RAPID-CTCA

Statistical Analysis Plan

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0.01	Creation of new SAP	3 June 2015
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0.03	Update following meeting with Prof Gray and Steff Lewis	21 July 2015
0.04	Finalising (following release of version 3 of protocol)	27 January 2016
0.05	Version to be sent to DMC/TSC for comment	8 February 2016
1.0	Finalised	9 February 2017
2.0	Updated following observations from SCOT-HEART and subsequent changes to protocol	19 August 2020

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List of Abbreviations

ABBREVIATION	FULL NAME
°C	Degrees centigrade
µMOL	Micromole
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ARB	Angiotensin II receptor blockers
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CM	Centimetre
CTCA	Computed tomography coronary angiography
CVD	Cardiovascular disease
DMC	Data monitoring committee
ECG	Electrocardiogram
ECTU	Edinburgh Clinical Trials Unit
ED	Emergency departments
G	Gramme
GRACE	Global Registry of Acute Coronary Events
GTN	Glyceryl trinitrate
HR	Hazard Ratio
ITT	Intention to treat
KG	Kilogramme
L	Litre
LMWH	Low molecular weight heparin
M	Metre
MG	Milligramme
MGY	milligray
MI	Myocardial infarction
ML	Millilitre
MMHG	Millimetres of mercury
MMOL	Millimoles
MRI	Magnetic Resonance Imaging
N	Number of patients with an observation
NHS	National Health Service
QC	Quality Control
RAPID-CTCA	Trial acronym for 'Rapid Assessment of Potential Ischaemic Heart Disease with CTCA'
SAP	Statistical analysis plan
SAS	Statistical Analysis Software (a proprietary analysis package) [1]
SCOT-HEART	Trial acronym for 'Scottish Computed Tomography of the Heart' trial
SD	Standard Deviation
SOP	Standard operating procedure
SPO2	Peripheral capillary oxygen saturation
TNK/TPA	Tenecteplase/Tissue plasminogen activator
TSC	Trial Steering Committee
U	Units
Y/N	Yes/No

1. Introduction

This document details the criteria to be used for the definition of the analysis populations and the statistical methodology for analysis for the RAPID-CTCA trial, a randomised controlled trial of early computed tomography coronary angiography (CTCA) in patients presenting with suspected/confirmed acute coronary syndrome (ACS) to Emergency Departments (ED) and Medical Assessment Units.

This document has been compiled according to the Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "Statistical Analysis Plans" ECTU_ST_04 and has been written based on information contained in the study protocol version 7.0, dated 24 February 2020.

RAPID-CTCA is a multicentre, randomised, parallel-group open trial. Randomisation is at the individual level with a 1:1 allocation ratio, and is stratified by study site. Patients are randomised to either CTCA in addition to standard care or standard care alone. The aim was originally to recruit 2,500 patients in about 30 NHS tertiary and district hospitals (with or without on-site coronary angiography facilities) with emergency departments, acute medical, radiology, and cardiology services. This was updated to a size of at least 1735 in protocol version 7.

2. Statistical Methods section from the protocol

The trial will be reported on an intention-to-treat basis. The primary outcome is defined as first event of all cause death or subsequent non-fatal MI type 1 or 4b. Time to primary outcome is defined as time from randomisation to primary outcome. Patients discontinuing the study (for any reason) prior to reaching primary outcome will have their time to primary outcome censored at the last contact date. The relationship between intervention and the primary outcome will be analysed using Cox proportional hazard regression adjusted for study site (used to stratify the randomisation), baseline GRACE score, and previous CAD. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The individual elements of the composite primary outcome will be reported separately. Subgroup analysis on the primary outcome is planned for age, sex, baseline GRACE score, previous CAD, baseline ECG result, baseline troponin concentration, and presentation to a study site with or without on-site invasive coronary angiography facilities. These will be assessed by examining the effect of entering the treatment by subgroup interaction into the Cox regression model. Secondary outcomes will be analysed using appropriate methods: logistic regression for binary outcomes and linear regression for normally distributed continuous outcomes, adjusted as described above. Continuous outcomes that are not normally distributed will be analysed using appropriate nonparametric techniques. Every effort will be made to minimise missing data, and our primary analysis will be a complete case analysis. If there is a sufficient level of missing data for it to affect our conclusions, a multiple imputation analysis will be undertaken, using clinically appropriate variables, as a sensitivity analysis. Significance testing will use a hierarchical approach – for the primary outcome and the key secondary outcomes, statistical significance will be declared if the outcome in question, and all prior outcomes listed, have $p<0.05$. P-values will be reported for all other outcomes but will not be declared to be significant. A full statistical analysis plan will be written during the trial and finalised prior to database lock.

