



The RATPAC Trial Protocol

1. Project Title: The RATPAC Trial (HTA 06/302/19) (Randomised Assessment of Treatment using Panel Assay of Cardiac markers)

A randomised controlled trial of point-of-care cardiac markers in the emergency department

2. Planned investigation

2.1 Research objectives

We will evaluate the clinical effectiveness and cost-effectiveness of the 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)*, we will measure 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

We also plan to use trial data and blood samples to:

1. Evaluate clinical prediction rules, such as the TIMI and GRACE scores
2. Evaluate potential new or alternative markers, such as ischaemia modified albumin, ultrasensitive cardiac troponin, B-type natriuretic peptide, myeloperoxidase and fatty acid binding protein.

*Throughout this proposal, we define AMI according to European Society of Cardiology / American College of Cardiology (ESC/ACC) criteria for acute, evolving or recent AMI¹. 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 AMI. This definition identifies patients who are most likely to benefit from treatments that usually require hospital admission. Hence it provides a pragmatic definition of a patient group whose suspected condition requires hospital admission. Setting a higher threshold for positivity would risk excluding from the definition patients who might benefit from hospital admission, whereas broadening the definition to include cases of troponin negative acute coronary syndrome (ACS) would involve relying upon subjective (clinician determined) definitions of ACS and would define many patients who would not benefit from admission to hospital as having ACS.

2.2 Existing research

Chest pain due to suspected but not proven AMI is responsible for a substantial number of emergency department attendances and emergency hospital admissions in the NHS². Current recommendations suggest that these patients should receive diagnostic testing with a troponin sample taken 12 hours after their symptom onset^{3,4}, the delay being necessary because troponin sensitivity does not reach optimal levels until this time. This approach is inconvenient and potentially costly because it requires many patients to be unnecessarily admitted to hospital until the time delay has elapsed. Most patients with suspected AMI do

not actually have AMI, so their admission will ultimately prove avoidable. Cost-effectiveness analysis suggests that admitting patients for cardiac marker testing is not a cost-effective use of health service resources⁵.

Evidence also suggests that these guidelines are often not followed in a busy emergency setting where acute beds are limited. Collinson et al⁶ 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 al⁷ 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. Our recent national survey of emergency departments⁸ asked the lead consultant what proportion of patients with undifferentiated chest pain would be admitted to hospital. Estimates varied from less than 20% to over 80%. Hence it appears that the theoretical ideal of a 12-hour troponin is not realised in practice and, as a result, patients are inadvertently discharged home with AMI.

Rapid point-of-care testing using a panel of markers offers an alternative approach that may be more effective and cost-effective than current practice⁹. A combination of markers is measured on arrival and a short time later (usually 90 minutes). The gradient of these markers (the difference between the presentation and 90 minute levels) has been shown to provide improved early sensitivity (95%) without unacceptably compromising specificity^{10,11}. A typical panel will use a combination of early markers, such as myoglobin or CK-MB(mass), and a more definitive marker, such as troponin I or T. Because the point-of-care tests can be used quickly in the emergency department, they can potentially rule-out AMI during emergency department assessment, thus avoiding hospital admission and the pressure to select only high-risk patients for further diagnostic assessment.

Meta-analyses have estimated the diagnostic accuracy of individual cardiac markers^{12,13}, but there have been no systematic reviews of point-of-care cardiac panels¹⁴. Our literature review found that studies of the diagnostic accuracy of point-of-care markers have focussed upon a panel using CK-MB(mass), myoglobin and troponin I measured at presentation and 90 minutes later. These studies have shown that the panel has high sensitivity (over 95%) and can accurately rule out AMI by 90 minutes after presentation¹⁵⁻¹⁹. This results in earlier identification of AMI than laboratory testing¹⁷ and expedited decision-making with turnaround times reduced by 55%¹⁸. Meanwhile, comparison of patient management with the panel to previous practice showed a 40% reduction in coronary care unit admissions¹⁹.

