Statistical Analysis Plan

High-STEACS

High-Sensitivity Troponin in the Evaluation of patients with Acute Coronary Syndrome (High-STEACS): a randomised controlled trial

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Authors:	Catriona Keerie, Christopher Weir
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Chief Investigator:	Professor Nicholas L Mills

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Signatures

Chief Investigator
Prof Nicholas L Mills
BHF Centre for Cardiovascular Sciences
University of Edinburgh

Signature on file — Signature

16 May 2018 — Date

Trial Statistician
Prof Christopher Weir
Edinburgh Clinical Trials Unit
Usher Institute of Population Health Sciences & Informatics
University of Edinburgh

Signature on file — Signature

16 May 2018 — Date

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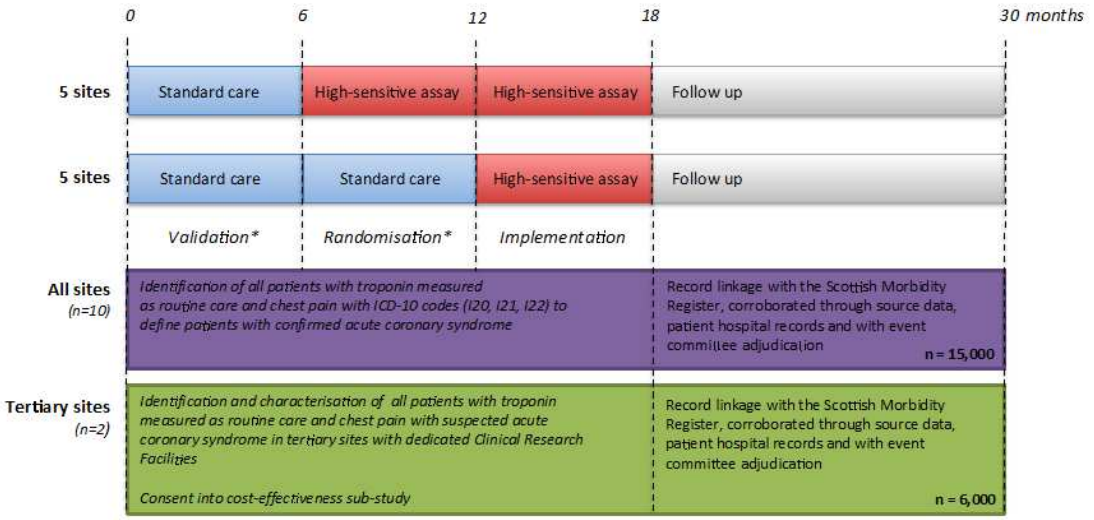
2 List of Abbreviations

A&E	Accident and emergency
ACE	Angiotensin converting enzyme
AIC	Akaike's Information Criterion
ARB	Angiotensin receptor blocker
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass graft
CI	Confidence interval
CONSORT	CONsolidated Standards of Reporting Trials
DAPT	Dual anti-platelet therapy
ECTU	Edinburgh Clinical Trials Unit
eGFR	estimated Glomerular Filtration Rate
FA	Full analysis
GRACE	Global Registry of Acute Coronary Events
Inj	Myocardial injury
IHD	Ischaemic heart disease
LBBB	Left bundle branch block
MI	Myocardial infarction
NInj	No myocardial injury
PCI	Percutaneous coronary intervention
PPI	Proton pump inhibitor
Q1	Lower quartile
Q3	Upper quartile
RInj	Reclassification with myocardial injury
RMI	Reclassification with myocardial infarction
SAP	Statistical analysis plan
SD	Standard deviation
SIMD	Scottish Index of Multiple Deprivation
SOP	Standard operating procedure
URL	Upper reference limits

3 Introduction

3.1 Study Design

In this prospective stepped wedge cluster randomised controlled multi-centre trial, there will be three 6-month study phases: *validation*, *randomisation*, and *implementation*. The ARCHITECT *STAT* high-sensitivity troponin I assay will be run in parallel with the existing contemporary sensitive troponin I assay (standard care) throughout the trial. During the *validation* phase, all sites will report results from the contemporary assay and the diagnostic threshold for myocardial infarction will remain unchanged. This phase will provide baseline information on patients with suspected acute coronary syndrome for each site. In the *randomisation* phase, participating centres will be randomised 1:1 to introduce the high-sensitivity assay or continue with the contemporary assay and existing diagnostic thresholds (standard care). Centres will be matched by number of admissions and type of health care provider (secondary and tertiary care). Finally, in the *implementation* phase, all centres will implement the high-sensitivity assay for at least 6 months (see diagram below).



