PROJECT TITLE: RATPAC CBE (RANDOMISED ASSESSMENT OF TREATMENT USING PANEL ASSAY OF CARDIAC MARKERS – CONTEMPORARY BIOMARKER EVALUATION)

Research objectives

1. To test the diagnostic accuracy for an AMI of highly sensitive troponin assays and a range of new cardiac biomarkers of plaque destabilisation, myocardial ischaemia and necrosis.
2. To test the prognostic accuracy for adverse cardiac events of highly sensitive troponin assays and this range of new cardiac biomarkers.
3. To estimate the potential economic impact (clinical effectiveness and cost-effectiveness) of using highly sensitive troponin assays or this range of new cardiac biomarkers instead of an admission and 12-hour troponin measurement.

Existing research

Chest pain due to suspected but not proven acute myocardial infarction (AMI) is responsible for a substantial number of emergency department attendances and emergency hospital admissions in the NHS[1]. Current recommendations suggest that these patients should receive diagnostic testing with measurement of cardiac troponin (now considered to be the definitive test of myocardial necrosis) in a sample taken 12 hours after symptom onset[2]. This delay is necessary because the diagnostic activity of troponin measurement using current assays does not reach peak diagnostic sensitivity until this time. This approach is inconvenient and potentially costly because it requires many patients to be unnecessarily admitted to hospital until the 12-hour sample can be obtained and measured. The majority of patients with a suspected AMI do not actually have an AMI, so their admission will ultimately prove avoidable. Cost-effectiveness analysis suggests that admitting patients for cardiac marker testing is not an efficient use of health service resources[3]. Evidence also suggests that these testing guidelines are often not followed in a busy emergency setting where acute beds are limited. Collinson *et al*[4] showed that 7% of patients discharged after emergency department assessment for acute chest pain had elevated troponin levels at follow-up two days later. Goodacre *et al*[5] showed that in the routine care arm of a randomised trial of a chest pain unit, 14% of patients with an elevated troponin level at two-day follow-up had been sent home from the emergency department.

To overcome the limitations of waiting for 12 hours a number of approaches have been suggested. These include rapid, early sampling[6], the use of cardiac marker panels, including markers which may be detected earlier than troponin[7] and the use of novel markers of ischaemia[8] or of plaque destabilization and rupture[9;10]. Early studies comparing cardiac troponin to other biomarkers suggest that measurement of cardiac troponin is equivalent to the other currently used markers such as myoglobin and the MB isoenzyme of creatine kinase[11]. Meta-analyses have estimated the diagnostic accuracy of individual cardiac markers[12], but there have been no systematic reviews of cardiac panels.

Recent developments have improved the measurement technology for cardiac troponins and have suggested that much earlier sampling with serial measurement and calculation of rate of rise[13] (the significant difference between two consecutive measurements) can be utilised[14]. To date there have been very few studies of the value of biomarker panels in the general chest pain population and none that have examined the new, more sensitive, troponin assays and compared them with biomarker panels. The recent National Institute of Clinical Excellence draft guidance on chest pain specifically identifies the need

for further research into high sensitivity troponin assays and recommends comparison with high sensitivity troponin assays as part of any biomarker evaluation in chest pain patients.

Research methods

Design

We plan to use blood samples collected from patients recruited to an HTA-funded trial of point of care cardiac markers to test the diagnostic and prognostic accuracy of new cardiac markers and highly sensitive troponin assays.

The RATPAC Trial (HTA 06/302/19) (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) was a prospective randomised controlled trial of point-of-care cardiac markers in the emergency department. The research objectives of the study were to evaluate the clinical effectiveness and cost-effectiveness of the currently most promising point-of-care cardiac marker panel currently used in the emergency department.

In patients presenting to the emergency department with suspected but not proven acute myocardial infarction (AMI) the study measured the effect of using a point-of-care cardiac marker panel upon:

1. The proportion of patients successfully discharged home after emergency department assessment
2. Health utility and satisfaction with care
3. The use of coronary care beds and cardiac treatments.
4. Subsequent re-attendance at and/or re-admission to hospital
5. Major adverse events (death, non-fatal AMI, life-threatening arrhythmia, emergency revascularisation or hospitalisation for myocardial ischaemia)
6. Health and social care costs.