These studies show that the point-of-care combination of CK-MB(mass), myoglobin and troponin I measured at presentation and 90 minutes has appropriate diagnostic accuracy, but they do not reliably tell us whether the panel will alter patient care, improve outcomes or reduce health service costs. Early diagnostic accuracy and reduced turnaround times will only lead to changes in practice if clinicians act upon the additional diagnostic information. Although interesting, the before and after study by Ng¹⁹ may be confounded by changes in coronary care referrals over time and, originating from the United States where coronary care usage is much higher than the United Kingdom, may not be applicable to the NHS. Audit data from the United Kingdom suggest that point-of-care cardiac testing can reduce hospital admissions, but this finding is based on before and after audit that has yet to be published in a peer reviewed journal²⁰.

Randomised trials of point-of-care testing are few in number and report conflicting results. The only randomised trial specifically of cardiac tests, by Collinson et al²¹, showed that point-of-care measurement of troponin T in patients admitted to a coronary care unit reduced overall length of hospital stay. By comparison, Kendall et al²² showed that use of a variety of point-of-care tests for a heterogeneous group of patients in the emergency department produced shorter decision times, but did not reduce overall length of stay in the department. There are no published randomised trials evaluating the clinical impact of point-of-care cardiac markers in diagnostic assessment of acute chest pain.

We have searched the National Research Register and ClinicalTrials.gov for research in progress into point of care cardiac markers and have identified one relevant study²³. This is a randomised trial being undertaken in the United States to compare point of care troponin I testing to laboratory testing in acute coronary syndrome to determine whether bedside use leads to shorter decision times in emergency care. It will therefore provide useful data for North American decision-makers to determine whether replacing laboratory with point of care troponin testing leads to more efficient patient processing. However, it will not determine whether a rapid rule-out point of care strategy is more effective or cost-effective than routine care, particularly in the UK.

2.3 Research methods

We will undertake a pragmatic randomised controlled trial and economic evaluation of a point-of-care cardiac marker panel in the management of patients with suspected, but not proven, AMI in six emergency departments in the United Kingdom.

Emergency department staff will identify eligible patients, provide trial information and obtain written consent. Participants will then be randomly allocated to receive either: a) Diagnostic assessment using the point-of-care biochemical marker panel, or b) Conventional diagnostic assessment without the panel.

The Sheffield Clinical Trials Research Unit (CTRU) will generate a simple randomisation sequence, stratified by centre, which will not be revealed to any person involved in patient recruitment. Emergency department staff will telephone the CTRU randomisation service when they recruit a participant and will provide full participant details to the CTRU. The CTRU will reveal the participant's allocated treatment group to the emergency department only after the participant's details have been recorded, written consent has been confirmed and the participant irrevocably entered into the trial.

Details of patient selection are outlined in section 3.5, the interventions are outlined in section 3.4 and follow-up and outcomes are outlined in section 3.6.

This is a pragmatic trial that is intended to determine whether point-of-care testing should be standard practice for patients presenting to the emergency department with suspected AMI. It is designed to compare two pragmatic alternatives (management with and without point-of-care testing) under routine conditions to determine whether use of the test changes costs or outcomes. This pragmatic design has the following implications:

1. After randomisation we will not attempt to blind clinical staff, patients or carers to the allocated treatment group.
2. Although the point-of-care test will be provided with a recommended protocol for use, management decisions will ultimately be at the discretion of the clinical staff.
3. All other diagnostic tests and the use of laboratory blood tests in the control group will be at the discretion of the clinical staff.
4. Blood samples will only be taken for the purposes of clinical management. We will not take additional blood samples to evaluate theoretical management strategies or to evaluate the accuracy of diagnostic assessments. We will not take additional samples to evaluate new markers (as set out in the secondary objectives) but will use residual blood from point-of-care tests.