** During the validation and randomisation phases of the study both the standard and high sensitivity assays will be run in parallel. During the validation phase and following randomisation in those sites randomised to standard care, only results of the standard assay will be made available with clinical decisions based on existing diagnostic thresholds.*

The use of a cluster-randomised design permits the inclusion of all patients with suspected acute coronary syndrome, prevents selection bias and limits the potential for confusion amongst clinicians who would otherwise be required to simultaneously assess patients using different diagnostic criteria for acute myocardial infarction. It is anticipated that approximately 23,800 patients will be included in total across the three phases of the trial.

This document details the criteria to be used for the definition of the analysis populations and the statistical methodology for analysis for the High-STEACS trial. It has been compiled according to the Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "ECTU_SOP_ST_04 Statistical Analysis Plans" and has been written based on information contained in the study protocol version 7.0.

3.2 Study Objectives

To determine whether use of a high-sensitivity cardiac troponin I assay to identify the 99th percentile upper reference limit as the diagnostic threshold for myocardial infarction is appropriate in patients with suspected acute coronary syndrome.

3.3 Original Hypothesis

Implementation of the ARCHITECT *STAT* high-sensitive troponin I assay will reduce recurrent myocardial infarction and cardiovascular death at one year in patients with suspected acute coronary syndrome.

4 Statistical Methods Section from the Protocol

This section repeats the statistical analysis section from the protocol to allow any necessary changes from the planned methods to be clearly presented.

The analysis will take account of the cluster-randomised nature of the stepped wedge design. The primary end-point of 12-month event-free survival (reinfarction and cardiovascular death) will be compared before and after implementation of the high-sensitivity assay using a logistic regression generalized linear mixed model. Primary endpoint survival times will also be summarised descriptively using Kaplan-Meier survival curves and analysed formally using a Cox proportional hazards model incorporating a site level random effect and fixed effects for assay and covariate effects. The proportional hazards assumption will be verified by plotting log-cumulative hazard versus log-time for the high sensitivity and standard care troponin assay groups. Model validity will be further explored using plots of Cox-Snell and Martingale residuals.

Secondary efficacy endpoint (i), duration of stay, will be analysed using Kaplan-Meier survival curves and a Cox proportional hazards model as above, with death in hospital being treated as a censoring event. Secondary efficacy endpoints (ii)-(vii) and safety outcomes will be analysed using the same methods as used for the primary efficacy endpoint.

5 Overall statistical principles

5.1 SAP Objectives

The objective of this SAP is to describe the statistical analyses contributing to the final report and primary publication(s) of the High-STEACS study. This SAP does not address the analyses required for the proposed sub-studies and exploratory analyses.

The planned analyses will be performed in a staged manner, according to the availability of the relevant study data. In particular, analyses of the adjudicated MI and RMI populations (defined

in Section 5.3) and the adjudicated diagnosis (Section 6.2) will be deferred and will not be reported at the same time as the other analyses. Further phasing of the reporting may also be implemented according to the subsets of the analyses listed in this SAP which would be required for scheduled conference presentations and peer reviewed journal publications.

5.2 General Statistical Principles

Hypothesis tests will be performed at the two-sided 5% significance level. Categorical variables will be summarised with the number and percentage of subjects falling in each category. Continuous variables will be summarised using the mean, median, standard deviation (SD), lower quartile (Q1), upper quartile (Q3), minimum and maximum values. P-values will be stated to two significant figures after the decimal point, with exceptionally small p-values being reported as "<0.0001".

In all time to event analyses, observations will be censored at the earlier of study end date or, if recorded, the date of migration out of Scotland. Event times will be measured from the arrival date and time of the index presentation.