The study finished recruiting after external review carried out on behalf of the HTA suggested that the study had achieved its primary outcome.

Setting

The study was performed in six emergency departments in the United Kingdom. Emergency department staff identified eligible patients, provided trial information and obtained written consent. Participants were then randomly allocated to receive either: a) Diagnostic assessment using the point-of-care biochemical marker panel, or b) Conventional diagnostic assessment without the panel.

Target Population

People who presented to the emergency department with chest pain due to suspected but not proven AMI in whom a negative cardiac marker test measured by point-of-care marker testing could potentially rule out an AMI and allow discharge home. The following classes of patients were excluded.

1. Patients with diagnostic ECG changes for an AMI or high-risk acute coronary syndrome (>1 mm ST deviation or >3 mm inverted T waves). These patients have a presumptive diagnosis of myocardial infarction (both ST elevation myocardial infarction and non ST elevation myocardial infarction) and are at high risk of adverse outcome and require inpatient care even if marker tests are negative.
2. Patients with known coronary heart disease presenting with prolonged (>1 hour) or recurrent episodes of typical cardiac-type pain. These patients have unstable angina and require inpatient care for symptom control even if marker tests are negative.
3. Patients with proven or suspected serious non-coronary pathology (e.g. pulmonary embolus) that required inpatient care even if an AMI is ruled out.
4. Patients with co-morbidity or social problems that require hospital admission even if an AMI can be ruled out.

5. Patients with an obvious non-cardiac cause (e.g. pneumothorax or muscular pain), in whom an AMI could be excluded as a possible cause without resorting to further diagnostic testing.
6. Patients presenting more than 12 hours after their most significant episode of pain, for whom a single troponin measurement have been more appropriate than point-of-care panel testing.
7. Previous participation in the RATPAC trial.
8. Patients who were unable to understand the trial information due to cognitive impairment.
9. Non-English speaking patients for whom translation facilities were not available.

Participants were randomised to receive either: diagnostic assessment using the point-of-care biochemical marker panel, or conventional diagnostic assessment without the panel. The only difference between the two arms of the trial was that patients in the intervention arm received testing with the point-of-care panel. The use of all other tests and treatments, and decision-making in the emergency department, was at the discretion of the attending clinician.

The point-of-care cardiac marker panel utilised was CK-MB(mass), myoglobin and troponin I, measured at presentation and 90 minutes later, using the Stratus-CS point-of-care analyser. Of the systems currently available the latest version of the Siemens Stratus CS has the most data as an instrument suitable both for the emergency laboratory and for use as a POCT instrument. The troponin method available on this instrument also meets the criteria for diagnosis of an AMI according to the most recent criteria proposed by the European Society of Cardiology.

Patients randomised to the point of care arm had a blood sample taken at study enrolment and 90 minutes later for analysis by point of care testing. At the same time that blood was taken for point of care testing, they consented to allow (without the need for additional venopuncture) the clinical staff to take an extra tube of blood. The additional blood sample was transported to the hospital laboratory where it was allowed to clot, centrifuged, the serum separated into two aliquots and frozen to –20 °C in a timely manner. Other than obtaining consent, collecting data, and random allocation to use of the point-of-care test, the only change to routine practice was taking the additional blood sample for subsequent biomarker assessment.

Batches of samples were then transported frozen on dry ice to St Georges Hospital and are stored at –70 °C prior to analysis. Previous extensive stability studies have shown that cardiac biomarkers which are clinically useful and usable are fully stable with this storage regimen.

Follow-up

All participants were followed up until 90 days after initial attendance. A postal questionnaire consisting of the EQ-5D health utility questionnaire and a resource use questionnaire was sent to all participants at 30 and 90 days with one remailing to non-responders. Hospital records were reviewed at 90 days to identify all adverse events, hospital attendances and admissions.

