Imperial College London

Statistical Analysis Plan

TRIAL FULL TITLE	Remote Acute Assessment of Patients with High Cardiovascular Risk Post-Acute Coronary Syndrome (TELE-ACS)
SAP VERSION	1
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2 Abbreviations and Definitions

AE	Adverse Event
CAD	Coronary Artery Disease
CI	Confidence Interval
HR	Hazard Ratio
ITT	Intention to Treat
NSTE-ACS	Non-ST-segment Acute Coronary Syndrome
SAP	Statistical Analysis Plan
STEMI	ST-segment Elevation Myocardial Infarction
UA	Unstable Angina

3 Introduction

Myocardial infarction remains one of the leading causes of mortality in the UK, despite cutting edge medical and interventional therapy. As length of stay in hospital for myocardial infarction decreases in line with global trends, UK unplanned re-admission rates remain high.

The utilisation of telemedicine devices has the potential to provide remote, clinically necessary, diagnostic information, without the need for hospital attendance. One such device is the smartheart™ (SHL Telemedicine), which is a CE/ FDA-approved personal mobile 12-lead ECG device, that produces and transmits hospital-grade electrocardiograms (ECGs) within 30 seconds, via Bluetooth and cellular communication. Indeed, use of SHL Telemedicine devices along with their bespoke call centre and mobile intensive care unit has previously been demonstrated to reduce post-acute myocardial infarction readmission rates to 5.3% in a retrospective study

The TELE-ACS trial will the efficacy of telemedicine devices to provide remote, clinically necessary, diagnostic information, without the need for hospital attendance.

4 Study Objectives and Endpoints

4.1 Study Objectives

The study will assess the following research questions:

Primary objective:

- To examine if telemedicine devices reduce the time to hospital readmission

Secondary objectives:

- To examine if telemedicine devices reduce the length of stay in hospital, attendances at A&E, number of GP visits and symptoms experienced

4.2 Endpoints

4.2.1 Primary outcome measure

The primary study outcome is the time to first hospital readmission (formal admissions and not emergency room visits) during the first 6 months of follow up. This will be a considered as a survival-type outcome, and calculated as the number of months from the date recruitment of to the date of readmission.

4.2.2 Secondary outcome measures

The secondary outcome variables are:

- Readmission during the 0-3, 3-6, and 6-9 month follow-up periods.
- Total length of stay (LOS) during first 6 months of follow up, as well during 0-3, 3-6, and 6-9 month follow-up periods.
- Myocardial infarction, stroke and all-cause mortality at 9-months. We will also report data on heart failure and cardiovascular mortality and morbidity.
- Medical intervention for acute coronary syndromes or heart failure, including coronary angiography/ angioplasty, injectable therapy or oxygen therapy
- Time to first Emergency Room (A&E) visit not requiring admission or further intervention during first 6-months of follow-up, along with A&E occurrence during the 0-3, 3-6, and 6-9 month follow-up periods
- GP visits during the periods 0-3, 3-6 and 6-9 measures
- Patient symptoms (chest pain, shortness of breath, palpitations, dizziness) at 3, 6 and 9 months

5 Study Methods

5.1 General Study Design and Plan

The study is a two-arm parallel group randomised control trial. Patients will be randomised to receive either telemedicine device (Intervention group) or standard care without a telemedicine device (Control group).

Patients in the intervention group will be discharged from hospital with the telemedicine package. In this arm when patients seek medical attention by performing an ECG, the data provided by the telemedicine package will be acted upon, as appropriate, by the trial team. Conversely, in the control arm, standard routine clinical care will be carried out, with remote follow up over the phone at 3, 6 and 9 months.

5.2 Inclusion-Exclusion Criteria

Inclusion criteria

All included patients will meet the following three criteria:

1. ACS Patients diagnosed with elevated high-sensitivity troponin I who have undergone coronary intervention for non-ST-segment acute coronary syndrome (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) or unstable angina (UA).
2. In addition, the patients must have at least one additional cardiovascular risk factors:
    - Current or ex-smoker
    - Diagnosed with hypertension
    - Diabetes mellitus
    - Hypercholesterolaemia.
    - Male aged > 50 years
3. The patient must have access to a smartphone or smart device.

Exclusion criteria

Patients meeting either of the following will be excluded:

- The inability to apply the telemedicine equipment/ transmit the ECG via Bluetooth or cellular connectivity/ engage in a virtual consultation
- Life expectancy of 9 months or less

5.3 Randomisation and Blinding

Patients will be randomised to ether “telemedicine” or “standard care” on a 1:1 basis using computer randomisation software.