5.3 Analysis Populations

Eligible sites are secondary and tertiary hospitals in Scotland which use the ARCHITECT platform. The number of subjects who were screened (patients in whom cardiac troponin was requested) and included will be reported. All patients whom the treating physician requested a cardiac troponin measurement for suspected acute coronary syndrome who have valid paired cardiac troponin I measurements on both the contemporary and high-sensitivity assay during the index presentation will be included in the study. If data are missing on whether suspected acute coronary syndrome was the reason for the cardiac troponin measurement request, the patient will be included in the study. Readmissions during follow-up are not be eligible for entry to the study as a new participant. Patients who are not resident in Scotland will be excluded as follow-up via routinely collected sources will not capture the primary outcome for these individuals. Reasons for non-inclusion will be summarised, as will the number of participants completing the study. All included patients with evidence of myocardial necrosis (high-sensitivity cardiac troponin concentration >99th centile using sex-specific upper reference limits [URL] on presentation or subsequent testing) will be identified and two investigators will independently review all clinical information, including non-invasive and invasive investigations from presentation to 30 days. Patients will be classified as having type 1, type 2, type 4a, type 4b and type 5 myocardial infarction, or having myocardial injury according to the universal definition of myocardial infarction. Type 1 myocardial infarction will be defined as myocardial necrosis in the context of an isolated presentation with suspected acute coronary syndrome with chest pain or evidence of myocardial ischemia on the electrocardiogram. Patients with symptoms or signs of myocardial ischemia due to increased oxygen demand or decreased supply (e.g. tachyarrhythmia, hypotension or anaemia) and myocardial necrosis will be classified as type 2 myocardial infarction. Peri-procedural myocardial infarction type 4a will be defined in patients with a rise of 20% in cardiac troponin concentration if values are elevated and are stable or falling prior to angioplasty; type 4b will be defined in patients with stent thrombosis documented at coronary angiography or at autopsy; type 5 will be defined in patients following cardiac surgery when cardiac troponin concentrations are >10 × 99th percentile during the first 48 hours from a normal baseline. Myocardial injury will be defined as evidence of myocardial necrosis in the absence of any clinical features of myocardial ischaemia. Any discrepancies will

be resolved by the adjudication of a third independent reviewer. The adjudication committee will be blinded to study phase.

Details regarding the interpretation of troponin results and the classification of patients based on these values are provided in Appendix 1.

Full analysis (FA) population
Patients who have paired cardiac valid troponin I measurements on both the contemporary and high-sensitivity assay within 24 hours of the index presentation arrival date/time.

Myocardial injury (Inj) and myocardial infarction (MI) populations
Patients with myocardial injury (Inj) are defined as those with elevated cardiac troponin I concentrations identified by the contemporary assay (≥50 ng/L in NHS Lothian; 0.04 ng/mL in NHS Greater Glasgow & Clyde). Within this population, patients with myocardial infarction (MI) will consist of those with an adjudicated diagnosis of type 1 or type 4b myocardial infarction.

Reclassification with myocardial injury (RInj) and myocardial infarction (RMI) populations
Patients reclassified with myocardial injury (RInj) are defined as those with elevated cardiac troponin I concentrations identified using the high-sensitivity assay (>99th percentile sex-specific upper reference limit [URL], 34 ng/L in men and 16 ng/L in women) in whom concentrations were below the diagnostic threshold on the contemporary assay. Within this population, patients reclassified with myocardial infarction (RMI) will consist of those with an adjudicated diagnosis of type 1 or type 4b myocardial infarction.

No myocardial injury (NInj) population
Patients with cardiac troponin I concentrations ≤99th percentile sex-specific URL using the high-sensitivity assay.

All analyses and data manipulations will be carried out using SAS [1].

6 List of analyses

6.1 Recruitment

CONSORT type [2] flowchart, adapted for stepped wedge design, including details of:

- Number of sites
- Number of sites dropping out (if any)
- Issues with intervention delivery or timing within the sites (if any).
- Number of participants recruited overall and within each site
- Number of participants recruited within each intervention/control condition, within each site
- Number of participants providing complete follow-up data within each intervention/control condition, within each site
- Number of participants included in the primary analysis within each intervention/control condition, within each site

A schematic representation of the actual study design will be reported with hospital sites, randomised groups, and intervention start points.