Health Technologies Being Assessed

The archived blood samples from the RATPAC study represents an ideal opportunity to extend the findings of the RATPAC trial in a cost effective way. The existing patients enrolled are fully characterized and have been followed up for major adverse cardiac events. The population is also unique as it represents one found within the emergency department which has been selected on the basis of low cardiac risk rather than enrolled in a clinical trial with a high prior probability of cardiovascular disease. This is a major limitation of many existing biomarker studies and has been highlighted in recent editorials and the consensus statement on biomarker series of the working group of the European Society of Cardiology.

The samples will be analysed using state of the art high sensitivity troponin assays, two sensitive cardiac troponin I and one sensitive cardiac troponin T assays. These assays have been previously independently

analytically validated and the findings published in peer reviewed journals[15-17]. In addition, samples will be analysed for heart fatty acid binding protein, myoglobin, copeptin, interleukin-6, sensitive C-reactive protein and B-type natriuretic peptide (measured as the N terminal pro-hormone, NT pro-BNP). All of these assays are either commercially available or due to be launched on analytical platforms in wide spread clinical use in laboratories world wide. Finally, prior to project start the literature will be surveyed to see if there are any additional markers which need to be considered.

Measurement of myoglobin will allow independent confirmation of the results obtained by point of care testing and allow a definitive statement to be made as to the additional value, or not, of myoglobin measurement for the very early diagnosis of myocardial injury when compared with a sensitive troponin assay[18]. Heart fatty acid binding protein[19–21] and copeptin[22] have been proposed as alternative early markers to detect or exclude myocardial injury. Interleukin-6, sensitive C reactive protein and NT pro-BNP[23;24] have all been proposed and published in peer-reviewed literature as additional tests for risk stratification in patients presenting with chest pain. To date, no studies have been done in the general chest pain population to confirm or refute these claims.

Measurement of cost and outcomes

Diagnostic outcome

The study will examine the diagnostic performance based on the final consensus diagnosis from the RATPAC study. The diagnostic criteria used for acute myocardial infarction will be those recognised by the European Society of Cardiology in the new universal definition of myocardial infarction based on the troponin values obtained from the Stratus CS. This assay meets the performance characteristics recommended in the new universal definition of myocardial infarction. According to this definition, a troponin level above the 99th percentile of the values for a reference control group is considered positive, and in the context of a patient with ischaemic symptoms (i.e. chest pain) would satisfy the diagnosis for an AMI. This definition identifies patients who are most likely to benefit from treatments that usually require hospital admission. The individual diagnostic performance of each biomarker alone and in combination will be assessed by construction of receiver operator characteristic curves (ROC curves) and compared by calculation of the C statistic, the area under the curve. In addition, multivariate regression analysis will be performed to determine which marker or combination of markers will independently add significant diagnostic efficiency and predictive ability to obtain the final diagnosis.

Prognostic outcome

An independent assessment the ability to predict outcome in a multivariate risk model will be examined. This will include comparison with other risk predictive models (scoring systems derived from registry studies such as TIMI and GRACE risk scores). We will analyse the association between marker levels and adverse events within 30 days. The individual prognostic ability of each biomarker alone and in combination will be assessed by construction of ROC curves and compared by calculation of the C statistic. In addition, multivariate regression analysis will be performed to determine which marker or combination of markers is able to optimally predict outcome. The objective will be to determine whether the additional biomarker information helps diagnose patients or predict outcome by itself and whether they add to scoring systems (such as the TIMI & GRACE scores) and other clinical variables.

Economic analysis

The economic analysis will be based initially on cost minimisation analysis. The base case will be full laboratory cost to achieve diagnosis and comparison of costs for individual marker and marker panel strategies. Laboratory costs will be calculated using the ABC laboratory cost package and include cost per reportable result (including quality assurance and calibration based on routine laboratory performance) and total tests cost (NHS price) including staff and overhead costs. The laboratory at St George's hospital has already performed this work for it existing cardiac biomarker tests, so will be able to utilize the same methodology to allow direct comparison of the biomarker is included in the study. In addition, cost

modelling utilising hospital episode costs will be performed to estimate cost benefit of increased test costs compared with reduction in length of stay.