5.4 Demographic and Baseline Variables

The following demographic and baseline characteristics of the study participants will be collected:

- Patient demographics (including age, gender, ethnicity, BMI)

- Procedure characteristics
- Risk factors (including smoking status, diabetes, family history CAD)
- History of heart disease
- Other health conditions
- Blood results (including creatinine, eGFR, platelets, cholesterol, troponin)
- Use of cardiac and other drugs
- Pre-discharge observations (including symptoms, heart rate, respiratory, blood pressure, body temperature

5.5 Safety measurements

Safety measurements will consist of the measurement of adverse events. Data on all adverse events experienced will be recorded.

6 Sample Size

The sample size was based on showing a difference between study groups for the primary outcome, time to first readmission, assuming to be a time-to event 'survival' outcome.

Local data for the primary outcome over the past 3 years showed a 30% readmission rate at 6 months (any admission to hospital). This readmission rate was assumed in the control group. A two-fold reduction in the risk of a readmission throughout the follow-up period would be a clinically significant improvement. Thus, a hazard ratio 0.5 between groups (Active/Control) was assumed. With a 5% significance level and 80% power it is calculated that 153 patients per group (306 in total) are required for the study. To allow for an estimated 10% of patients being censoring in the follow-up period (due to death or drop-out), it is proposed to recruit 340 patients into the study.

7 General Considerations

7.1 Timing of Analyses

A single analysis will take place at the completion of the study, after all data is collected. No interim analyses will be performed.

7.2 Analysis Populations

The primary analysis will analyse patients in the groups to which they were randomised, regardless of deviation from the protocol or whether they received the allocated intervention. In other words, analysing on an intention-to-treat (ITT) basis. The primary outcome population, time to readmission, will include all patients who remained in the study for 2 days or more. Patients completing less than 2 days of follow-up will be excluded.

Secondary outcomes considering just a portion of follow-up (e.g. 4-6 months) will include only patients remaining in the study during the whole period. Patients dropping out, withdrawn or dying during a given time period will be excluded from the analyses of data from that period.

7.3 Subgroups

It proposed that the analysis will be performed for all patients combined, with no subgroup analyses performed.

7.4 Missing Data

Only observed data will be analysed. Missing data will be assumed to be Missing At Random. No imputation procedures will be employed to deal with missing data.