Justification for choice of research methods

During the development of this proposal, we considered two other alternative methods of evaluation:

1. Systematic review and modelling
2. Cluster randomised trial

We propose a pragmatic trial, as opposed to systematic review and modelling, because key pieces of information that are central to the estimation of cost-effectiveness are not yet available. Firstly, as outlined in section 3.2, whilst there are abundant data available to

estimate the diagnostic accuracy of the constituent point-of-care panel tests, only limited data are available to estimate the diagnostic performance of the overall panel, with no studies based in the UK. This is potentially important as differences in patient characteristics and presentation patterns are likely to have an impact on sensitivity and specificity.

Secondly, even if these data were used, the behavioural consequences of the test results are unknown; which patients will and will not be admitted, how long will they be admitted for? Likewise, as identified by our previous work in this area^{5,7}, it is very difficult to determine how patients receiving point-of-care testing would have been managed if the point-of-care test were not available. Assuming that all patients would have been admitted to hospital for laboratory troponin testing at 12 hours after symptom onset is inappropriate and would overestimate the comparative cost-effectiveness of point-of-care testing.

Finally, if we were to model admission rates as a function of sensitivity/specificity using our previous work, and then interpolate the sensitivity/specificity estimates for point-of-care panels, we would have to make cavalier assumptions about the form that the relationship takes due to the paucity of data points.

Taken together, we firmly believe that there would currently be excessive uncertainty around key parameters in any cost-effectiveness model. However, based on the results of this study and others that may be published in the meantime, we feel that sufficient evidence will be available for different panels to be evaluated using the model developed as part of this proposal. The need for any further research will also be evaluated using a value of information analysis based around this model²⁴.

We propose to randomise individual patients, rather than using cluster randomised methods, because the advantages of cluster randomised methods, of reducing the risk of contamination or non-compliance in the control group, are outweighed by the disadvantages of selection bias due to loss of allocation concealment and loss of statistical power.

Cluster methods based upon randomising periods of time, such as days of the week, would not significantly reduce the risks of contamination, so we would have to randomise large clusters, such as members of staff or whole hospitals. This would involve substantial loss of statistical power. More importantly, there would be a substantial risk of selection bias because recruiting staff would be aware of whether patients would be allocated to point-of-care testing or not and might apply exclusion criteria in differential manner, depending upon whether they wanted to use point-of-care testing or not. This could result in patients being recruited to the point-of-care arm of the trial if they were considered appropriate for point-of-care testing, and recruited to the control arm if they were considered appropriate for routine care. This would represent a substantial flaw.

Individual patient randomisation allows us to achieve allocation concealment and avoid the risk of selection bias. Although it carries the risk of contamination and non compliance in the control group we can explore for evidence of contamination by examining changes in control group practice and admission rates over time. We will minimise the risk of non compliance in the control group by limiting the availability of point-of-care testing to consecutively numbered test “strips” that are only used in recruited intervention group patients and are recorded and accounted for at the end of the trial.

2.4 Planned interventions

Participants will be randomised to receive either:

1. Diagnostic assessment using the point-of-care biochemical marker panel, or
2. Conventional diagnostic assessment without the panel.

The only difference between the two arms of the trial will be that patients in the intervention arm will receive testing with the point-of-care panel. The use of all other tests and treatments,

and decision-making in the emergency department, will be at the discretion of the attending clinician.

The point-of-care cardiac marker panel will comprise CK-MB(mass), myoglobin and troponin I, measured at presentation and 90 minutes later, using the Stratus-CS point-of-care analyser. As outlined in section 2.2, this combination has been widely evaluated in practice¹⁵⁻¹⁹. Of the systems currently available or soon to be available the latest version of the Dade Behring Stratus CS has the most data as an instrument suitable both for the emergency laboratory and for use as a POCT instrument²⁵.