3. Overall Statistical Principles

The intention-to-treat (ITT) population will include all patients who have been randomised into the RAPID-CTCA trial, and who did not withdraw consent for any of their data to be stored in the trial database. Patients will be analysed in the group to which they were allocated to, regardless of the

intervention they actually received. Analyses will be based on the ITT population, unless otherwise specified.

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, lower and upper quartiles and number of patients with an observation (N). Data will be split by intervention group and time point where applicable.

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. 95% (2-sided) confidence intervals (CIs) will be presented. All analyses are testing superiority, rather than equivalence or non-inferiority. Significance testing will use a hierarchical approach – for the primary outcome and the key secondary outcomes, statistical significance will be declared if the outcome in question, and all prior outcomes listed, have $p<0.05$. P-values will be reported for other outcomes but will not be declared to be significant.

Where there is missing data for an outcome variable, in the first instance, those records will be removed from any formal statistical analysis relating to that outcome variable (complete case analysis), unless otherwise specified. In tabulations, numbers of missing observations will be provided, but percentages will not include them.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots. If the distributional assumptions for the parametric approach are not satisfied, further data transformation (to alleviate substantial skewness (i.e. normalizing) or to stabilise the variance), or other suitable methods will be considered. This will be documented in the statistical results report together with the reasoning supporting the action taken, if applicable.

In general, analyses will be adjusted for study site (used to stratify the randomisation), baseline GRACE score (continuous) , and previous CAD (yes/no), unless otherwise specified. Of note, study site will be included as a random effect (as there will be a large number of sites); whilst GRACE score, and previous CAD will be included as fixed effects. GRACE score will be adjusted for using a restricted cubic spline with 3 knots (thus using 2 degrees of freedom). The knots will be placed at the following percentiles of the predictor's marginal distribution: 0.1, 0.5, 0.9. Age is contained within GRACE score and will therefore not be adjusted for separately. Baseline GRACE score will be calculated from individual components, using the formula for predicting death or non-fatal MI within 6 months of admission with ACS [2], rather than using the GRACE score field in the database.
All analyses and data manipulations will be carried out using the most up to date version of SAS available [1].

4. List of Analyses

4.1 Recruitment and retention

Number of patients assessed for eligibility; number of patients who were excluded (with a tabulation of reasons for exclusion); number of patients who were randomised; number of randomised patients who withdrew consent including to use of data; number of patients allocated to each treatment arm; number of patients who completed follow-up to 12 months (or who died) with a tabulation of reasons for discontinuing early, number of patients included in analysis of primary outcome, by allocated treatment and overall. Person-years of follow-up for patients included in analysis of primary outcome by treatment arm, with proportion of this time that was after the start of the COVID-19 pandemic.

Graph of cumulative number randomised over time.

Dates of first and last patients randomised.

A tabulation of numbers of patients randomised by study site, split by allocated treatment (and overall), to show balance by this stratification factor.

4.2 Baseline characteristics

The following baseline characteristics are to be tabulated by allocated treatment, and overall. No formal statistical testing of the baseline characteristics will be performed. The first relevant observation will be presented if more than one observation was collected

Age at randomisation (years) [continuous, and as <65 or ≥65], Sex [binary], GRACE score [continuous, and using groups of <109, 109-139, 140 or more], Elevated first cardiac troponin [Y/N], Previous CAD [Y/N], Result from first ECG [categorical], Rhythm on first ECG [categorical], Admission at site with on-site invasive coronary angiogram facilities [Y/N].

Admission: Mode of presentation [categorical], Initial area of assessment [categorical]

Primary presenting complaint: Presenting complaint [categorical], Time from first onset of presenting complaint to randomisation [calculate in hours, present in days, continuous], Type of pain [categorical], Pattern of pain [categorical], Location of pain [categorical], Any radiation of pain [Y/N], Radiation to areas of the body [each a separate Y/N variables], Any aggravating factors [Y/N], Detailed aggravating factors [each a separate Y/N variable]; Any relieving factors [Y/N], Detailed relieving factors [each a separate Y/N variable]

Risk factors: Diabetes mellitus [Y/N], Hypertension [Y/N], Hyperlipidaemia [Y/N], Smoking [categorical], Cocaine abuse [Y/N], First degree relative with CAD onset aged <60 [Y/N], Killip classification [categorical], Body Mass Index (kg/m^2) [continuous]

Past history of coronary artery disease: Previous MI [Y/N], Angina with positive diagnostic test [Y/N], Previous CABG [Y/N], Previous angiography [Y/N], Stenosis >50% on previous angiography [Y/N], Previous coronary angioplasty/PCI [Y/N], Previous CTCA [Y/N], Known CAD on CTCA [Y/N], Unproven Clinical label of CAD [Y/N].

