events will be adjudicated by a blinded independent committee.
	Secondary Endpoints and Evaluations: The following secondary endpoints (in rank order of importance) will be evaluated using a time to event analysis: • Hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS) • Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation) • Cardiovascular death • All cause mortality • Hospitalisation for heart failure • Hospitalisation for unstable, new or worsening angina • Hospitalisation for coronary revascularisation* • Hospitalisation for cerebral revascularisation* • Hospitalisation for transient ischaemic attack (TIA) • Hospitalisation for non-fatal cardiac arrest • Hospitalisation for venous and peripheral arterial vascular thrombotic event • Hospitalisation for arrhythmia with no evidence of ischaemia * Not formally adjudicated The following endpoints will be evaluated as an incidence rate: • Cardiovascular mortality • APTC events in each treatment arm **Exploratory Efficacy Endpoint(s) and Evaluation(s):** The proportion of patients whose sUA level is ≥6.0 mg/dL, <6.0 mg/dL and <5.0 mg/dL after each year of treatment. **Independent Data Monitoring Committee** An independent data monitoring committee (IDMC) will receive and review un-blinded patient data on an on-going basis. The IDMC will meet on a regular basis to provide appropriate recommendations for the continuation of the study.
Statistical Methods:	**Sample Size Determination** Cohorts of patients who were dispensed allopurinol from 1994 to 2002 were defined from the Tayside Medicines Monitoring Unit (MEMO) database[i]. The Scottish Morbidity Record One (SMR1) database of hospitalisations and the General Registrar Office (GRO) database of deaths in Scotland were then searched for events occurring in these patients up to 2002. Tables of event rates were generated. For patients with chronic hyperuricaemia aged 60 years or over who were initially free from cardiovascular events, the APTC event rate was 5.4% at Year 1, 10.1% at Year 2 and 14.0% at Year 3.

	Power Calculations 456 APTC events are required to show non-inferiority between the febuxostat and allopurinol treatment arms assuming a non-inferiority limit for the hazard ratio of 1.3, with 80% power and a one sided alpha of 0.025. Non-inferiority will be claimed if the upper limit of the 95% confidence interval (CI) for the hazard ratio is ≤1.3 for the per-protocol analysis. Assuming a 12 month accrual period, an average of 36 months evaluation period after completion of accrual and an APTC cardiovascular event rate at 3 years on the allopurinol treatment arm of 10%, 2282 patients will be required in each treatment arm to detect 456 events. Assuming a dropout rate of 20% from the per-protocol population, we intend to recruit 2853 patients in each treatment arm, 5706 patients overall and to continue follow-up for an average of at least 3 years and until at least 456 APTC events are identified in the per-protocol set. The overall withdrawal rate will be monitored and the sample size may be increased if the withdrawal rate is higher than expected. Analyses will be performed for both the ITT and per-protocol (PP) populations, and results for the two populations will be compared. **Evaluations** Recruitment and blinded accumulation of study endpoints will be reviewed by the study steering committee on an ongoing basis to assess the need for changes to study conduct and/or design.

Study Flow Diagram



Schedule of Events

Visit	Screening	Allopurinol Lead In [a]	Random-isation[b]	Febuxostat Post- Rand.	Febuxostat Titration	2 Monthly Follow Up	Annual
Procedure							
Informed Consent	X						
Inclusion/exclusion	X						
Personal Details	X	X	X	X	X	X	X
Demographics (Including Lifestyle Factors)	X						
Medical History	X						
Concomitant Medication	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Blood Pressure & Pulse Rate	X						
Waist Circumference	X						
Hip Measurement	X						
Height	X						X
Weight	X						X
Urinalysis	X						
Blood Sample:							
U&E	X[d]						X[f]
Creatinine	X[d]						X[f]
ALT	X[d]						X[f]
AST	X[d]						X[f]
Bilirubin	X[d]						X[f]
Alkaline Phosphatase	X[d]						X[f]
Glucose	X[d]						

sUA	X[d]	X		X[e]	X[e]		X[f]
FBC	X[d]						
Prothrombin Time	X[d]						
Genetic sample (optional)	X[d]						
Adverse Events		X[G]	X[G]	X[G]	X[G]	X[G]	X[G]

a. Patients will have their allopurinol dose optimised based on their sUA levels according to clinical judgement, EULAR recommendations and the current SmPC. Patients will repeat the procedures for visit 2 at 2-week intervals until they achieve a sUA level of <6 mg/dL or reach the MTD/MLD.

b. Randomisation will be stratified according to whether or not the patient had a history of cardiovascular events (myocardial infarction [MI], stroke or hospitalisation due to congestive heart failure [CHF] or peripheral vascular disease [PVD]).

c. Concomitant medications will be tracked during the treatment period.

d. Serum creatinine, Liver function tests, transaminases, potassium, sodium, urea, glucose, eGFR, prothrombin time and a full blood count. Serum will be stored for future baseline analyses. For patients who sign an additional informed consent, a genetics sample will be collected and stored for potential pharmacogenetic and other baseline analyses outside of this study (see section 7.2).

e. sUA levels will be determined after 2 weeks of febuxostat treatment, and again 2 weeks later in patients being treated with febuxostat 120 mg.

f. Each patient's sUA, serum creatinine determinations, liver function tests and eGFR calculations will be monitored at a central laboratory annually (±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study. Additional laboratory assessments including sUA measurements may be undertaken at the discretion of the primary care physicians as part of the standard clinical care, EULAR recommendations and according to the current SmPC.

g. AEs are to be collected during the treatment period by record linkage in countries where this is possible (from NHS and practice databases) and patient self-reporting.

2. Introduction

Gout affects at least 1% of the population in Western countries and is the most common inflammatory joint disease in men older than 40 years of age. The UK prevalence of gout was reported to be 1.4% in 1999. Historically a disease of affluent, middle-aged or older men, gout has now affected more women and a wider range of socioeconomic groups.

Gout progresses from episodic flare-ups of acute inflammatory arthritis to a disabling chronic disorder characterised by deforming arthropathy, destructive deposits of crystals (tophi) in bones, joints and other organs, impairment of kidney functions and urolithiasis.

Gout is a true crystal deposition disease caused by the formation of monosodium urate crystals in and around joints.

Hyperuricaemia, usually defined as a serum uric acid (sUA) level >7 mg/dL, may be present in up to 18% of some populations. It results from inadequate renal excretion of uric acid relative to its production; the imbalance is most often due to a defect in the complex excretory mechanisms of the kidney. The overproduction of urate due to hereditary disorders of purine metabolism or other clinical disorders, as well as exogenous factors including diet, alcohol, and certain medications, can overwhelm these excretory mechanisms. When the blood level of urate, the end-product of purine metabolism, reaches its physiologic limit of solubility, it may crystallise into monosodium urate (MSU) in the tissues and cause gout flare. The diagnosis is confirmed if monosodium urate crystals are present in synovial fluid.

The risk of developing gout is directly related to the degree of hyperuricaemia. In a prospective study, the annual incidence of gout was 0.1% in men whose sUA levels were <7 mg/dL, 0.5% for levels between 7.0 and 8.9 mg/dL, and 4.9% for levels >9.0 mg/dL. In another study, the 5-year prevalence of gout was 0.6% in patients with urate levels <7 mg/dL, but 30% in patients with levels >10 mg/dL.

Cardiovascular disease is frequently observed in patients with elevations in sUA[ii,iii,iv,v,vi,vii]. While theories as to the specific causal relationship between elevated sUA and cardiovascular disease/mortality vary, the correlation between the two is widely recognised. sUA levels are increasingly believed to be an independent predictor of death in patients at high risk of cardiovascular disease.

Recently, the European League against Rheumatism (EULAR 2007) recommendations for gout management have been released[viii,ix]. First-line therapies for systemic treatment of acute gout are oral colchicine and/or non-steroidal anti-inflammatory drugs (NSAIDs). After the first gout flare, modifiable risk factors (e.g., high-purine diet, alcohol use, obesity, diuretic therapy) should be addressed.

Urate lowering therapy (ULT) is indicated in patients with recurrent acute flares, arthropathy, tophi or radiographic changes of gout. Nevertheless, there are no precise guidelines as to when to start ULT. A lengthy period of asymptomatic hyperuricaemia often precedes the first attack of gouty arthritis, and an even longer period may be required for tophi to form. After their first gout flare, however, most untreated patients will experience a second episode within two years.

For patients with severe established gout, ULT should be recommended, but opinion ranges from initiation of ULT after the first gout flare, through to waiting until further gout flares occur. Each clinical decision must be individualised according to specific patient characteristics.

The therapeutic goal of ULT is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the sUA below the saturation point for monosodium urate (≤357 µmol/L or ≤6 mg/dL). The ultimate goal of gout therapy is the prevention of recurrent flares and the resolution of tophi by lowering sUA to <6.0 mg/dL. Proof of the validity of this concept has emerged from clinical studies that have documented that reduction to and maintenance of sUA levels in this sub-saturating range of <6.0 mg/dL is accompanied by reduction in the incidence of gout flares over time[x], diminished numbers of residual urate crystals in the fluid aspirated from gouty joints[xi], and diminution in the size and number of tophi[xii].