Clinical staff will be trained to use the test and given guidance in interpretation of the results. We will provide a recommended protocol that will advise a first panel test immediately after initial emergency department assessment and a second panel test 90 minutes later. Other than obtaining consent, collecting data, and random allocation to use of the point-of-care test, the only change to routine practice will be that we will ask clinical staff to take an additional quantity of blood for storage (without repeating venepuncture) each time a blood sample is required.

The additional blood remaining after point-of-care testing has been performed will be transported to the hospital laboratory where it will be centrifuged and refrigerated. Batches of samples will be transported quarterly to St Georges Hospital for analysis to address the secondary objectives of the study.

2.5 Planned inclusion/exclusion criteria

We will recruit people presenting to the emergency department with chest pain due to suspected but not proven AMI in whom a negative point-of-care marker test could potentially rule out AMI and allow discharge home.

We will exclude the following:

1. Patients with diagnostic ECG changes for AMI or high-risk acute coronary syndrome (>1mm ST deviation or >3mm inverted T waves). These patients 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 requires inpatient care even if AMI is ruled out.
4. Patients with co-morbidity or social problems that require hospital admission even if AMI can be ruled out.
5. Patients with an obvious non-cardiac cause (e.g. pneumothorax or muscular pain), in whom AMI can 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 would clearly be more appropriate than point-of-care panel testing.
7. Previous participants in the RATPAC trial.
8. Patients who are unable to understand the trial information due to cognitive impairment.
9. Non-English speaking patients for whom translation facilities are not available.

The research nurse at each hospital will regularly check emergency department attendance lists to identify patients attending with chest pain and record basic demographic details and reason for exclusion, thus allowing completion of a CONSORT flow chart.

2.6 Proposed outcome measures

The primary outcome will be the proportion of patients successfully discharged home after emergency department assessment, defined as discharge with no adverse event (as defined below) during the following three months.

Secondary outcomes will include:

1. Health utility measured using the EQ-5D self-complete questionnaire at one and three months after attendance.
2. Satisfaction with care measured at one month after attendance using a modified Group Health Association of America questionnaire that has been used successfully in previous studies of diagnostic strategies for acute chest pain.
3. The proportion of patients managed on the coronary care unit, receiving cardiac medications (such as heparin, clopidogrel or glycoprotein IIb/IIIa inhibitors) or receiving cardiac interventions (such angiography, percutaneous intervention or bypass grafting).
4. Re-attendance at and/or re-admission to hospital over the following three months.
5. Adverse events (death, non-fatal AMI, **life-threatening arrhythmia**, emergency revascularisation or hospitalisation for myocardial ischaemia).
6. The proportion of admitted patients ultimately diagnosed as having AMI by ESC/ACC criteria¹.

We have selected successful discharge home as the primary outcome because the main purpose of point-of-care cardiac marker testing in this patient group is to facilitate discharge home. This outcome is beneficial for patients, who avoid the inconvenience and risks of hospital admission, and is beneficial for the health service, which avoids unnecessary admissions and pressure upon acute and emergency services. Patients who suffer an adverse event after discharge will not be classified as a successful discharge home because it is possible that they would have benefited from hospital admission. We will also record the proportion of admitted patients who are ultimately diagnosed as having AMI to provide a measure of the appropriateness of admissions.

Assessment of outcomes

Recruiting staff will record baseline data, the results of initial assessment (including any biochemical cardiac tests), data required for TIMI²⁶ and GRACE²⁷ scoring and admission/discharge decision from the emergency department. Research nurses will use emergency department and hospital inpatient notes to record management decisions at initial attendance and admission, extract resource use data and identify subsequent attendances / admissions and adverse events up to three months.