Other comorbidities/past medical history: Other structural heart disease [Y/N], Chronic heart failure [Y/N], Cerebrovascular disease [Y/N], Peripheral vascular disease [Y/N], Malignancy [Y/N], Chronic obstructive pulmonary disease [Y/N], Asthma [Y/N], Chronic renal failure/chronic kidney disease [Y/N], Liver cirrhosis [Y/N], Chronic infectious disease [Y/N].

Routine admission blood tests: Urea (mmol/L) [continuous], Creatinine (µmol/L) [continuous], Estimated glomerular filtration rate ($ml/minute/1.73m^2$) [categorised], Alanine aminotransferase (Units/L) [continuous], Haemoglobin (g/L) [continuous], White blood cell count ($x10^9/L$) [continuous], Random blood glucose (mmol/L) [continuous], Cholesterol (mmol/L) [continuous].

Observations within 60 minutes prior to randomisation: Respiratory rate (breaths per minute) [continuous], Oxygen saturation (SpO_2 %) [categorical], Fraction inspired oxygen (%) [categorical], Heart rate (beats per minute) [continuous], Systolic blood pressure (mmHg) [continuous], Diastolic

blood pressure (mmHg) [continuous], Capillary blood glucose (mmol/L) [continuous], Temperature (°C) [continuous].
Treating clinical impression at time of randomisation: ACS [categorical], Diagnosis [categorical], Diagnosis certainty ((0-10 where 0 is the least certain and 10 is the most certain) [continuous]

Concomitant medication: Beta blocker, Calcium channel blocker, ACE Inhibitor or ARB, Nicorandil, Oral nitrate, Buccal or sublingual nitrate, Oral hypoglycaemic, Insulin, Statin, Aspirin, Clopidogrel, Prasugrel, Ticagrelor, TNK/TPA, LMWH, Tirofiban or equivalent 2B3A inhibitors, Intravenous nitrate (including infusion), Fondaparinux, Unfractionated heparin, Bivalirudin, Novel anticoagulants, Intravenous morphine/opiate, Diuretic, Proton Pump Inhibitor, Ivrabradine, Warfarin, Ranolazine.
Table: N (%) with any of medications listed prescribed before admission [Y/N] and N (%) for each medication, by treatment arm, and overall.

4.3 Trial treatment details, and adherence

No formal statistical testing will be performed.

The protocol defines:
Crossover *Any patient in the control group that has a CTCA as part of routine care within 30 days of randomisation will be defined as a crossover and does not need to be recorded as a deviation.*
Non-adherence *This will be defined as to have occurred in any participant not receiving a reported CTCA if randomised to it within 72 hours of the randomisation and this would be recorded as a deviation. This allows ambulatory CTCA to be delivered when appropriate.*

Non-adherence
Table: For those allocated to the CTCA arm, the number of patients who received the allocated treatment within 72 hours of randomisation, later than 72 hours, or not at all. Only those who received CTCA within 72 hours of randomisation received the treatment as allocated.

Table: For those allocated to the CTCA arm, who did not receive CTCA as the trial intervention, reasons for not receiving CTCA as trial intervention

Histogram: For patients allocated to CTCA arm, time from randomisation to receiving CTCA as trial intervention

Crossover
Table: For those allocated to the control arm, the number of patients who did not receive CTCA during trial, who did receive CTCA more than 30 days after randomisation, or who received CTCA within 30 days of randomisation. Those who received CTCA within 30 days are crossovers.

Trial treatment details
Table: For those allocated CTCA, who received CTCA, a table showing the following: scan quality, inpatient or ambulatory scan appointment, type of scan [e.g. prospective, retrospective, flash], beta blocker administered [Yes, No], GTN administered [Yes, No], number of detectors/slices.

4.4 Primary outcome

The primary outcome will be all-cause death or subsequent non-fatal type 1 or type 4b MI at one year, measured as time from randomisation to first such event. MI will be defined according to the most recent Universal Definition [3] and will be adjudicated by two independent cardiologists blinded to the intervention. Patients discontinuing the study (for any reason) prior to reaching primary outcome

will have their time to primary outcome censored at the last contact date. The level of missing data is low, so a multiple imputation analysis for missing data is not necessary.