As initiation of ULT can induce acute flare by causing urate mobilisation and rapid urate flux, concurrent prophylaxis with low-dose colchicine (0.5 to 1.0 mg daily) and/or an NSAID (with gastro-protection if indicated) for three to six months is used to prevent or minimise acute flares during initiation or upward titration of allopurinol as it has been shown to reduce the risk of flare-ups.

Allopurinol, a xanthine oxidase (XO) inhibitor, is currently the first-line urate-lowering therapy. Although approved for use in the US at a dose range from 100 to 800 mg daily, and from 100 mg to 900 mg in Europe, allopurinol is commonly dosed at 100 to 300 mg daily[xiii,xiv] despite recent evidence that sUA levels <6.0 mg/dL are achieved in less than 50% of current gout patients receiving 300 mg of allopurinol[xv]. Among other limitations of allopurinol therapy are: rashes, occasionally severe or life-threatening, in approximately 2% to 5% of treated patients, and a rare but frequently fatal allopurinol hypersensitivity syndrome. For all these patients uricosuric drugs (probenecid or sulfinpyrazone) are used as alternative treatment. However, they are contraindicated for patients with any degree of renal impairment and uric acid stones. In addition, in patients with impaired renal function, the reduced clearance of the allopurinol's active metabolite, oxypurinol, restricts increasing the dose above that recommended for any given level of glomerular filtration rate.

Febuxostat is a novel xanthine oxidase inhibitor indicated for treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred.

The febuxostat Phase III randomised controlled trials demonstrated that febuxostat 80 mg was superior to allopurinol 300 mg in achieving and maintaining the target sUA level of <6.0 mg/dL. The persistence of efficacy was demonstrated by data from the long-term, open-label extension studies in which the long-term maintenance of sUA levels <6.0 mg/dL was observed with up to 5.5 years of febuxostat treatment. These two studies confirmed that maintaining serum urate levels <6.0 mg/dL under treatment with febuxostat results in gout flares virtually disappearing (<1 gout flare per year on average) and in the resolution of tophi. The majority of patients had at least 75% reduction in tophus size with almost 50% of patients having complete resolution.

Febuxostat can be prescribed to patients with mild to moderate renal impairment without the need for dose adjustment. Mild to moderate renal insufficiency is common in patients with gout, with a prevalence ranging from 50% to 70%[xvi,xvii]. This subgroup of gout patients represents a challenge for successful urate-lowering therapy, as reduction of allopurinol dose is recommended for these patients[xviii] frequently resulting in failure to achieve the urate-lowering goal range[xiv]. Therefore, febuxostat provides an important alternative in the treatment of hyperuricaemia in gout patients with renal impairment. As an additional benefit, no dosage adjustment is necessary in elderly patients or in patients with mild hepatic impairment.

Febuxostat has shown no significant drug interactions with commonly used drugs and can safely be administered concurrently with a wide variety of drugs. Concomitant use of drugs acting on XO inhibition is not recommended. Potent inducers/inhibitors of UGT enzymes may be used with caution (monitoring of serum uric acid is recommended). See the SmPC for detailed information on drug interactions.

The safety profile of febuxostat has been evaluated over several years in clinical development supporting that febuxostat is well tolerated. In total, 4072 patients have received at least one dose of febuxostat for up to 5.5 years across Phase I, II, and III trials, ranging in doses from 10 mg to 300 mg, in the US clinical programme. The most commonly reported adverse drug reactions (ADRs) were liver function abnormalities (5.0%), diarrhoea (2.7%), nausea (1.3%), headache (1.2%) and rash (1.2%).

A numerically greater incidence of investigator-reported cardiovascular events was observed in the febuxostat total group compared to the allopurinol group in the combined Phase III (0.7 versus 0.6 events per 100 patient years) and long-term extension studies (1.2 versus 0.6 events per 100 patient years), although no statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction (MI), or of congestive heart failure.

2.1 Background

The European Union (EU) Risk Management Plan (RMP) for febuxostat (Version 2.0; 19 February 2008) indicates that a post marketing study to evaluate cardiovascular effects of febuxostat is to be conducted as part of the Pharmacovigilance Plan. An outline synopsis of this study was presented as Annex 5 of the RMP.

The present protocol is intended to fulfil this objective and describes a large safety study of febuxostat versus standard urate lowering therapy with allopurinol for chronic symptomatic hyperuricaemia. This study will compare the relative cardiovascular safety of the two treatment strategies.

2.2 Rationale for Study

A numerical but non-significant increase in cardiovascular events (the Anti-Platelet Trialists' Collaboration composite endpoint to non-fatal MI, non-fatal stroke and cardiovascular death: APTC) was seen with febuxostat when compared to allopurinol in the pivotal Phase III studies and long-term extension (LTE) clinical studies. Nevertheless, the incidence of primary APTC events was well within the range expected for patient populations with gout and a similar cardiovascular risk profile, based on published literature.

This study will use a prospective, randomised, open, blinded endpoint evaluation (PROBE) design. An open design allows real-world use of these drugs to be compared and it also allows for dose adjustments of the drug during the study phase when required.

There is an increasing trend towards PROBE-design studies in Phase IV, as they are easier to conduct and resemble clinical practice, for example, the ASCOT trial[xix].

Whilst the open label design resembles real-life clinical practice, the study is only open to the patients and the treating physicians with respect to the treatment received. Conversely, the primary endpoint evaluation will be blinded and will be performed by an independent endpoint committee who are not otherwise involved in the conduct of the study and who adhere to strict endpoint evaluation guidelines. The PROBE study design has produced equivalent results to double-blind, placebo controlled studies[xx].

3. Trial Objectives and Study Endpoints

The primary study objective is to compare the cardiovascular safety profile (in terms of Anti-Platelet Trialists' Collaboration [APTC] events) of febuxostat versus allopurinol when taken for an average of 3 years in patients 60 years of age or older with chronic hyperuricaemia in conditions where urate deposition has already occurred.

The secondary study objectives are to evaluate other cardiovascular adverse events for both products.

3.1 Primary Endpoints

The primary analysis will be the time from randomisation to first occurrence of any event included in the APTC composite endpoint of:

- Hospitalisation for non-fatal MI/biomarker positive ACS
- Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation)
- Death due to a cardiovascular event

Cardiovascular events will be adjudicated by a blinded independent committee.

3.2 Secondary Endpoints (in rank order of importance)

The following secondary endpoints (in rank order of importance) will be evaluated using a time to event analysis:

- Hospitalisation for non-fatal MI/ biomarker positive ACS
- Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation)
- Cardiovascular death
- All cause mortality
- Hospitalisation for heart failure
- Hospitalisation for unstable, new or worsening angina
- Hospitalisation for coronary revascularisation*
- Hospitalisation for cerebral revascularisation*
- Hospitalisation for transient ischeamic attack (TIA)
- Hospitalisation for non-fatal cardiac arrest
- Hospitalisation for venous and peripheral arterial vascular thrombotic event
- Hospitalisation for arrhythmia with no evidence of ischaemia

* Not formally adjudicated but counted for analysis
The following endpoints will be evaluated as an incidence rate:

- Cardiovascular mortality
- APTC events in each treatment arm

3.3 Exploratory Efficacy Endpoint

The proportion of patients whose sUA level is ≥6.0 mg/dL, <6.0 mg/dL and <5.0 mg/dL after each year of treatment.

3.4 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will receive and review un-blinded patient data on an on-going basis. The IDMC will meet on a regular basis to provide appropriate recommendations for continuation of the study. The structure, procedure and work-flow of the committee will be described in detail in a separate charter to be finalised prior to the IDMC's first review of study data.

4. Trial Design

4.1 Overall Trial Design

This randomised, parallel group clinical trial utilises the prospective, randomised, open, blinded endpoint (PROBE) design. For this study, patients with clinically diagnosed symptomatic hyperuricaemia who are 60 years of age or older, with at least one additional CV risk factor, and who

are currently prescribed allopurinol for chronic hyperuricaemia in conditions where urate deposition have already occurred will be identified in the setting of either primary or secondary care.

Trial centres will be set up in Scotland, England and Denmark. Other European countries could be set up in case of slow rate recruitment, e.g. Sweden and the Netherlands. The estimated ratio of male to female patients is 70% to 30% respectively.

All consented and screened patients potentially eligible for the study will receive allopurinol treatment prior to randomisation according to EULAR recommendations and the current SmPC (allopurinol lead-in phase). All patients will have their sUA levels determined. If the patient is below the target sUA level of 6 mg/dL, no dose escalation is required. Patients with a sUA level of ≥6 mg/dL will have their allopurinol dose optimised according to clinical judgement, EULAR recommendations and the current SmPC. This process will continue until the physician considers that the optimal allopurinol dose level has been reached for each patient, by achieving either a sUA level of <6 mg/dL, or reaching either the maximum tolerate dose (MTD) or the maximum licensed dose (MLD) with due regard to their renal function.

At the end of the allopurinol lead-in phase, patients with a sUA level of <6 mg/dL or receiving the MTD/MLD of allopurinol will be randomised in a 1:1 ratio to receive either febuxostat or allopurinol treatment. Randomisation will be stratified according to whether or not the patients had a history of the following cardiovascular events: MI, stroke or hospitalisation for congestive heart failure (CHF) or peripheral vascular disease (PVD).

Patients randomised to receive treatment with allopurinol or febuxostat will be treated in accordance with standard clinical practice as determined by the patient's study physician, EULAR recommendations and the current SmPC.