Research nurses will check patient status (dead or alive) at one and three months, using hospital information systems. Deceased patients will be assumed to have a score of zero on EQ-5D and will be excluded from other patient-based assessments. Participants who are not recorded as dead will be mailed a questionnaire at one and three months from the University of Sheffield to identify adverse events and hospital attendances, health and social care resource use, and to measure EQ-5D and satisfaction with care (satisfaction at one month only). Our previous study suggests a 70-80% response rate to this questionnaire⁷. We will therefore contact the General Practitioner of all participants who do not respond at three months after attendance to identify any serious adverse events or deaths that have not been recorded by hospital information systems or case notes. Classification of cases of AMI and adverse events will be done by blind independent review of the relevant data.

2.7 Proposed sample size (N=3130)

We anticipate that 50% of subjects will be successfully discharged in the group managed without the marker panel⁷. With 1565 evaluable subjects in each arm of the trial we will have 80% power to detect a 5% improvement (to 55% of patients successfully discharged) at the two-sided significance level of 5%. The same sample size will provide 80% power to detect a reduction from 4% to 2% in major cardiac events (death, non-fatal AMI, emergency

revascularisation or hospitalisation for myocardial ischaemia), again at the 2-sided 5% level of significance.

Based on previous studies by members of our research team, we estimate that we will require six hospitals to recruit for 12 months each to achieve the sample size of 3130, assuming that we recruit 70% of those eligible^{7,28-30}. We have undertaken a number of studies of this specific patient group and have shown that recruitment of 550 suitable patients per year is attainable at a typical hospital.

Previous studies have also shown that we can anticipate a response rate of 70-80% for postal questionnaires^{7,28}, thus providing an effective sample size of at least 1000 in each of the two groups to evaluate health utility, satisfaction with care and health service resource use.

2.8 Statistical analysis

The primary outcome will be analysed through logistic regression, fitting concurrently with intervention group the effect of centre and appropriate baseline measures (including age, gender and past history of coronary heart disease). The results will be presented as adjusted odds-ratios along with their corresponding 95% confidence intervals. A similar analysis will be undertaken on major cardiac events. The primary analysis will be undertaken on an intention to treat basis. A secondary analysis will exclude those who were not managed according to their allocated strategy.

We will undertake a descriptive assessment to explore whether use of biochemical cardiac markers or admission rates change over time in either the intervention or control group, either as a result of staff "learning curves" in the intervention group or as a result of contamination of the control group.

Analysis of secondary objectives

The secondary objectives of evaluating clinical prediction rules, such as the GRACE and TIMI scores, will be addressed by analysing the proportion of participants in each risk stratum of the score who suffer an adverse event over 30 day follow-up. Receiver-operator characteristic (ROC) curves will be constructed to estimate the discriminant power of the scores for adverse events.

Blood stored at St George's Hospital will be used to analyse potential alternative cardiac markers and any new cardiac markers that are developed. We will analyse the association between marker levels and adverse events within 30 days. The data will then be split into derivation and validation datasets. ROC curves will be constructed using the derivation dataset to estimate the discriminant power of the markers and to identify, alongside economic modelling, optimal thresholds for decision-making. The validation set will then be used to estimate sensitivity and specificity at the optimal threshold.

2.9 Economic evaluation

An economic evaluation will be undertaken alongside the trial using recommended practice³¹. To supplement this analysis, a cost-effectiveness model will be developed to duplicate the trial results (as a way of validation), extrapolate the results to longer follow-up periods, and incorporate a value of information analysis. The NHS perspective undertaken and other methods will be in line with NICE Technology Appraisal Guidelines³², although data on production losses will be collected for a supplementary analysis.

Resource use data will be collected for all patients covering the length of time in the emergency department, the use of diagnostic tests, admissions, readmissions, outpatient reviews, cardiac procedures, and time off work. Cost and outcome data will be collected using patient notes and self-completed questionnaires as described previously. A small micro-costing study will also be carried out at each site for a fortnight (to include around 30 patients), gathering data on staff times relating to the care of patients. Emergency

department cost per minute will be based on a study previously undertaken by the investigators⁷, and amended using the micro-costing data from this study. Panel costs will be based on purchase price, and the remaining costs will be valued using national unit costs^{33,34}. Total NHS cost up to three months after initial attendance will then be calculated. Quality adjusted life years (QALYs) will be calculated by the trapezium rule using the EQ5D tariff values at all follow-up points.