Primary analysis
If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and the primary outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

If the adjusted analysis p-value is <0.05, this will be declared as a statistically significant p-value, and formal statistical testing will continue to the key secondary outcomes. If the adjusted p-value is not <0.05, formal statistical testing of outcomes will stop at this point, and further p-values will be presented for information only.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment - The p-value on the plot will be the p-value from the adjusted Cox regression analysis above..

A tabulated of the individual elements of the composite primary outcome will be produced – this table will specify whether each patient's primary outcome was death or MI.

Subgroup analysis
Subgroup analysis on the primary outcome is planned for age (<65/≥65 years), sex (Male/Female), baseline GRACE score (grouped as <109, 109-139, 140 or more), previous CAD (Y/N), baseline ECG result (normal/abnormal), baseline troponin concentration (initial measurement above/below the 99th centile for the site-preferred assay – sex specific where available), and presentation to a study site with or without on-site invasive coronary angiography facilities.
These will be assessed by examining the effect of entering the treatment by subgroup interaction into the Cox regression model. The ratio of hazard ratios, plus 95% confidence interval, will be given for the interaction. Within subgroup treatment effect estimates and confidence intervals will also be presented. If time allows, this will be presented as a forest plot.
We will also prepare a table or graph of effect size by centre for the primary outcome, for the 5 largest sites (all randomised >100 patients). This will not involve any formal statistical testing.

4.5 Key secondary outcomes

1. Coronary Heart Disease (CHD) death or subsequent non-fatal MI; 2. Cardiovascular Disease (CVD) death or subsequent non-fatal MI; 3. Subsequent Non-fatal MI; 4. Coronary Heart Disease death; 5. Cardiovascular death; 6. All-cause death.

These outcomes are measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the relevant outcome will have their time to outcome censored at the last contact date. Patients who die from a cause that is not part of the relevant outcome, before achieving the relevant outcome, will have their time to outcome censored at the date of death.

The analysis will use adjudicated outcome data, where these are available and relevant.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and each key secondary outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment. If the adjusted p-value from the primary outcome is <0.05, then formal statistical testing will continue into the key secondary outcomes. If this is the case, for each key secondary outcome in turn, in the order as listed above, an outcome will be declared as a statistically significant if the adjusted p-value<0.05, and if this is so, then formal statistical testing will continue to the next outcome in the list. If the adjusted p-value is not <0.05, formal statistical testing of outcomes will stop at this point, and further p-values will be presented for information only.

4.6 Other secondary outcomes

Any p-values presented will be for descriptive purposes only, and should not be considered as formal statistical significance testing.

1. Coronary Heart Disease (CHD) death or subsequent non-fatal MI (type 1 or 4b);
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die from a cause that is not part of the outcome, before achieving the outcome, will have their time to outcome censored at the date of death.

The analysis will use adjudicated outcome data, where these are available and relevant.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

2. Subsequent Non-fatal MI (type 1 or 4b);
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die from a cause that is not part of the outcome, before achieving the outcome, will have their time to outcome censored at the date of death.

The analysis will use adjudicated outcome data, where these are available and relevant.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results

will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

3. Non-cardiovascular death;
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die from a cause that is not part of the outcome, before achieving the outcome, will have their time to outcome censored at the date of death.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

4. Invasive coronary angiography;
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die before achieving the outcome, will have their time to outcome censored at the date of death.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

5. Coronary revascularisation;
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die before achieving the outcome, will have their time to outcome censored at the date of death.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The

primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

6. Percutaneous coronary intervention;
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die before achieving the outcome, will have their time to outcome censored at the date of death.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

7. Coronary artery bypass graft;
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die before achieving the outcome, will have their time to outcome censored at the date of death.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

8. Proportion of patients prescribed ACS therapies during index hospitalisation;
Table: N (%), odds ratio with 95% confidence interval, of patients prescribed ACS therapies during index hospitalisation; using logistic regression adjusted as specified earlier, with unadjusted analysis also presented.

Note: ACS therapy includes TNK/TPA, LMWH, tirofiban or equivalent 2B3A inhibitors, intravenous nitrate, aspirin, clopidogrel, prasugrel, ticagrelor.

9. Proportion of patients discharged on preventative treatment or have alteration in dosage of preventative treatment during index hospitalisation;

Table: N (%), odds ratio with 95% confidence interval; using logistic regression adjusted as specified earlier, with unadjusted analysis also presented.

Primary or secondary prevention treatment includes beta blocker, calcium channel blocker, ACE inhibitor or ARB, nicorandil, oral nitrate, buccal or sublingual nitrate, oral hypoglycaemic, insulin, statin, aspirin, clopidogrel, prasugrel, ticagrelor.