All patients will undergo a washout period of one week (window 7 to 21 days) after randomisation and prior to initiating study treatment during which they must not receive ULT. Patients requiring allopurinol dose titration should continue to receive gout flare prophylaxis during the washout period. Patients who do not require allopurinol dose titration will commence gout flare prophylaxis when they start randomised medication after the washout period.

All patients randomised to allopurinol will receive allopurinol at the dose determined before randomisation. During the course of the study, the dose can be adjusted according to clinical judgement as determined by EULAR recommendations and the current SmPC.

All patients randomised to febuxostat will initially receive febuxostat 80 mg daily. Patients will have their sUA level determined after two weeks (range 9 to 24 days) of febuxostat treatment after randomisation, and patients with a sUA level of ≥6 mg/dL will have their dose increased to febuxostat

120 mg daily. Patients will then continue to receive treatment according to clinical judgement, EULAR recommendations and the current SmPC.

Dose adjustments with either drug will be permitted where necessary, according to sUA levels or clinical need (for example intolerance requiring dose reduction) for both products, and according to renal function for allopurinol. These dose adjustments will be made as part of usual care, according to the respective SmPC. All changes will be approved by the patient's doctor or a study doctor. This will be documented using the Additional Patient Information Form and updated on the Study Portal.

Prescription of treatment for gout flares (preventive or curative) will be in accordance with EULAR recommendations and the current SmPC.

Four gout flare prophylaxis regimens will be available to the trial investigator or designee:

First line: colchicine 0.5 mg once or twice daily.

Second line: naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Third line: meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Fourth line: diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Patients requiring allopurinol dose titration should receive prophylaxis for gout flare for 6 months from the start of the allopurinol lead-in phase and for 6 months following any subsequent increase in ULT. Patients who do not require allopurinol dose titration will commence gout flare prophylaxis when they start randomised medication after the washout period. Training on the current recommendations for the management of gout (ULT and prevention of gout flares) will be given to the trial investigators before study initiation.

Patients will be followed up for an average of 3 years from randomisation by two-monthly (± one month) follow-up (by phone, email, letter or visit to the patient) and record-linkage with hospitalisations and deaths in countries where this is possible. Each patient's sUA, serum creatinine determinations, liver function tests and eGFR calculations will be measured at a central laboratory annually (±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study. Additional laboratory assessments including sUA measurements may be undertaken at the discretion of the primary care physicians as part of the standard clinical care, EULAR recommendations and according to the current SmPC.

The study will terminate after patients have been followed up for an average of at least 3 years and until at least 456 APTC events are identified in the per-protocol set, unless insufficient APTC adjudicated events have accrued to ensure 80% power to show non-inferiority, in which case the study will continue until sufficient events have occurred. This will compare the strategies of treating

symptomatic hyperuricaemia patients with current standard ULT (allopurinol) or treating with febuxostat in normal patient care.

4.2 Allopurinol Dose Optimisation

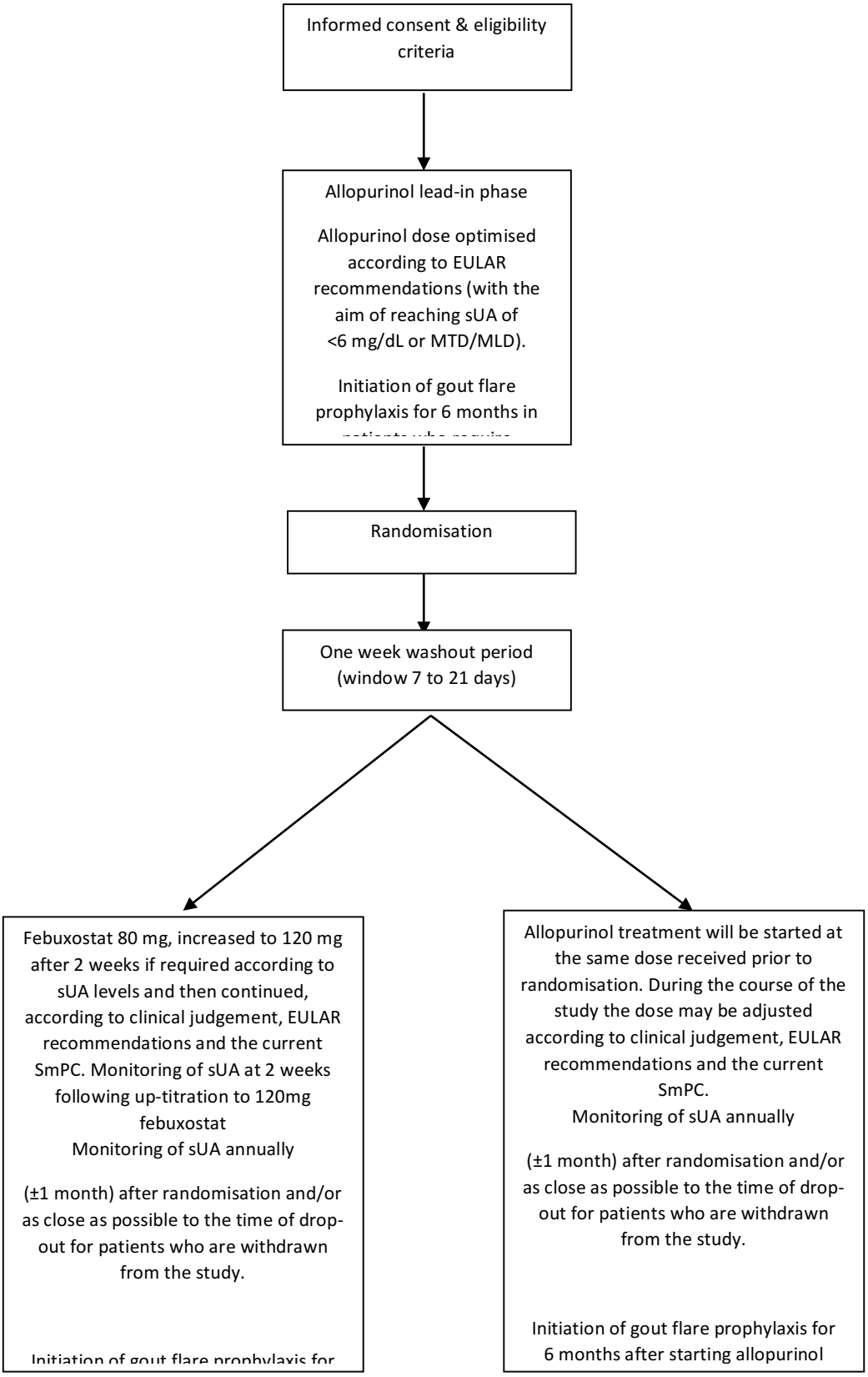
Data from 578 males aged 60 or over found that 37% received 100 mg allopurinol, 14.5% received 200 mg, 46% received 300 mg, 1.7% received 600 mg and only one patient received 900 mg. 36% had a sUA level at or less than 6 mg/dL, a further 18% were within 1 mg/dL of target, 15% had sUA between 7 and 8 mg/dL, 11% had sUA between 8 and 9 mg/dL and 20% were above 9 mg/dL.

Data from 324 women aged 60 or over found that 49% received allopurinol 100 mg or less, 17% got 200 mg, 33% got 300 mg with only three women getting higher doses. 35% had sUA at or less than 6 mg/dL, 13% were between 6 and 7 mg/dL, 15% were between 7 and 8 mg/dL, 11% were between 8 and 9 mg/dL and 26% were above 9 mg/dL.

From these figures it is apparent that about one third of patients enrolled in the study will require no change in allopurinol dosage. Guidelines suggest that sUA levels are reduced by 1 mg/dL for each dose increment of 100 mg of allopurinol[ix].

4.3 Trial Duration

The trial is designed to result in an average of three years exposure to randomised therapy as summarised in the figure below.


Informed consent & eligibility criteria
Allopurinol lead-in phase
Allopurinol dose optimised according to EULAR recommendations (with the aim of reaching sUA of <6 mg/dL or MTD/MLD).
Initiation of gout flare prophylaxis for 6 months in
Randomisation
One week washout period (window 7 to 21 days)
Febuxostat 80 mg, increased to 120 mg after 2 weeks if required according to sUA levels and then continued, according to clinical judgement, EULAR recommendations and the current SmPC. Monitoring of sUA at 2 weeks following up-titration to 120mg febuxostat
Monitoring of sUA annually
(±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study.
Initiation of gout flare prophylaxis for
Allopurinol treatment will be started at the same dose received prior to randomisation. During the course of the study the dose may be adjusted according to clinical judgement, EULAR recommendations and the current SmPC.
Monitoring of sUA annually
(±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study.
Initiation of gout flare prophylaxis for 6 months after starting allopurinol

5. Patient Selection

5.1 Study Population

Patients who fulfil the inclusion criteria will be recruited from the populations of participating European countries.

5.2 Regional Study Centres

Regional study centres will co-ordinate the study sites in their area. Regional centres will be responsible for recruiting and liaising with local study sites.

5.3 Study Sites

In the primary care setting a study site will be a participating general practice. Each practice will have at least one study site coordinator who will be a primary care physician who has received training in Good Clinical Practice (GCP). The study site coordinator will be responsible for facilitating the study within the practice, selecting suitable patients from an electronic search of possible patients within the general practice population and for reporting adverse events (AEs) leading to discontinuation of randomised study treatment, serious adverse events (SAEs) and possible study endpoints.