Sample Size

1132 patients were enrolled into the intervention arm of the study of whom 1076 had blood samples taken for measurement of biomarkers on at least one occasion. The incidence of acute myocardial infarction was 130/1076 (12.1%). This means that at conventional statistical significance, the study will be powered to detect the inability of the candidate tests to improve diagnostic sensitivity if they fail to detect more than five cases of myocardial infarction when compared to the predicate test. In total 2263 patients were recruited with follow up obtained (to date) in 1930 (85.3%) with 14 (0.7%) with non fatal MI and a death rate of 2 (0.1%) including an AMI.

Economic cost of chest pain

A typical District General Hospital will see around 6500 patients presenting with chest pain of suspected cardiac origin each year. In those admitted, 70% will have myocardial infarction excluded. Length of stay is typically 1 to 2 days. Only a minority of cases have active coronary artery disease requiring intervention. One study estimated that 50 to 75% of admissions did not require hospital stay. There is therefore a considerable economic cost in terms of bed occupancy and inappropriate investigation. A strategy which allows very rapid discharge of patients at low risk would result in significant improvement in the use of scarce NHS resources. A number of different strategies to this have been proposed including the use of multiple cardiac marker panels and novel cardiac markers.

Biomarker costs

A typical hospital laboratory within the UK will perform 20,000 troponin assays annually. The cost of troponin measurement has fallen substantially from a typical cost of £20 per test to £2–£3, so annual spend is £60,000, corresponding to a national cost of approximately £15 million. The use of a rapid troponin-based protocol which shortens hospital stay for chest pain to 2 to 3 hours from 12 to 24 hours would have significant economic benefit. Based on the average bed cost of £100 per day a typical hospital with 5000 chest pain attendances per annum could potentially exclude 2500 patients with a reduction in bed occupancy from 1250–2500 bed days to 312 bed days, a saving of £2.2 million. If it can be shown that a rapid biomarker based strategy utilising modern assay technology or new markers can be used safely to substantially reduce hospital stay nationwide considerable savings to the health-care budget could be made.

The use of a multiple marker panel or a new range of cardiac by markers would result in a substantial increase in laboratory costs. If this were truly offset by significant reduction in hospital stay, utilisation of novel biomarkers would be cost effective. If the use of more sensitive troponin assays makes measurement of novel biomarker or biomarker panels unnecessary, a significant waste of resources would occur. Assuming a typical market entry price for a novel biomarker of £20 or for a panel of tests, £20 per biomarker panel, and assuming the same pattern of utilisation as that used for troponin requesting, annual cost would be £400,000 for a typical hospital. On a UK wide basis it can be estimated that moving to a novel biomarker or a biomarker panel which is more expensive and not significantly diagnostically superior to optimal use of the existing testing, or utilization of the next generation of troponin assays, could cost an additional £20–£100 million per annum without conferring health-care benefits.

Market impact

The UK market for diagnostics has been estimated at between £100 and £250 million per annum. An evidence-based strategy for biomarker measurement would offer a significant competitive advantage for any UK based company.