10. Length of stay for index hospitalisation;
This will be reported in Hours
Table: Descriptive statistics [continuous data].
Table: Difference between the intervention groups with 95% confidence interval, using Hodges Lehmann estimator of location shift, with a Moses distribution free confidence interval based on the Wilcoxon Rank Sum test.

11. Representation or rehospitalisation with suspected ACS/recurrent chest pain within 12 months [NB this is being interpreted as time from randomisation, not time from index hospitalisation]
This will be measured as the time from randomisation to the first relevant event. Patients discontinuing the study (for any reason) prior to reaching the outcome will have their time to outcome censored at the last contact date. Patients who die before achieving the outcome, will have their time to outcome censored at the date of death.

If the proportional hazards assumption holds, using visual inspection, then the relationship between intervention and this outcome will be analysed using Cox proportional hazard regression. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The primary analysis will be adjusted as specified in the Overall Statistical Principles section of this document. An unadjusted analysis will also be presented, as a sensitivity analysis.

The number of patients with an outcome event (by treatment group) will be tabulated, and the following statistics will be presented: adjusted HR (and 95% CI, p value), unadjusted HR (and 95% CI, p value). A Kaplan-Meier plot will be produced, showing results by allocated treatment.

12. Chest pain symptoms up to 12 months;
Table: N (%) of patients with 'No chest pain', 'Non-exertional chest pain', 'Chest pain on exertion' will be presented at month 1, 6, and 12 and summarised by allocated intervention group. No formal statistical testing will be performed.

13. Patient satisfaction at 1 month;
Data to be tabulated, without formal statistical testing.

14. Clinician certainty of presenting diagnosis after CTCA;
Table [continuous]: Present data on change from baseline, in addition to final values.
Note: clinician certainty of presenting diagnosis is on a scale of 0-10 where 0 is least certain and 10 is most certain

15. Quality of Life (measured by EQ-5D-5L up to12 months).
NB Analysis of this outcome will be done by the health economics team, not the statistical team, and details are in the Health Economic Analysis Plan.

4.7 Safety

1. Summary table of adverse events, by treatment group and overall. Number of events and number of patients who had an event, showing all adverse events, serious adverse events, and non-serious adverse events. Table to include related/not related, and any categorisation provided by the Chief Investigator.

2. Radiation exposure from CTCA in patients allocated CTCA, who received CTCA as the trial intervention. Number of patients in this category, plus summary of the effective radiation dose for this group of patients. A dose length product to mSv conversion factor of 0.014 mSv/mGy/cm will be used. Number of patients who had radiation exposure that met the criteria for deviation, split by whether patient had (deviation=dose-length product>686 mGy.cm) or did not have (deviation=dose-length product >1500 mGy.cm) typical characteristics (typical = heart rate during scan <70 beats per minute, heart in sinus rhythm, and BMI <25 kg/m^2)

3. Other cardiac and non-cardiac findings in patients allocated CTCA, who received CTCA as the trial intervention (categorical).

4.8 Other analyses

Cost effectiveness analysis is specified in the Health Economics Analysis Plan

Clinical investigations during trial (these may be re-categorised after taking in to account the text from the 'other relevant' category):

- Echo (Yes/No)
- Radionuclide scan (Yes/No)
- 24 hour tape (Yes/No)
- Abdominal ultrasound (Yes/No)
- Upper gastrointestinal endoscopy (Yes/No)
- Exercise test (Yes/No)
- MRI angiography (Yes/No)
- Stress echo (Yes/No)
- Result of final ECG
- Rhythm of final ECG
- Abnormal final troponin (Yes/No)
- Other relevant, as specified on categorisation of 'other investigations' by Chief Investigator

Clinical process:

- Most applicable disposition place (place sent after initial attendance location)
- Most applicable discharge diagnosis

5. Validation and QC

The following will be done by a second statistician:

1. Separate programming and checking of primary outcome results and conclusions.

2. The statistical report will be read and sense-checked.

6. Data sharing

A file, or set of files, containing the final analysis data will be prepared as part of the final analysis. Within the University of Edinburgh environment, under certain safeguards, these de-identified datasets can be shared. If a fully anonymised version is required for external sharing, further discussion is needed.

7. References

1. SAS® Institute Inc. SAS for Windows. SAS Institute Inc.: Cary, NC, U.S.A
2. Fox et al for the GRACE Investigators. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006; 33:1091-1094.
3. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Eur Heart J. (2012); 33:2551-67.

RAPID-CTCA_SAP v2.0

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