General practices may also operate as Patient Identification Centres (PICs) allowing access to their database for identification of potential patients. Searches in these practices will be carried out by practice staff or delegated study personnel with Caldicott Guardian or equivalent approval in all participating countries. Identified patients will be approved as eligible by a GP or delegated study doctor and invited to attend a screening visit either in the practice or at a convenient location such as Clinical Research Centre (CRC), regional site or other nearby clinical facility.

5.4 Study Patients: Selection Criteria

5.4.1 Primary Care

Potential study patients will be selected from their practice by carrying out a search of those patients aged 60 years or more who are taking chronic allopurinol in conditions where urate deposition has already occurred. Chronic allopurinol is defined as 60 days or more (or 2 or more prescriptions where the total duration of ULT cannot be precisely determined), prescribed in the previous six-month period.

A list of patients meeting the selection criteria will be produced. The case records of these patients will then be scrutinised by the regional centres' investigator or delegate (i.e. suitably trained Research or Practice Nurses) to determine eligibility according to inclusion and exclusion criteria (see sections 5.6 and 5.7). Research Nurses will be trained to carry out this task. These Research Nurses will sign a practice-specific confidentiality agreement, and approval to examine case records will be granted by the patient data protection and confidentiality guardian (Caldicott Guardian in the UK).

At the end of this process a list of potential study patients who appear to meet the inclusion criteria will be produced. It will then be examined by one or more practice physicians or delegated study doctor in order to remove from the list the patients who, based on the criteria in sections 5.6 and 5.7, and in the opinion of the physician, should not be approached for recruitment. The final list will then be signed by the study site coordinator or identified GP or study doctor within a PIC attesting that in his or her opinion the patients meet the study inclusion criteria. Invitation letters from the practice will be sent to these patients.

Practices will be encouraged to repeat the screening process periodically during the study period to identify new potential patients.

5.4.2 Secondary Care

Patients may also be recruited from hospital and clinic sites as well as general practice sites. Patients recruited by this method will be invited to participate directly by their physician, by letter or by inviting them to an information evening. Eligible patient volunteers who respond directly to study adverts/posters will also be screened for inclusion to this study.

5.4.3 Consented Patient Databases

Databases of consented patients including, but not limited to, resources such as UK Biobank, Tayside Bioresource, and Share will be utilised to contact patients to invite them to take part in the study. Patients in these databases have consented to be contacted about further studies.

Search strategy will be supplied by the Study Centre in Dundee but all searches and contact will be undertaken by the database owners who will send approved letters of invitation.

Patients recruited in this manner will be seen at regional centres, a local GP practice if already participating in the study, or other suitable location.

5.5 Method of Recruitment

Primary Care Physicians will write personally to those patients in their practice who appear to be potential study patients inviting them to participate in the study or to attend an information meeting about gout and the FAST study (or both) or to go to a website to find out more and sign up to the study. Patient information will be enclosed with this letter and will also be available on the patient recruitment website.

Patients who respond favourably to this invitation either by letter or by registering on the website, whether or not they attended an information meeting will be interviewed by Research Nurses either in person or by telephone. Subjects who sign up to the website who are clearly ineligible will be emailed to inform them of this. Subjects who sign up to the website and consent and who appear eligible will be contacted by the research nurse to further confirm their eligibility. Nurses, Study Site Co-ordinators or other delegated individuals will explain the trial in detail, answer any questions, further determine patient eligibility. For patients who attend a visit in person the nurse, Study Site Co-ordinator or other delegated individual will take formal written informed consent from eligible patients who wish to participate. The study site coordinator or study doctor will be available to answer any question the patient would like to address directly to him or her regarding the study information.

5.6 Inclusion Criteria

1. Male or female patients aged 60 years or older with at least one additional risk factor:
    - Age ≥70 years (male) or ≥75 years (female)
    - Smoking (current or within the last 2 years)
    - Diabetes mellitus
    - Impaired glucose tolerance
    - Hypertension (SBP >140 mmHg and/or DBP >90 mmHg) or receiving treatment to lower blood pressure
    - Dyslipidaemia (investigator assessment)
    - Chronic kidney disease (CKD)
    - Microalbuminuria or proteinuria
    - Family history of coronary heart disease or stroke in first degree relative at age <55 years
    - Inflammatory arthritis (investigator assessment – including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis)
    - Chronic NSAID therapy (investigator assessment)
    - Previous CV event (MI, CVA or transient ischaemic attack)
    - Peripheral vascular disease (investigator / clinical assessment)
    - Chronic obstructive pulmonary disease (COPD)
    - Body mass index >30 kg/m^2
2. Patients who, in the opinion of the recruiting physician, require treatment for chronic hyperuricaemia where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis) fulfilling the recommendation for treatment with urate lowering therapy

3. Patients who have received ≥60 days treatment with allopurinol, or ≥2 allopurinol prescriptions, within the previous 6 months.
4. Patients, who in the opinion of the recruiting physician or study site coordinator, are eligible for treatment (with reference to the summary of product characteristics) with either allopurinol or febuxostat.
5. Patients who are willing to give permission for their paper and electronic medical records, hospitalisation data, prescribing data, and (in the event of their death) their death certification data to be accessed and abstracted by trial investigators.
6. Patients who are willing to be contacted and interviewed by trial investigators or delegates (suitably trained research nurses), should the need arise (e.g., for adverse event assessment and to determine whether an episode of acute gout has occurred).

5.7 Exclusion Criteria

1. Patients who have any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics) or any of the components of their formulations.
2. Patients who are not receiving allopurinol as ULT.
3. Patients with severe renal impairment (eGFR <30 mL/min as defined by the Cockroft-Gault formula (http://www.nephron.com/cgi-bin/CGSI.cgi) according to creatinine, age, sex and body weight).
4. Patients with moderate or severe hepatic impairment i.e. cirrhosis with clinical and/or biological decompensation (i.e. ALT or AST >3x reference value, ascites, lower limb oedema, icterus or increased prothrombin time >2x reference value).
5. Patients with a life-threatening co-morbidity or with a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol.
6. Patients with a diagnosis of, or receiving treatment for malignancy (excluding minor skin cancer and indolent cancers that are not thought to be life threatening and require no treatment) in the previous 5 years. (Investigator opinion)
7. Patients who have experienced either a myocardial infarction or stroke within the 6 months prior to the screening visit.
8. Patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV.
9. Patients whose behaviour or lifestyle would render them less likely to comply with study medication (i.e., abuse of alcohol, substance misuse, debilitating psychiatric conditions or inability to provide informed consent).
10. Patients with a current acute gout flare or who are within 14 days of the resolution of a gout flare.
11. Patients currently participating in another clinical trial or who have participated in a non-interventional clinical trial in the previous 1 month or an interventional clinical trial in the previous 3 months.

6. Trial Treatments

Study Drugs

The trial treatments will be either febuxostat or allopurinol.

Febuxostat 80 mg or 120 mg will be supplied in packs for administration. Dosing will be adapted according to clinical judgement, EULAR recommendations, the current SmPC and sUA levels during the study as per usual care.

Allopurinol 100 mg or 300 mg will also be supplied in packs for administration. Allopurinol doses will be optimised according to clinical judgement, EULAR recommendations and the current SmPC (renal function and sUA level), as per usual care.

Prophylactic Medications

Four gout flare prophylaxis regimens will also be available:

First line:	colchicine 0.5 mg once or twice daily.
Second line:	naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.
Third line:	meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.
Fourth line:	diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Colchicine, naproxen, diclofenac, omeprazole, meloxicam and ranitidine will be supplied as commercially available tablets.

6.1 Allocation of Treatment

A central randomisation facility based at the Robertson Centre for Biostatistics, University of Glasgow will be contacted either by telephone or by a web-based service and randomised therapy, either febuxostat or allopurinol, will be assigned. Randomisation will be stratified according to whether or not the patient had a history of the following cardiovascular events: MI, stroke or previous hospitalisation for CHF or PVD.

6.2 Drug Supplies

Study Drugs

Febuxostat will be supplied as film coated tablets. Allopurinol will be supplied as tablets. Both drugs will be administered orally.

Tablets will be included in packs containing the adequate number of units required for each treatment period.

Different dosages of both febuxostat and allopurinol are available and will be supplied for the purpose of the study:

- Febuxostat dosage strength will either be 80 mg or 120 mg.
- Allopurinol dosage strength tablets will be either 100 mg or 300 mg. Note however that the dose range for allopurinol is up to 900 mg per day.

Both drugs will be packaged for clinical use. IMPs will be supplied all along the study in order to make sure that appropriate quantity of either febuxostat 80 mg or 120 mg or allopurinol 100 mg or 300 mg are delivered to the study patients, according to the treatment arm they have been assigned and the drug dosage required by their GP. An acknowledgement of receipt form will be provided with each shipment.

A Batch Release Certificate will be issued for every batch and a copy distributed to Dundee University (MEMO Unit) where it will be held on file.