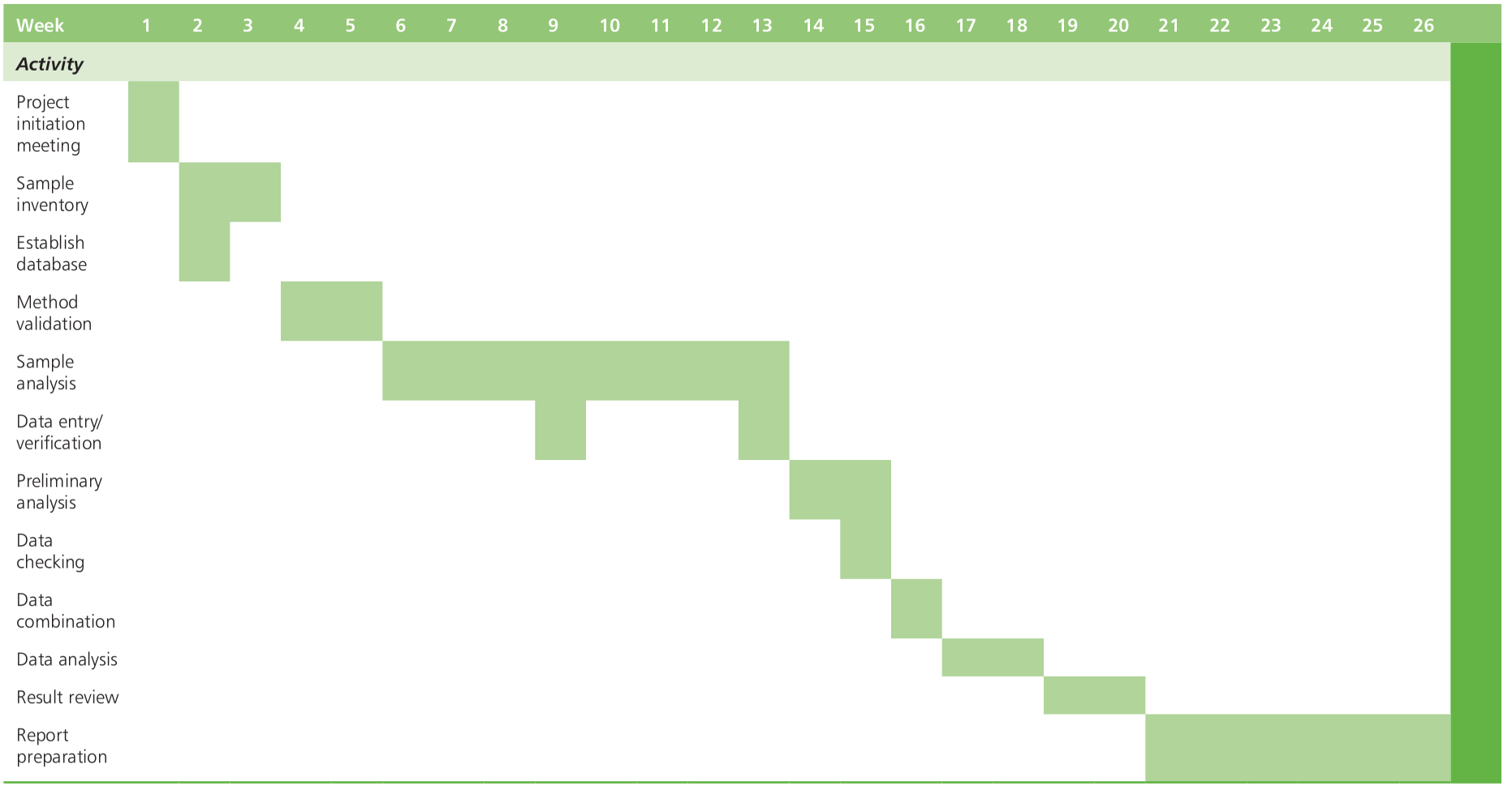
Relationship with evidence based practice

Finally, the UK is developing a national catalogue of laboratory tests. This will ultimately include assessment of cost effectiveness and test efficiency. This study will serve to inform this national initiative.