Sites were paired based on expected number of presentations and one site randomised to early implementation and the other to late implementation. For pragmatic reasons (shared lab

facilities), the Vale of Leven and Royal Alexandra Hospital, Paisley were grouped and randomised together. This enabled implementation of the high-sensitivity assay to occur on the same date at both sites and allowed the same lab processes to be followed at both sites.

6.2 Baseline Characteristics

Baseline participant and site characteristics will be summarised before and after implementation of the ARCHITECT *STAT* high-sensitivity troponin I assay for each study site and for the FA. Baseline characteristics will also be summarised for the Inj and RInj populations, MI and RMI populations, and the NInj populations. No formal hypothesis testing of the baseline characteristics will be performed.

The site characteristics considered will include:

- Hospital size
- Location (Glasgow & Clyde, Lothian)

The participant characteristics considered will include:

- Age (years)
- Sex (male/female)
- Cardiovascular risk factors
    - Smoking status (current/ex/never)
    - Hyperlipidaemia (yes/no)
    - Diabetes mellitus (yes/no)
    - History of hospitalisation with heart failure
- Past medical history
    - Ischaemic heart disease (IHD)
    - Myocardial infarction (MI)
    - Cerebrovascular disease
    - Previous percutaneous coronary intervention (PCI)
    - Previous coronary artery bypass graft (CABG)
- Scottish Index of Multiple Deprivation (SIMD) (quintile)

- Medical therapy on presentation (yes/no)
    - Aspirin
    - Clopidogrel
    - Prasugrel
    - Ticagrelor
    - Dual antiplatelet therapy (DAPT)[1]
    - Angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB)
    - Beta blocker
    - Statin
    - Oral anticoagulant
    - Calcium channel blockers
    - Nicorandil

[1] As indicated by aspirin and any other of three anti-platelet medications (clopidogrel, prasugrel or ticagrelor)

- Ivabradine
- Spironolactone
- Loop diuretic
- Proton pump inhibitor (PPI)

Clinical presentation (Index admission)

- Time interval, symptom onset to troponin sampling (hours)
- Time interval, presentation to troponin sampling (minutes)
- Time interval, troponin sampling at presentation to first repeat sample (minutes)
- Primary symptom (chest pain, dyspnoea, syncope, palpitation, other)
- GRACE score [3]
- Measurements at initial assessment:
  - Heart rate (bpm)
  - Systolic / diastolic blood pressure (mmHg)
  - 12-lead electrocardiogram
    - Rhythm (SR, AF/Flutter, SVT, VT/VF, other)
    - Ischaemic changes (yes/no)
    - ST elevation (yes/no)
    - ST depression (yes/no)
    - T wave inversion (yes/no)
    - LBBB new (yes/no)
    - LBBB old (yes/no)

Haematology and clinical chemistry

- Haemoglobin
- Creatinine
- eGFR

Troponin concentrations

- Presentation high-sensitivity cardiac troponin concentration (ng/L)
- Maximum high-sensitivity cardiac troponin concentration (ng/L)
- Proportion of patients with serial measurements (2 or more) during index presentation (%)

Adjudicated diagnosis

- Type 1 myocardial infarction (STEMI, NSTEMI)
- Type 2 myocardial infarction
- Type 4a myocardial infarction
- Type 4b myocardial infarction
- Type 5 myocardial infarction
- Myocardial injury
- Other clinical diagnosis

6.3 Management and discharge

Management during the index hospitalisation and therapies at discharge will be summarised before and after implementation of the ARCHITECT *STAT* high-sensitivity troponin I assay for each study site and overall for the FA population. These characteristics will also be summarised

for the Inj and RInj populations, MI and RMI populations, and the NInj populations. The following variables will be reported:

- Duration of stay, hours
- Coronary angiography (yes/no)
- Percutaneous coronary revascularisation (yes/no)
- Surgical coronary revascularisation (yes/no)
- Medical therapy from electronic discharge summary
    - Aspirin
    - Clopidogrel
    - Prasugrel
    - Ticagrelor
    - Dual antiplatelet therapy (DAPT)
    - Angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB)
    - Beta blocker
    - Statin
    - Oral anticoagulant
    - Calcium channel blockers
    - Nicorandil
    - Ivabradine
    - Spironolactone
    - Loop diuretic
    - Proton pump inhibitor (PPI)

6.4 Primary Outcome

6.4.1 Event summaries

FA, Inj, RInj, MI, RMI, NInj populations
Myocardial infarction (type 1 or type 4b) following index presentation or cardiovascular death at 1 year will be summarised (n, %) by study site and overall before and after implementation of the ARCHITECT *STAT* high-sensitivity troponin I assay.

6.4.2 Primary analysis: logistic regression mixed modelling with covariate adjustment

RInj population
The primary outcome will be compared before and after implementation of the high-sensitivity assay using a logistic regression generalised linear mixed model following the model structure described in Hussey and Hughes (2007) [4] (see Appendix 2). The effect of implementation of the high-sensitivity assay will be presented as an odds ratio and its 95% confidence interval (CI).

The event rate will be modelled using a logistic mixed-effects regression model, adjusting for hospital site, season (Spring, Summer, Autumn, relative to Winter[2] as the reference category), time of patient presentation since start of study (days), and an indicator variable for whether the high-sensitivity assay has been implemented or not. Hospital site will be fitted as a random

[2] Spring (March, April, May) Summer (June, July, August) Autumn (September, October, November) Winter (December, January, February) as per the UK Met Office definitions http://www.metoffice.gov.uk/learning/learn-about-the-weather/how-weather-works/when-does-spring-start

effect and age, sex and SIMD 2016 quintile will be included as fixed patient-level covariates in the model. The age variable will be centred on the mean age in the RInj population.

Time of patient presentation since start of study (the date on which the validation phase started in the first study site) will be initially modelled as a linear term; alternatives will be considered if the data do not support the linearity assumption. Time since start of study will be centred on the mid-point of the study recruitment period and scaled to a range similar to that of the age covariate in order to minimise model convergence issues. Should the primary analysis modelling fail to converge, one covariate at a time will be omitted from the model until convergence is achieved. Covariates will be considered for omission in the order sex, age, SIMD 2016.

In order to accommodate the closure of the Western Infirmary Glasgow (WIG) and Victoria Infirmary Glasgow (VIG) during the study, and the subsequent redirection of patients in their catchment areas to the new Queen Elizabeth University Hospital (QEUH) on the site of the Southern General Hospital (SGH), patients will be analysed according to the site at which they were treated. QEUH will be considered a continuation of the Southern General Hospital site. The assumptions in this approach will be investigated in a sensitivity analysis in which SGH and QEUH patients from the WIG or VIG catchment areas are excluded from the analysis.

The above modelling will be repeated for the FA, Inj, MI, RMI, NInj analysis populations to provide supporting information. For each population the odds ratio and 95% CI will be displayed graphically by site using a forest plot (where feasible, based on the number of participants and outcome events in each site for a given analysis population).

6.4.3 Sensitivity analysis: logistic regression mixed model with interaction term

RInj population
A sensitivity analysis will be performed in which additional terms will be included in the primary analysis model fitted in section 6.4.2, according to the extension outlined in Hemming *et al* [5], to fit a site by intervention interaction random effect. This is intended to aid interpretation of the primary analysis results, with regard to intervention-effect heterogeneity across sites. This will be repeated for the FA, Inj, MI, RMI, NInj analysis populations as supporting information. Prospective simulation studies suggest that model fitting with this additional interaction term have a 3% to 21% risk of non-convergence of the model, depending on the scenario simulated. The covariate-omission strategy described in section 6.4.2 will be used to maximise the chances of convergence.

6.4.4 Secondary analysis: Unadjusted logistic regression mixed model

RInj population
A secondary analysis not adjusting for patient-level covariates will also be performed. This will be repeated for the FA, Inj, MI, RMI, NInj analysis populations as supporting information.