Labelling of IMP treatment wallets will be done in compliance with GMP annex 13 and will include a subject number and the core label texts for all packaging units will be translated or adjusted, in official languages of each country involved in the clinical trial. A description of the core text of the IMP labels is displayed below:

- Sponsor name, address and telephone number
- Pharmaceutical dosage form, route of administration, quantity of dose units, product name and strength
- Batch number
- Study number
- Study subject identification, visit number
- Name of investigator
- Directions for use
- "For clinical trial use only" or similar wording
- Storage conditions
- Period of use (MM/YYYY format)
- "Keep out of reach and sight of children"

The investigator, or designee, will only administer IMP to patients included in this study. Each patient will only be given the IMP carrying his/her number. The administration for each patient will be documented in the electronic case report form (eCRF).

Patients will be supplied with study drug as detailed in the operations manual.

Prophylactic Medications

Colchicine, naproxen, diclofenac, omeprazole, meloxicam and ranitidine will be labelled with the original active ingredient as well as a label identifying the study number.

The investigator, or designee, will only administer prophylaxis to patients included in this study.

Patients will be supplied with prophylaxis as detailed in the operations manual.

6.3 Administration

Patients will take randomised medication and prophylaxis according to clinical need and following usual clinical practice. Specifically, (as above) the dose of treatment shall be determined by the recruiting physician or study site coordinator and may be increased or decreased during the trial as appropriate, according to clinical judgement, EULAR recommendations and the current SmPCs. All

changes will be approved by the patient's doctor or a study doctor. This will be documented using the Additional Patient Information Form and updated on the Study Portal.

6.4 Compliance

All study medication supply will be recorded on the eCRF and drug supply data for all drugs supplied to randomised patients will be accrued from patients' records to the eCRF. This will allow a cumulative record of supplied and returned medication so that adherence to study medication over any given period can be calculated. Compliance will be measured as the number of supplied doses minus the number of returned doses divided by the number of days of treatment averaged over the duration in the trial. It is possible that study medication and prophylaxis medication may be temporarily discontinued during the study and this will also be recorded on the eCRF so that an analysis of events occurring by current exposure will be possible.

The Sponsor will distribute study drug and prophylaxis to all study patients and will log all drug returns (as above).

6.5 Discontinuation of Randomised Therapy

If a period of 56 days elapses from the estimated end of the last supplied medication, or if a GP prescription is written for ULT other than that allocated at the time of randomisation, the patient will be contacted to determine whether they have discontinued therapy and, if appropriate, a study drug discontinuation form will be completed. If further clarification is required the study site coordinator will be contacted and, if necessary, practice or hospital case records will be abstracted to further define the reason for treatment discontinuation. Participants will continue to be followed up until the end of the study. Note that rescue gout prophylaxis (with the exception of the alternative study treatment) may be added at the discretion of physicians in order to maintain patients on randomised treatment.

6.6 Concomitant Medications

All concomitant prescribed medications will be tracked by either questioning patients at the 2-monthly (± one month) follow-up visits or abstracting prescription data from practice or central databases. Of particular interest are new prescriptions for aspirin, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), steroids and uricosuric drugs.

6.7 Dosage Adjustment

6.7.1 Efficacy

Patients who experience inadequate therapeutic efficacy may have their dosage increased according to clinical judgement, EULAR recommendations and the current SmPC for both drugs. Similarly, GPs are free to decrease the dose of either drug if they feel this is appropriate. Changes in dose must be recorded on the eCRF.

6.7.2 Tolerability

Patients who experience any SAEs (i.e. related or unrelated to treatment) or non-serious treatment related AEs may have their dosage adjusted according to clinical judgement. Study site coordinators, recruiting physician, a physician from the Sponsor's pharmacovigilance group or other delegated study personnel will report such events as adverse reactions or events as appropriate.

7. Trial Procedures

7.1 Patient Selection

As previously described, patient selection will be performed from practice or hospital records or at clinics, or from searches of databases who have previously agreed to take part in future research such as UK Biobank or SHARE. Patients who appear to meet the trial criteria will be contacted directly by their physician or the consented database owner, by letter or invited to an information meeting where they will be informed about the current treatment options for gouty conditions and the rationale for the trial. Depending on local circumstances, this might take the form of a telephone conversation, a one-to-one face-to-face meeting or a group meeting. Patients will subsequently be asked if they wish to participate in the trial and are amenable to being screened. A patient information leaflet will be provided to patients interested in the study and an appointment for a screening visit will be scheduled in case of confirmed interest.

7.2 Screening

Patients who attend for screening will initially be seen by a study research nurse, appropriately trained practice nurse or physician, who will explain the study in detail and go over the patient information sheet to ensure that patients understand the study. Once this has been done, the recruiting physician or the study site coordinator or delegate (study research nurse or practice nurse) will determine if the patient is eligible to be recruited and fully understands and consents to take part. The patient will then be consented and will enter the screening phase of the study, which will commence at the same visit.

The recruiting physician or study site coordinator or delegate will complete the eCRF detailing patient demographics (age, sex, race), lifestyle factors (smoking history, alcohol consumption), past personal and family medical history, and planned future hospitalisations. Patients will then have baseline measurements taken which will include height, weight, systolic and diastolic blood pressure, blood tests and urine tests.

Patients will have a checklist of inclusion and exclusion criteria completed. Blood tests for serum creatinine, liver function tests, transaminases, urea, potassium, sodium, glucose, estimated glomerular filtration rate (eGFR), prothrombin time and serum uric acid and a full blood count will be taken. Samples will be sent to and processed by a central laboratory at Ninewells Hospital in Dundee. The laboratory data will be reviewed as soon as they are available.

Serum will also be stored for the analysis of other baseline biochemistry parameters (calcium, phosphate, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, high sensitivity troponin and high sensitivity C-reactive protein). Tests done at the screening visit will not be repeated.

For patients who sign an additional informed consent, a whole blood sample will be stored for pharmacogenetic analysis outside of the scope of this protocol.

7.3 Allopurinol Lead-in Phase

If a patient's sUA level is <6 mg/dL during the screening period whilst the patient is taking their usual dose of allopurinol then the patient will continue directly to randomisation. However, if a patient's sUA level is ≥6 mg/dL at screening, the patient's dose of allopurinol will be optimised according clinical judgement, EULAR recommendations and the current SmPC.

Patients requiring allopurinol dose titration should receive 6 months prophylaxis for gout flare from the start of the allopurinol lead-in phase. Prescription of treatment medication for gout flares (preventive or curative) will be in accordance with EULAR recommendations and the current SmPC. Patients who do not require allopurinol dose titration will commence gout flare prophylaxis when they start randomised medication after the washout period.

Four gout flare prophylaxis regimens will be available to the trial investigator or designee:

First line: colchicine 0.5 mg once or twice daily.

Second line: naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Third line: meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Fourth line: diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

After two weeks of allopurinol therapy (9 to 24 days) a further sUA level will be determined. The actual sUA levels will be measured. If the patient is below the target sUA level no further dose escalation is required, but if the patient is above the target sUA level a further allopurinol dose escalation should be considered.

This process will continue until the physician or delegate considers that the optimal allopurinol dose level has been reached for each patient.

Note that for doses of allopurinol above 300 mg/day, doses will be divided. Each allopurinol dose of 100 mg might be expected to reduce serum urate levels by about 1 mg/dL. The slow upward titration of allopurinol has been endorsed by the EULAR[ix].

7.3.1 Renal Impairment

Dosing of allopurinol will take due regard of the renal function of the patient. Thus each patient shall have an eGFR calculated according to the Cockroft-Gault formula[xxi].

No dose increase will be allowed beyond the doses defined in the SmPC of the country where the patient is receiving treatment and patients considered to possibly benefit from higher doses will be required to withdraw from the study.

7.4 Randomisation Visit

At the end of the allopurinol dose optimisation phase, eligible patients with a sUA level of <6 mg/dL or receiving the MTD/MLD of allopurinol will be randomised but will be instructed not to take any ULT during the washout period. The randomisation will be stratified according to whether or not the patients had a history of the following cardiovascular events: MI, stroke or of hospitalisation due to CHF or PVD.

A central randomisation facility will be contacted either by telephone or by a web-based service and randomised therapy, either febuxostat or allopurinol, will be assigned.

7.5 Post Randomisation Trial Period

7.5.1 Washout Period

After randomisation, all patients will undergo a washout period of one week (window 7 to 21 days) during which they will not receive ULT. Patients who require allopurinol dose titration should continue to receive gout flare prophylaxis during the washout period. Gout flare prophylaxis will not be given during the washout period to patients who do not require allopurinol dose titration.

7.5.2 Allopurinol Treatment

Patients randomised to receive treatment with allopurinol will receive the same dose determined prior to randomisation, which may subsequently be adjusted during the course of the study by the patient's study physician, in accordance with clinical judgement, EULAR recommendations and the current SmPC.

Prescription of treatment medication for gout flares (preventive or curative) will be in accordance with EULAR recommendations and the current SmPC.

Four gout flare prophylaxis regimens will be available to the trial investigator or designee:

First line: colchicine 0.5 mg once or twice daily.

Second line: naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Third line: meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Fourth line: diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Patients should receive 6 months prophylaxis for gout flare from the start of the allopurinol lead-in phase and for 6 months following any subsequent increase in ULT.

Monitoring of sUA, serum creatinine determinations, liver function tests and eGFR calculations at a central laboratory will be performed annually (±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study. Additional laboratory assessments including sUA measurements may be undertaken at the discretion of the primary care physicians as part of the standard clinical care, EULAR recommendations and according to the current SmPC.