Economic Analysis

Both cost and QALY analysis will compare bootstrap estimates of the mean cost per patient of the two groups. Cost-effectiveness analysis will estimate the incremental cost per quality-adjusted life year of using point-of-care cardiac marker testing compared to management without point-of-care testing. Results will be plotted on the cost-effectiveness plane and then transformed into cost-effectiveness acceptability curves with their associated frontier³⁵. A sensitivity analysis will be undertaken that will include production losses as reported by the patient.

We anticipate that some of the resource use and QALY data will be incomplete (missing). Thus, in order to maximise the information that is collected from the trial we will impute missing values using multiple imputation³⁶. The idea of multiple imputation draws from the fact that missing values from incomplete data are unknown, and the technique of multiple imputation imputes more than one likely value for the missing data, hence providing a representation of uncertainty³⁷. Thus an additional set of results will be produced including the imputed cost and QALY data.

Decision analytic model

We will also construct a decision analytic model to describe the care observed in the trial, and likely care pathways subsequent to it. This will allow us to systematically investigate the impact of subsequent costs, quality of life and survival. These values will initially be based on population norms, but replaced with literature review estimates where appropriate. The decision analytic model will be probabilistic, but with conventional sensitivity analysis used to assess the impact of structural uncertainties³⁸.

One important aspect of the model will be to investigate the relationship between sensitivity/specificity and admission rates. This will be modelled using all available studies of diagnostic testing in emergency departments. This part of the model is important as it will help us to estimate cost-effectiveness of different panels in the future.

The decision analytic model will be used to produce a value of information analysis. In particular, the analysis will generate partial expected value of perfect information estimates for each parameter in order to help prioritise future research.

2.10 Ethical arrangements

All participants will be asked to provide written, informed consent. This will include consent to allow research staff to examine their hospital records and contact their GP. Although participants will be recruited in an emergency setting and there will only be a limited amount of time available for considering trial information, the nature of the selected group (in particular the exclusion of people clearly requiring hospital treatment) ensures that eligible patients should not be incapacitated by their medical condition. We do not therefore plan to recruit incapacitated patients, and do not need to make provision for recruitment by personal or professional legal representatives.

Risks to participants are small, but include the following:

1. Inappropriate recruitment of high-risk patients or those with other serious non-cardiac pathology leading to risk of inappropriate discharge home. We will minimise this risk using regular review by the research nurses to identify inappropriately recruited participants. Inappropriate discharge of high-risk patients is, of course, a risk outside

the confines of this trial. Indeed, a potential benefit to participants is that inclusion in a carefully audited trial should reduce their risk of mismanagement.

2. Failure of point-of-care testing to identify AMI leading to inappropriate discharge home. We have minimised this risk by choosing a widely used point-of-care test that has been shown to have high sensitivity for AMI in previous studies¹⁵⁻¹⁹. Furthermore, our own previous studies^{6,7} show that routine care (i.e. without point-of-care testing) is associated with a significant risk of inappropriate discharge home that appears to be reduced when rapid diagnostic testing protocols are available.
3. Distress to participants or their relatives if the postal questionnaire is sent to someone who is seriously ill or recently deceased. We will minimise this risk by ensuring that the research nurses check patient status on hospital information systems at one and three months, before questionnaires are mailed.

Submission to a Multicentre Research Ethics Committee is currently underway. We will complete Local Research Ethics Committee reviews during the first six months of the timetable (see section 4).

2.11 Research governance

This trial will be conducted in accordance with MRC Guidelines for Good Clinical Practice in Clinical Trials. It does not involve a medicinal product and is not covered by the Medicine for Human Use (Clinical Trials) Regulations 2004. The University of Sheffield will act as the Sponsor for the trial.