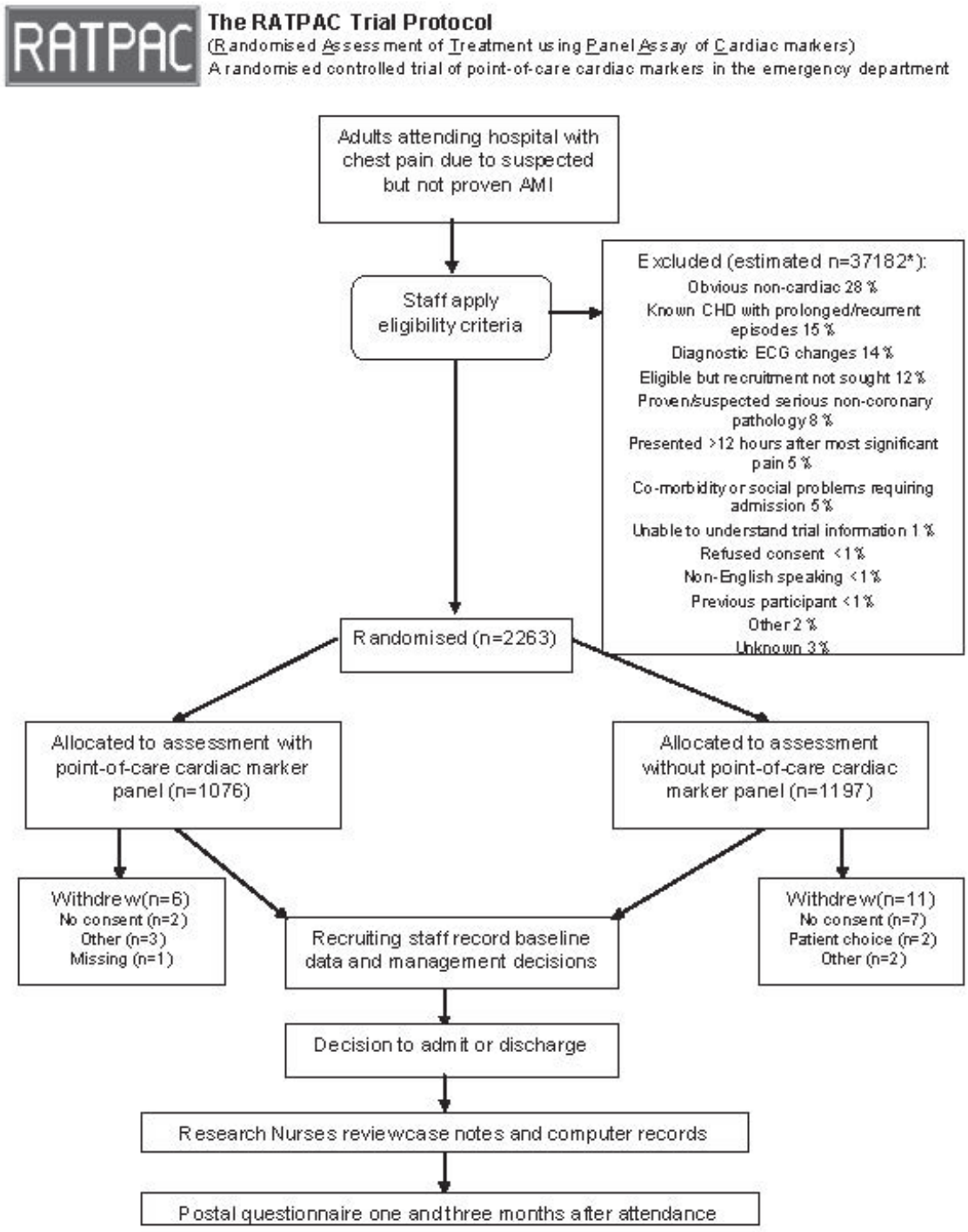
Outcomes

The objective of the study is to provide a benchmark for the new sensitive troponin assays. In addition, it will establish using a very well validated clinically relevant cohort the true role, or otherwise of the new proposed markers such as heart fatty acid binding protein. It will establish, for the first time, if inflammatory markers and markers of heart failure have a role to play in the general chest pain population. The routine and research laboratories at St. George's Hospital, contains a range of state of the art equipment representative of that seen in a typical hospital laboratory. The samples will therefore be analysed under typical laboratory conditions so that findings can be used throughout the UK and abroad.

Project Timetable



RATPAC recruitment chart



* Patients were sampled on pre-determined screening days to assess the number of patients not recruited.
Estimated number of patients not recruited = number not recruited on screening days × $\frac{\text{total days recruiting}}{\text{total days screening}}$

Percentages are out of the total number of non-recruited patient notes screened (n=9109)

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