The annual sUA levels will be analysed as an exploratory efficacy endpoint.

7.5.3 Febuxostat Treatment

All patients randomised to febuxostat will initially be prescribed febuxostat 80 mg, and the febuxostat dose may be increased to 120 mg if the patient's sUA level is >6 mg/dL after two weeks (9 to 24 days). During the course of the study, the dose may be adjusted according to clinical judgement, EULAR recommendations and the current SmPC. Prescription of treatment medication for gout flares (preventive or curative) will be in accordance with EULAR recommendations and the current SmPC. Four gout flare prophylaxis regimens will be available to the trial investigator or designee:

First line: colchicine 0.5 mg once or twice daily.

Second line: naproxen 250 mg or 500 mg twice daily in conjunction with omeprazole 20 mg once daily or ranitidine 300 mg twice daily.

Third line: meloxicam 7.5 mg or 15 mg once daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily

Fourth line: diclofenac 50 mg twice or three times daily with omeprazole 20 mg once daily or ranitidine 300 mg twice daily..

Patients should receive prophylaxis for gout flare for 6 months from the start of the allopurinol lead-in phase and for 6 months following any subsequent increase in ULT.

Monitoring of sUA, serum creatinine determinations, liver function tests and eGFR calculations at a central laboratory will be performed annually (±1 month) after randomisation and/or as close as possible to the time of drop-out for patients who are withdrawn from the study. Additional laboratory assessments including sUA measurements may be undertaken at the discretion of the primary care physicians as part of the standard clinical care, EULAR recommendations and according to the current SmPC.

The annual sUA levels will be analysed as an exploratory efficacy endpoint.

7.6 'Rescue' Medication

In order to maintain patients on randomised treatment, rescue gout prophylaxis (other than the study drug in the alternative arm) will be allowed. The use of such medication will be recorded and prescriptions tracked throughout the study.

7.7 Treatment Period

The study will conclude after patients have been followed up for an average of at least 3 years and until at least 456 APTC events have been identified in the per-protocol population. If insufficient APTC events have occurred the study will continue until the target number of validated primary study endpoints is reached (see section 10.2). Thus patients who enter the study early may have a longer duration of follow-up than those who enter later.

7.8 Follow-Up

Follow-up will be scheduled at two monthly intervals (± one month) by phone, letter, email or visit to the patient by the study nurses, study site coordinator, medical staff or other delegated study personnel. On an ongoing basis, study site personnel or delegates will record details of all SAEs and AEs considered related to study treatment in the eCRF as outlined in section 9.

The follow-up of outcomes will be done by record-linkage to hospitalisations and deaths and by direct reporting by study site coordinators or other delegated study staff.

Recruiting physicians or study site coordinators or designee can also report endpoint events, any SAEs (i.e. related or unrelated to treatment) and non-serious AEs considered related to study treatment whether they occur within or outside the country where the patient resides that may come to their attention.

SAEs will be cross-referenced to record-linkage derived events in regions where this is taking place to ensure that reports are not duplicated. Note that all hospitalisations and deaths reported by record-linkage will also be communicated back to study site coordinators.

Data on discontinuations from randomised therapy including changes in therapy will be tracked from the prescribing records and the reasons for these will be identified by the study coordinator and recorded in the eCRF.

Data on new prescriptions for gout flares (colchicine, NSAIDs, steroids) will be tracked from the prescribing records and the reasons for this identified by the study site coordinator and recorded in the eCRF.

Data on new prescriptions including aspirin will also be tracked from the practice prescribing records or information supplied by the patient at two-monthly (±one month) follow-up visits.

During the course of the study it may become necessary to contact study patients by letter or telephone or even to meet them face to face to clarify issues that arise (for example: clarifying aspects of a SAE).

7.9 Patient Withdrawal

7.9.1 Withdrawal from Randomised Therapy

Any physician involved in the usual care of patients may withdraw patients from randomised treatment using their clinical judgement. This might occur due to the occurrence of an AE, the onset of symptoms that limit tolerability, or lack of therapeutic efficacy despite upward titration to the maximum dosage and any rescue gout prophylaxis. In line with current clinical practice, it will not be recommended to withdraw patients from the study who do not achieve the sUA level of <6 mg/dL after appropriate dosage increases of either febuxostat or allopurinol and any rescue gout prophylaxis. Patients withdrawn from randomised treatment will remain in the study for safety follow-up and subsequent events will be included in the ITT analysis but will be censored in the per-protocol analyses. Similar actions will be taken for patients where a change of treatment, such as an alternative ULT, is necessary. Patients will not be permitted to switch from one treatment arm to the other within the study protocol. Such patients would remain in the study for safety follow-up and subsequent events would be included in the ITT analysis but would be censored in the per-protocol analyses.

The study site coordinator or designee should inquire about the reason for withdrawal or treatment changes, if applicable.

Patients who move out of the country of recruitment (and cannot easily be followed up or record-linked) may stop being evaluable on the date of their moving from the country unless adequate arrangements for follow up can be put in place.

If patients co-enrol on another study unintentionally whilst taking part in FAST, the person becoming aware of this should report it to both study teams and to the Sponsor. A decision will be made about continuation of or withdrawal from the study(s) on a case by case basis. The process followed and decision made should be clearly documented in the Study Files.

7.9.2 Withdrawal of Consent to Follow-up

If at any time the patient formally withdraws his/her consent for future participation and disclosure of future information, no further evaluations will be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.9.3 Temporary Suspension of Randomised Therapy

Temporary discontinuation of randomised therapy may be permitted for justifiable reasons. These periods must be logged accurately. This is important as the analyses of the study will include an "on therapy" versus "off therapy" component.

7.9.4 Duration of Follow-up of Study Patients

Information for each study participant will by tracked until the earliest of the following occurrences:

- Death.
- Patient lost to follow-up. (These will be followed up for hospitalisations and death by record linkage alone if lost to follow up by regional centres)
- Withdrawal of consent to follow-up, includes patient moving out of the country of randomisation.
- Date to be specified by the study Steering Committee on the basis of achieving the required number of study endpoints or resulting from a decision to stop the study prematurely because of a recommendation from the study IDMC.

8. Assessments

8.1 Determination of Endpoints by Record Linkage or other means

For countries and regions where record linkage is possible detailed tables of the specific event codes used in the computerised searches for each of the endpoints will be detailed in the Endpoint Committee Charter.

8.2 Mortality

Mortality and certified cause-specific mortality will be retrieved regularly from the General Registrar's Office or equivalent for each country for all patients randomised.

8.3 Morbidity

All hospitalisations that occur in each country where record linkage is possible will be retrieved by this method for all randomised patients for the duration of the trial.

8.4 Data Abstraction

For each death and for each hospitalisation that is a potential endpoint, primary care and secondary care records and full death certification data will be retrieved as appropriate. Diagnostic validation forms will be completed to supplement scanned images of original case records relating to the endpoints in question. Scanned images of case records and the data validation forms will be collated. Any record of randomised treatment or personal identifiers will be removed before these collated documents are passed to the relevant endpoint committee for adjudication as to the hospital diagnosis or the cause of death. This process will be carried out by clinical staff in the Dundee Centre.

8.5 Primary Endpoint: APTC Endpoint

The primary analysis will be the time from randomisation to first occurrence of any event included in the APTC composite endpoint of:

- Hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome
- Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation)
- Death due to a cardiovascular event

8.5.1 Sensitivity Analysis of Primary Endpoints

All non-fatal circulatory system codes other than myocardial infarction and stroke will also be reviewed by the Pharmacovigilance Group in order to judge the sensitivity, specificity and completeness of the strategy of adjudicating only the APTC codes. If this analysis shows that endpoint events are missed by the more restrictive search a wider search will then be instigated.

8.6 Secondary Endpoints

The following secondary endpoints (in rank order of importance) will be evaluated using a time to event analysis:

- Hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome
- Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation)
- Cardiovascular death
- All cause mortality
- Hospitalisation for heart failure
- Hospitalisation for unstable, new or worsening angina
- Hospitalisation for coronary revascularisation*
- Hospitalisation for cerebral revascularisation*
- Hospitalisation for transient ischaemic attack (TIA)
- Hospitalisation for non-fatal cardiac arrest
- Hospitalisation for venous and peripheral arterial vascular thrombotic event
- Hospitalisation for arrhythmia with no evidence of ischaemia

* Not formally adjudicated but counted for analysis

The following endpoints will be evaluated as an incidence rate:

- Cardiovascular mortality
- APTC events in each treatment arm

8.7 Exploratory Efficacy Endpoint

The proportion of patients whose sUA level is ≥6.0 mg/dL, <6.0 mg/dL and <5.0 mg/dL after each year of treatment.

8.8 Adjudication of Endpoints

Endpoint data will be adjudicated by an independent endpoint committee blinded to randomised treatment. This committee will have due regard of the published consensus diagnostic criteria for myocardial infarction[xxii], stroke[xxiii], vascular death, heart failure[xxiv].

The role of the committee will be further defined in the cardiovascular clinical endpoint committee charter.