6.4.5 Secondary analysis: Time to event summaries

FA, Inj, RInj, MI, RMI, NInj populations
Primary outcome survival times will be summarised descriptively before and after implementation of the high-sensitivity assay using Kaplan-Meier survival curves (with

accompanying 95% confidence intervals). Differences before and after implementation will be tested using a log-rank test stratified by site.

6.4.6 Secondary analysis: Cox proportional hazards modelling

FA, Inj, RInj, MI, RMI, NInj populations
Survival times will be analysed formally using a Cox proportional hazards model following a similar form to the logistic regression model of Section 6.4.2, fitting hospital site as a random effect and age (centred on the analysis population mean), sex and SIMD quintile as patient-level fixed effects. The effect of implementing the high-sensitivity assay will be estimated by the hazard ratio and its 95% confidence interval. The proportional hazards assumption will be verified by plotting log-cumulative hazard versus log-time before and after implementation of the high-sensitivity assay. Model validity will be further explored using plots of Cox-Snell and Martingale residuals. Given the difficultly in assessing hazard proportionality in the presence of a hospital site random effect, the above checks will be performed for each hospital site separately. Should the proportional hazards assumption be invalid, survival analysis will be restricted to the descriptive Kaplan-Meier curves and log-rank tests of section 6.4.5 only.

6.5 Secondary outcomes

The following secondary outcomes will be analysed using the methods outlined in sections 6.4.1, 6.4.2, 6.4.3 and 6.4.4:

- Type 1 or type 4b myocardial infarction following the index presentation
- Unplanned coronary revascularisation after discharge
- Cardiovascular death
    - Any cardiovascular death
    - Cardiovascular death – Cardiac subset
    - Cardiovascular death – Non-cardiac subset
- All-cause death
- Hospitalisation for heart failure
- Ischaemic stroke

6.6 Safety analyses

Safety outcomes will be summarised before and after implementation of the ARCHITECT STAT high-sensitive troponin I assay for the FA population. Safety characteristics will also be summarised for the Inj, RInj, MI, RMI, NInj populations. The following safety outcomes will be reported:

- Major haemorrhage[3]
- Unplanned hospitalization within 30 days excluding acute coronary syndrome
- Non-cardiovascular death

[3] BARC Type 3 and BARC Type 5

6.7 Long term follow-up

Long term follow up at 3 and 5 years will capture relevant efficacy and safety outcomes. Analysis and reporting of long term follow-up data will be presented separately to the planned analyses documented here.

7 Derived variables

7.1 Timed endpoints

- Time from symptom onset to troponin sampling (minutes)
- Time from symptom onset to time of presentation (minutes)
- Time from presentation to troponin sampling (minutes)
- Time from troponin sampling at presentation to first repeat sample (minutes)

7.2 GRACE score

- The GRACE score and calculation of the predicted probability of in-hospital death [6] will be determined for all patients with elevated high-sensitivity cardiac troponin I concentrations above the sex-specific 99th centile upper reference limit.

7.3 Troponin sampling

- Presentation high-sensitivity cardiac troponin concentration (ng/L)
- Maximum high-sensitivity cardiac troponin concentration (ng/L)
- Proportion of patients with serial measurements (2 or more) during index presentation (%)

7.4 Primary endpoint

Myocardial infarction (type 1 or type 4b) following index presentation or cardiovascular death at 1 year will be captured as 2 separate variables from the adjudication database and a Yes/No flag will be created to summarise the primary endpoint.

8 Missing data

It is anticipated that SIMD quintile data will be missing in a small proportion of patients, for example due to the creation of additional postal code areas for new housing developments. As SIMD quintile is a key covariate for adjustment in the primary analysis, any missing SIMD quintile will be substituted, using single imputation, with the modal value observed on the other patients treated at the same study site.

No other imputation of missing data will be performed, apart from the handling of high sensitivity and contemporary assay troponin values and their measurement times as described in Appendix 1.

9 Validation

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.

10 Data sharing

A file, or set of files, containing the final data will be prepared, along with a data dictionary. These will be made available to the Chief Investigator within the Safe Haven secure area at the end of the analysis phase.