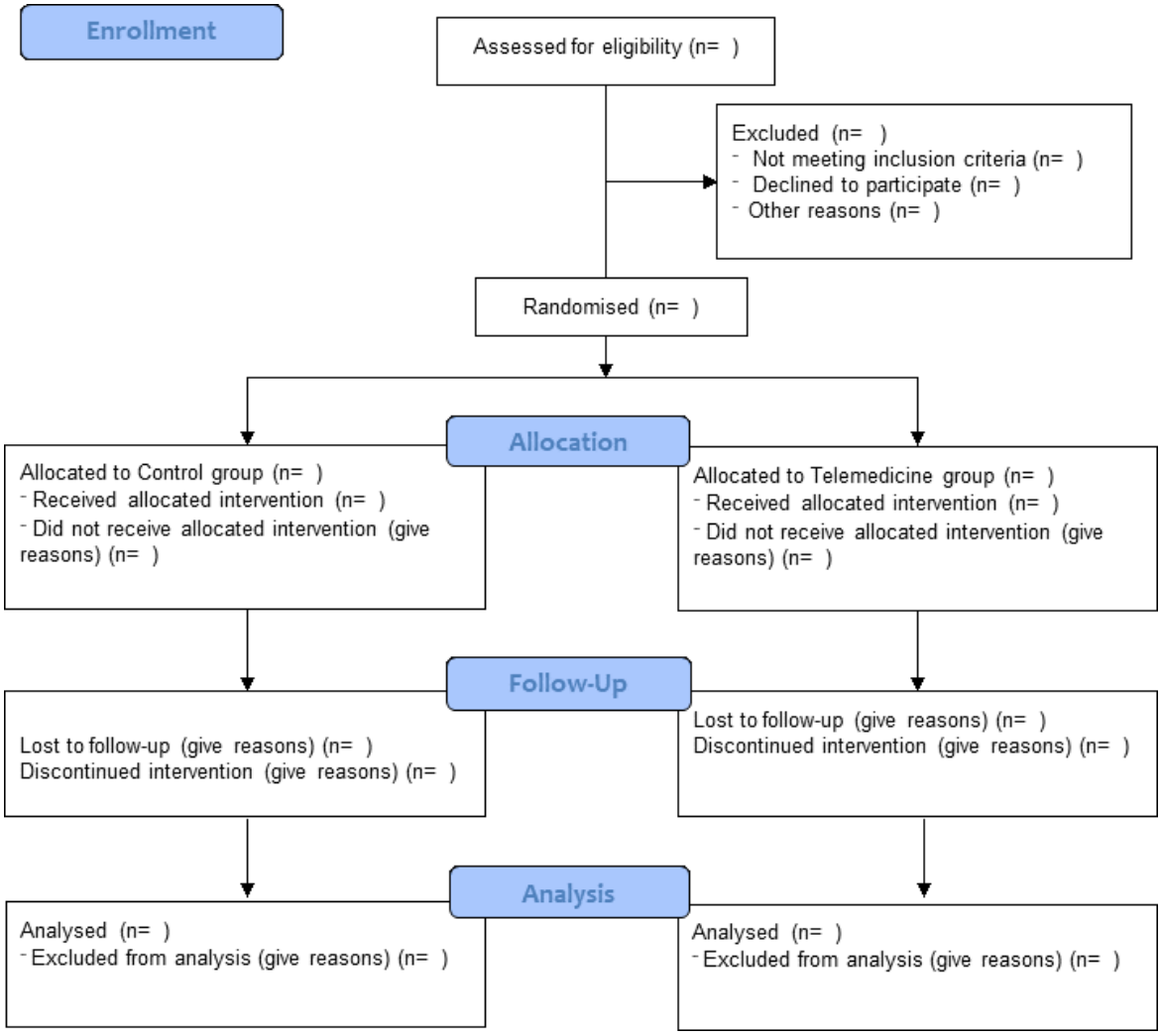
8 Summary of Study Data

8.1 Subject Disposition

A summary of the number of subjects that reached the various stages of the study will be summarised. Reasons for non-participation and withdrawal will be summarised.

A CONSORT diagram will be produced, such as Figure 1, which will illustrate the flow of patients throughout the study.

Figure 1: Outline CONSORT diagram



8.2 Descriptive Analysis Methods

Continuous variables will be summarised using the number of (non-missing) datapoints, mean and standard deviation if found to follow a normal distribution. Continuous variables not found to be normally distributed will be summarised by the number of datapoints, median and inter-quartile range. Categorical variables will be summarised by the frequency and percentage (based on the non-missing sample size) of values in each category.

8.3 Demographic and Baseline Variables

A summary of the demographic and baseline variables is given in section 5.4. Each of these measures will be summarised descriptively for the two study arms separately as described. No formal hypothesis tests will be used to compare the two groups for these measures.

9 Efficacy Analyses

9.1 Primary Efficacy Analysis

The primary study endpoint is the time to first readmission within the first six months of follow-up. This will be analysed as a survival-type outcome. Patients not experiencing a readmission will be censored at the point at which they exited the study, or 6-months, whichever is later

This outcome will be summarised in each group by the estimated percentage of patients free from readmission at 6-months, along with corresponding confidence interval (CI). These estimates will be calculated using Kaplan-Meier methods.

Cox regression will be used to compare the time to first readmission. The difference between groups will be expressed as a hazard ratio (HR), and corresponding CI. This will be calculated as hazard of readmission in the intervention group relative to the hazard in the control group.

A Kaplan-Meier plot will be used to display the results graphically.

The primary analysis will be performed using the primary analysis dataset, as outlined in Section 7.2.

9.2 Secondary Efficacy Analyses

The first secondary outcome, time to first A&E admission will be analysed using equivalent methods to the primary outcome, and using the equivalent dataset.

Binary secondary outcomes will be analysed using a two-sample test of proportions. The differences in percentage will be reported (calculated as Intervention – Control), and expressed with a corresponding CI.

All continuous outcomes are likely to have positively skewed distributions, and will be compared between groups using the Mann-Whitney test.

Additional outcomes were related to assistance calls. As this data will be relevant to the Active group only, this data will be analysed descriptively.

10 Safety Analyses

The main safety outcome is the occurrence of adverse events. The number of adverse events will be reported descriptively as outlined in section 8.2

11 Technical Details

The data analysis will be performed using the statistical software package Stata (version 15.1). Programs recording details of all data manipulation and data analyses will be produced and kept, so that the analyses can be externally inspected and, if necessary, re-run.

12 Changes from previous versions of the Analysis Plan

This is the first version of the SAP. If there are any revisions to the methods outlined in this document, or if any supplementary analyses are needed, these will be documented in a future version of the SAP. The reason for any changes/additions will also be documented.