9. Adverse Events

All observed or volunteered SAEs and AEs considered related to treatment with the investigational product(s), will be recorded on the AE page(s) of the eCRF. The site coordinators or designee will pursue and obtain information adequate to confirm whether it meets the criteria for classification as a SAE, determine the outcome of the AE and causality. Follow-up of the AE, even after the date of randomised therapy discontinuation, will occur if the AE or its sequelae persist. Follow-up will be done until the event or its sequelae have resolved or stabilised at a level acceptable to the site coordinator, investigators and the Sponsor.

For the purpose of the current study, primary and secondary study endpoints and their associated symptoms and laboratory abnormalities are not to be reported as SUSARs.

9.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. SAEs considered to be related or unrelated to treatment and AEs considered to be related to study treatment in the opinion of the investigator will be recorded in this study. Examples of AEs include but are not limited to:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Progression/worsening of underlying disease

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency

9.2 Abnormal Test Findings

Only abnormal test findings that are considered to be serious or to be related to study randomised treatment should be reported on the AE form in the CRF.

Additional criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the study site coordinator.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

9.3 Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Important medical events that require medical or surgical interventions to prevent serious outcome

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

9.4 Hospitalisation

AEs associated with hospitalisation or prolongation of hospitalisation are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalisation does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Elective same day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly physical exam)
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed might be reported if it meets the definition of a reportable AE.

Pre-planned treatments or surgical procedures should be noted in the baseline documentation for each individual.

Severity Assessment

If required on the AE case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with patient's usual function.
MODERATE	Interferes to some extent with patient's usual function.
SEVERE	Interferes significantly with patient's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a SAE. For example, a headache may be severe (interferes significantly with

patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs.

9.5 Causality Assessment

Causality will be assessed for all AEs (serious and non-serious). Causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. If the final determination of causality is not evaluable, then the event will be handled as “related to investigational product” for reporting purposes.

In addition, if the investigator determines a SAE is associated with trial procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

9.6 Withdrawal Due to Adverse Events

(See also section 7.9 Patient Withdrawal)

Withdrawal due to an AE should be distinguished from withdrawal due to insufficient response, according to the definition of AEs noted earlier, and recorded on the appropriate AEs eCRF page.

9.7 Reporting Requirements

Study site coordinators, recruiting physicians, study site coordinator or other delegated study personnel will be responsible for reporting patient-reported adverse events or other events that come to their attention. Reporting timelines will follow local and international regulations.

If an investigator becomes aware of a pregnancy in a patient or the partner of a patient, this should be reported to the Sponsor. The Sponsor will follow-up the pregnancy until its conclusion.

9.8 Serious Adverse Event Reporting Requirements

SAEs require notification to the sponsor within 24 hours, and this obligation begins from the time that the patient provides informed consent, which is obtained prior to the patient’s participation in the clinical trial, i.e., prior to undergoing any trial-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Additional new information (follow-up) on previously forwarded SAE reports also has to be notified to the sponsor within 24 hours. Investigators will be asked to report any reportable events that occur within 28 days of this date. These events will be promptly reported if a causal relationship to study drugs is suspected. SAEs will be followed up until resolution or death by study nurses who will liaise with study site coordinators and the patients to capture these data. This reporting process is described in detail in the Study's Operations Manual.

In the event that the recruiting physician or study site coordinator does not become aware of the occurrence of a SAE immediately (as may occur in the present study where record-linkage will identify hospitalised events and deaths in those countries where this is possible), the event will be notified to the sponsor within 24 hours after learning of it.

For all SAEs, the reporter (recruiting physician, study site coordinator, a physician from the Sponsor's pharmacovigilance group or other delegated study personnel) is obligated to pursue and provide information to the sponsor in accordance with the timeframes for reporting specified above. In addition, investigators may be requested to obtain specific additional follow-up information in an expedited fashion. The collated information should include a description of the AE in sufficient detail to allow for a medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses should be provided, if known. In the case of a patient death, a summary of available autopsy findings should be submitted as soon as possible.

Copies of all SAEs that occur during the trial will also be sent to MENARINI within 24 hours of sponsor first awareness.

9.9 Suspected Unexpected Serious Adverse Drug Reactions (SUSARS)

SUSARs need to be reported to the regulatory authorities within 7 calendar days if fatal or life-threatening and within 15 calendar days for all others. All Serious Adverse Reactions will be reported to the regulatory authorities in an annual report. Expected events for allopurinol treatment are defined in the SmPC of the supplied study medication, and for febuxostat in the SmPC of the EU.

Some SAEs and SUSARS that occur in this study will only become known to investigators after record-linkage has occurred in countries where this is possible. Current regulations require that fatal or life threatening SUSARS be reported within 7 calendar days after the sponsor becomes aware of these and other serious events within 15 calendar days. Whilst electronic records can be sent within this time frame after each record-linkage (in countries where this is possible), the inherent time-delays that occur with record-linkage may result in a delay before the sponsor becomes aware of events. Nevertheless potential events will be reported within the specified timelines once the Sponsor has become aware of the event and follow-up reports will contain further data on events that need to be validated by reference to case records.

9.10 Serious Adverse Event Reporting Process

The SAE may be reported in two ways: (a) by the site investigator or delegated study personnel, or (b) via record linkage in those countries where this is possible:

1. If the investigator reports on an AE they will make a preliminary recommendation of the seriousness and relatedness of the AE.
2. If the event is assessed as serious and related, or serious and the relationship is not provided, then this information will be entered into the eCRF and passed in real time to and reviewed by a pharmacovigilance group.

3. If the event is considered to be related and unexpected then a SUSAR will be reported to Regulatory Agencies. The pharmacovigilance group will also assess the relationship between study drug exposure and the SAE if this has not been done by the study site coordinator or other doctor.
4. MENARINI will be provided with details of all SAEs in a blinded format within 24 hours of the Sponsor being notified. Likewise, blinded CIOMS forms related to SAEs will be forwarded to MENARINI as soon as available.
5. In addition, a listing of all non-serious AEs considered to be related to treatment will be provided to MENARINI. These listings will be provided in a blinded format twice a year. The periodicity of the report may be varied on request of MENARINI following negotiation with the sponsor.
6. Any AE entered into the eCRF and not assessed as serious, but without a study drug relationship assessment or an unknown assessment, will be treated as being related to treatment until such a relationship is determined.

10. Data Analysis / Statistical Method

10.1 Sample Size Determination

Estimation of endpoint event rates in patients taking chronic ULT.

Cohorts of patients who were dispensed allopurinol in 1994 to 2002 were defined from the Tayside Medicines Monitoring Unit (MEMO) database[i].

The Scottish Morbidity Record One (SMR1) database of hospitalisations and the General Registrar Office (GRO) database of deaths in Scotland were then searched for events occurring in these patients up to 2002. Tables of event rates were generated.

For patients with chronic hyperuricaemia, aged 60 years or older who were free from cardiovascular events the APTC event rate was 5.4% at year 1, 10.1% at year 2 and 14.0% at year 3.

10.2 Power Calculations

456 APTC events are required to show non-inferiority between the febuxostat and allopurinol treatment arms assuming a non-inferiority limit for the hazard ratio of 1.3, with 80% power and a one sided alpha of 0.025.

Non-inferiority will be claimed if the upper limit of the 95% CI for the hazard ratio is $\leq$1.3 for the per-protocol analysis. The non-inferiority margin has been selected as representing a minimal difference of clinical interest, which has been found useful in a number of cardiovascular risk contexts, including FDA's guidance on cardiovascular risk in anti-diabetic compounds[xxv].

Assuming a 12 month accrual period, an average of 36 month evaluation period after completion of accrual and an APTC cardiovascular event rate at 3 years in the allopurinol treatment arm conservatively estimated at 10%, then 2282 patients will be required in each treatment arm to detect the 456 events.

Since an on-treatment analysis will result in reduced follow-up that is difficult to predict a-priori, assuming a dropout rate of 20% from the per-protocol population, we intend to recruit 2853 patients in each treatment arm, 5706 patients overall and to continue follow-up for an average of at least 3 years and until at least 456 APTC events are identified in the per-protocol set. The overall withdrawal rate will be monitored and the sample size may be increased if the withdrawal rate is higher than expected.

10.3 Primary Analysis

A full Statistical Analysis Plan will be developed.

The statistical method to be used will involve a Cox proportional hazards model including the randomised treatment group and strata (previous cardiovascular events) as covariates. Statistical significance for the treatment effect will be based on the Wald statistic and on 95% confidence intervals for the estimated hazard ratio comparing febuxostat to allopurinol.

The first analysis to be carried out will be a non-inferiority analysis of the primary outcome based on the per-protocol population (those patients remaining on randomised therapy) with a supporting non-inferiority analysis based on the ITT population. A patient will be considered to remain on the randomised therapy until a period of 56 days following the last recorded supply of the medication allocated at randomisation (see section 6.5) if a precise date of drug discontinuation is not known.

In order to capture potential endpoints of patients who have stopped randomised therapy for longer than 28 days they will be recorded within the study portal using the SAE reporting facility. Events occurring after 28 days will not be counted as part of the pharmacovigilance reporting for the study, but they maybe endpoints for the per-protocol analysis up to 56 days following the last intake of medication. Events which are identified as potential endpoints after this time will be included in the ITT analysis only.

Thus the per-protocol analysis will censor patients after:

- Discontinuation from original randomised therapy
- Death from non-cardiovascular causes
- Loss to follow-up

If non-inferiority is demonstrated, a superiority analysis will be carried out based on the ITT population.