11 References

1. SAS® Institute Inc. SAS for Windows. SAS Institute Inc.: Cary, NC, U.S.A

2. Campbell MK, Piaggio G, Elbourne DR, Altman DG, for the CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. BMJ 2012; 345:e5661.

3. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP et al. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 2003; 163:2345-2353.

4. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemporary Clinical Trials 2007; 28:182-191.

5. Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. Trials 2017;18:101.

6. Anderson F, FitzGerald G. Methods and formulas used to calculate the GRACE Risk Scores for patients presenting to hospital with an acute coronary syndrome. Copyright 1998-2014, Center for Outcomes Research, University of Massachusetts Medical School.

Appendix 1

1) Units
Contemporary troponin results: ng/mL (both Lothian and Glasgow)
High-sensitivity troponin results: ng/L (Lothian) or pg/mL (Glasgow) which are equivalent.

2) Thresholds:
Contemporary troponin assay
Glasgow: <0.04 ng/mL equivalent to 40 ng/L
Lothian: <0.05 ng/mL equivalent to 50 ng/L

High-sensitivity troponin assay for both Lothian and Glasgow
Women: 16 ng/L
Men: 34 ng/L

NOTE: for data analysis
** high-sensitivity troponin results are reported as integers to clinicians. Therefore, any value ≥16.5 ng/L for women and ≥34.5 ng/L for men will be "positive" for myocardial injury.

3) Presentation high-sensitivity troponin result
-where the initial high-sensitivity troponin is non-numeric (ie. IS= insufficient sample or TC= test cancelled), take next result as "presentation" result

4) Duplicate troponin results with same date/time
If there are duplicate troponin results with same date and time:
-take first result
-If non-numeric (ie. IS= insufficient sample or TC= test cancelled, then take next result)
-this does not apply to troponin results with time 00:00 (see below)

5) Sample time with 00:00 erroneously
- These results might have been inadvertently excluded because time 00:00 is before the presentation time
-Solution: For these patients, use result date/time from variable RESULTDATE.

6) Defining Reclassification subgroups
The following rule will be applied in a hierarchical fashion:

	C	HS
Inj	+	
RInj	-	+
Ninj	-	-

7) With regard to missing paired troponins
some patients with unpaired troponin may still be included
For example:

	C	HS
cannot classify [exclude]*	missing	+ (< 100 ng/L)
Inj	missing	+ (≥ 100 ng/L)
NInj	missing	-
Inj	+	missing
cannot classify [exclude]*	-	missing
cannot classify [exclude]*	missing	missing

*these troponin values will be excluded but patient will remain with other paired results.

8) Definition of presentation sample
First valid troponin result (contemporary or high-sensitivity).

9) Definition of serial sampling
Serial samples will be defined as two or more valid and clinically reported troponin results within 24 hours. Therefore, in the Validation phase this will be defined as two or more valid contemporary troponin result within 24 hours and in the Implementation phase, two valid high-sensitivity troponin result within 24 hours. Proportion of patients with serial sampling will be calculated for all patients and in the subset of patients who presented within 6 hours of chest pain onset.

Appendix 2

Statistical model for the analysis of the primary outcome

The statistical model for the analysis of the primary outcome (Section 6.4.2) is formally defined as follows:

The event rate μ_{ijk} in site *i*, season *j,* time of presentation since start of study T_k for patient k (*i*=1,…,10; *j*=1,2,3,4; *k* = 1, …) will be modelled in the linear component of the logistic regression as:

$$\mu + \alpha_i + \beta_j + \gamma T_k + \theta X_{ik}$$

where μ is the overall mean event rate on the logit scale;
α_i is a random effect for site *i*, $\alpha_i \sim N(0,\tau^2)$;
β_j is the fixed effect log-odds ratio for season *j*;
γ is the linear fixed effect for time of presentation since start of study;
θ is the fixed effect log-odds ratio for the high-sensitivity assay treatment;
X_{ik} is a (0/1) variable to indicate whether the high-sensitivity assay is implemented in site *i* for patient *k*.

Key patient-level covariates of age, sex and SIMD will also be included as fixed effects.