10.4 Sensitivity Analysis

A prospective sensitivity analysis will be done by censoring patient follow-up at 90-days beyond the per-protocol period or end of study, whichever comes first, to ensure that withdrawal or crossover is not a presage of disease. This will be done for both primary and secondary endpoints.

To adjust for the possibility of differential dropout in the per-protocol analysis, a further analysis will be carried out adjusting for age, sex, LDL- and HDL-cholesterol levels, systolic blood pressure, smoking status and histories of diabetes, hypertension and cardiovascular disease.

10.5 Subgroup Analyses and Prognostic Factors

Subgroup analyses will be carried out for each of the baseline covariates described below that are significant predictors of the primary endpoint in a Cox regression model including that variable alone plus the stratification categorical variable.

The following baseline covariates will be analysed:

- Age
- Sex
- Family history of CHD or stroke
- Baseline systolic blood pressure
- Baseline total and HDL cholesterol
- BMI (body mass index)
- Smoking status
- Diabetes
- Aspirin use
- Lipid lowering therapy use
- Antihypertensive drug use
- Baseline (pre-randomisation) sUA
- Pre-randomisation allopurinol dose

In addition a prognostic model for the primary endpoint using these variables will be derived using stepwise inclusion of variables in a Cox model with P-to-enter of 0.1 and P-to-remove of 0.05.

A risk score derived from this analysis will be used to define fifths of risk and the treatment effect assessed within each fifth.

In all sub-group analyses, p-values for the test of the interaction between the variable defining the sub-group and randomised treatment allocation will be derived using the Wald statistic.

Other subgroups may be explored and these will be detailed in the analysis plan.

10.6 Secondary and Exploratory Analyses

The secondary endpoints involving time to event analyses will be analysed in the same manner as the primary endpoint. For the incidence of cardiovascular mortality and APTC events, the groups will be compared using logistic regression including the randomised treatment group and strata (cardiovascular history) as covariates.

Differences between treatment groups in the proportion of patients whose sUA level is ≥6.0 mg/dL, <6.0 mg/dL and <5.0 mg/dL after each year of treatment will be assessed using 95% confidence interval using Cochran-Mantel-Haenszel methodology.

11. Trial Organisation and Feasibility

11.1 Progress of Trial

Details of the number of patients randomised, their age and sex will be available to investigators on a daily basis via the web portal. Patients will be the invited to attend update meetings to receive information on the progress of the trial.

11.2 Steering Committee

A steering committee will be constituted to oversee the conduct of the trial.

11.3 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee will be constituted and a charter will be drawn up to describe membership, roles and responsibilities. This committee will receive un-blinded data and will have the power to recommend to the steering committee modifications to study conduct including early discontinuation of the study based on a risk/benefit assessment of the study data. Formal stopping rules will be defined in the IDMC charter. However, thresholds for early stopping will require a high level of evidence (overwhelming evidence of difference between the two treatment groups for the primary and/or secondary endpoints) and a small number of times at which early stopping can be recommended such that there will be no meaningful impact on the study power calculations.

11.4 Independent Endpoint Adjudication Committee

An independent adjudication endpoint committee will be constituted and a charter will be drawn up to describe membership, roles and responsibilities. Endpoint data will be adjudicated for cardiovascular endpoints and heart failure endpoints.

This committee will be blinded to randomised treatment and will have due regard of the published consensus diagnostic criteria for myocardial infarction[xxvi], stroke[xxvii], vascular death and heart failure[xxviii].

12. Study Monitoring, Audit, Quality Control & Quality Assurance

The University of Dundee may sub-contract the monitoring of the study and the quality assurance to suitable experienced Clinical Trial Organisations (CROs). The University of Dundee will act as the trial sponsor.

13. Data Handling & Record Keeping

13.1 Case Report Forms / Electronic Data Record

An eCRF will be used to collect study data at each site. The eCRF will be developed by the study Data and Statistical Centre at the Robertson Centre for Biostatistics, University of Glasgow and access to the eCRF will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the eCRF. The recruiting physician or study site coordinators, or his/her designee will be responsible for all entries into the eCRF and will confirm (electronically) that the data are accurate and complete, and that they have reviewed all of the data contained in the eCRF.

The completed original eCRF data will be the joint property of the Universities of Dundee and Glasgow, and should not be made available in any form to third parties, except for authorised representatives of the Universities or regulatory authorities, without written permission from the Universities.

Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged to the regional site coordinators and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

Patient source documents are the physician's patient records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the eCRF must match those charts.

In some cases, the eCRF may also serve as the source document. In these cases, the monitoring guidelines will prospectively document which items will be recorded in the source documents and for which items the eCRF will stand as the source document.

13.2 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigators agree to keep records, including the identity of all participating patients (sufficient information to link records, all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition). The records should be retained by the study site coordinators and investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the recruiting physician or study site coordinator relocates, retires, or for any reason withdraws from the trial, the University of Dundee should be prospectively notified. The trial records must be transferred to an acceptable designee. The study site coordinator must obtain the Universities' written permission before disposing of any records, even if retention requirements have been met.

13.3 Data Handling

The Robertson Centre for Biostatistics at the University of Glasgow will be responsible for collating, cleaning and analysing the data for the study. The Robertson Centre will also be responsible for data back-up and security. This centre will also be responsible for Pharmacovigilance reporting on behalf of the sponsor, the University of Dundee.

13.4 Scottish-wide

There will be centres in Glasgow, Edinburgh, Grampian, Highland, and Tayside (who will also manage Fife and Forth Valley).

13.5 Multi-Centre International

A trial centre will be set up in Denmark under the auspices of the University of Southern Denmark. Record-linkage capabilities in Denmark are similar to those in Scotland. Further trial centres will be set up in England. Other European countries could be set up in case of slow rate recruitment, e.g. Sweden, and the Netherlands. However, in order to improve recruitment, countries without record-linkage capabilities may also take part in the study.

14. Legal Issues / Ethical Issues

14.1 Ethics Committee Review

The trial will be submitted to the UK Multi-Centre Research Ethics committee (MREC) and equivalent in other EU countries requesting prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable. All correspondence with the MREC will be retained in the Investigator File.

The only circumstance in which an amendment may be initiated prior to MREC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the MREC in writing within 5 working days after the implementation.

14.2 Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and applicable local regulatory requirements and laws.

14.3 Patient Information & Consent

All parties will ensure protection of patient personal data and will not include patient names on any reports, publications, or in any other disclosures.

The informed consent form must be agreed to by the MREC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The recruiting physician or study site coordinator must ensure that each trial patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator, study site coordinator or a person designated by the investigator will obtain written informed consent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by the MREC before use. The sponsor will retain the original of each patient's signed consent form.

The study will be also submitted for Independent Local Ethic Committees for approval for the various study site portions of the study.

Electronic copies of the individual consent forms will be stored within the study database for all regions with the exception of Sweden. All centres will store hard copies of the consent forms in their regional centres.

14.4 Other Regulatory Submissions

Within the UK, the study will be registered with the Medicines and Healthcare Product Regulatory Agency (MHRA) and conducted under the European Union Clinical Trial Directive. A Clinical Trial Authorisation will be obtained prior to commencement of the trial. Similar authorisation will be sought in other EU countries.

14.5 Study Sponsor

The study will take place as an academic study grant funded by MENARINI under a full legal agreement with MENARINI with the University of Dundee being the study sponsor and MENARINI representatives having only observer status on the steering committee.

14.6 Indemnity Insurance

MENARINI will provide product indemnity in relation to claims arising from the failure of febuxostat to comply with its specifications. The Sponsor (University of Dundee) will obtain clinical trials insurance cover for the legal liabilities arising from sponsoring the trial. NHS indemnity will apply to any NHS employees involved with the trial. The Medical & Dental Defence Union of Scotland has advised that GPs insured with them would be covered for professional liability arising from taking part in this type of trial.

15. End of Trial Arrangements

At the end of the trial the patient's treating physician or study doctor will prescribe appropriate therapy for treatment of their condition according to clinical judgement. Menarini will reimburse costs of febuxostat and allopurinol for patients retained this at the end of the study for 6-months or until the study results are published (whichever is the shorter period) .

16. Definition of End of Trial

The end of the trial will be determined by the steering committee and this will occur when more than the required number of primary endpoints has accrued.

Article 10 (c) of the EU Clinical Trial Directive 2001/20/EC requires the sponsor of a clinical trial to notify the competent authority of the Member State concerned that the clinical trial has ended. The sponsor must notify the end of trial within 90 days of the end of the clinical trial. Whenever a trial is terminated early the sponsor must notify the competent authority(ies) concerned within 15 days and clearly explain the reasons.

The University of Dundee will make an end of trial declaration when the trial ends in an individual EU Member State and when the complete trial has ended in all participating centres in all countries within and outside the EU.

17. Sponsor Discontinuation Criteria

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the MREC, drug safety problems, or at the discretion of the steering committee.

If a trial is prematurely terminated or discontinued, the University of Dundee will promptly notify the investigators. After notification, the investigator must contact all participating patients within 90 days and all trial materials must be collected and all study data completed to the greatest extent possible.

18. Publication of Trial Results

The study results will be presented at scientific meetings and will be submitted for one or more peer-reviewed publications at the discretion of the steering committee.

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