Three committees will be established to govern the conduct of this study:

- Trial Steering Committee
- Independent Data Monitoring and Ethics Committee
- Trial Management Group

The Trial Steering Committee will consist of the Principal Investigator, one of the co-applicants, an independent chair, two independent members and a consumer representative (Enid Hirst). We will also invite a representative of the HTA board to join the committee. The Data Monitoring and Ethics Committee will consist of a minimum of an independent statistician, emergency physician and cardiologist, who will be asked to review trial data at regular intervals and implement stopping rules in accordance with MRC guidance. The Trial Management Group will consist of the Principal Investigator, Co-applicants, Project Manager, Statistician, Health Economists and Research Nurses.

Data management

Trial data will be entered into a validated database system built to a specification agreed between Sheffield CTRU and the Principal Investigator. The system will be accessible remotely via a web browser, with the data stored securely on a central server. Access will be controlled by the use of assigned logins and encrypted passwords. The system will have a full electronic audit trail and will be regularly backed up. Quality control procedures will be applied to validate the trial data. Error reports will be generated where data clarification is required. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Principal Investigator. All activities will be performed in accordance with Sheffield CTRU Standard Operating Procedures.

3. Project timetable and milestones

The project will start on 1st April 2007. Months 1 to 6 will involve staff recruitment, local ethics and research governance, months 7 to 18 will involve patient recruitment, and months 19 to 24 will involve completion of follow-up, data analysis, writing-up and dissemination. The project will be completed by 31st March 2009. The GANTT below outlines the key milestones and shows when project staff will be employed.

	Month of project							
	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24
Trial Manager	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Trial Researcher			XXX	XXX	XXX	XXX		
Clerical Assistant	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Research nurses x 6		XX	XXX	XXX	XXX	XXX	XXX	X
Staff recruiting, ethics, R&D	XXX	XXX						
Patient recruitment			XXX	XXX	XXX	XXX		
Follow-up			XX	XXX	XXX	XXX	XXX	
Analysis								XXX
Writing-up								XXX

We will submit six monthly progress reports corresponding with the following milestones:

1. Completion of ethics and governance procedures and commencement of recruitment in all six sites.
2. Mid-point of recruitment, with a target of 1200 participants recruited (allowing for initial lag phase in recruitment).
3. End of recruitment, with 3130 participants recruited.
4. Completion of analysis and final report.

4. Expertise

The trial will be co-ordinated by a Trial Manager in the Sheffield Clinical Trials Research Unit, working with full statistical, clinical trials and health economic support. The applicants are a multi-disciplinary team with expertise in health service research, emergency medicine, cardiology, chemical pathology, epidemiology, health economics and statistics. The researchers are leading experts in the management of acute chest pain and have undertaken previous landmark investigations in this field, including the ESCAPE trial of chest pain units^{7,39} (SG, SC, SD), randomised evaluation of point-of-care cardiac markers in coronary care²¹ (PC), evaluation of ischaemia modified albumin in emergency care^{30,40} (JB, PC, SG), and evaluation of cardiac biomarkers (PC). We have also collaborated to successfully undertake a previous HTA-funded multicentre trial in emergency care, the 3CPO trial⁴¹ (AG, SG, DN, JB). The co-applicants from Leeds (AH,JB,TH) have recently undertaken studies of biomarkers in patients with acute chest pain and studies in AMI^{42,43}.

5. Service users

Enid Hirst, a health service user representative, has provided valuable input into previous projects undertaken by our team. She has agreed to provide user involvement in the development of the proposal and user representative on the Trial Steering Group. She has also created a coronary heart disease user group consisting of five people with coronary heart disease and their main carer/relative. This group has provided guidance to previous projects, notably our evaluation of the National Infarct Angioplasty Pilots. We are using this group to develop our proposal: specifically to identify relevant outcome measures, and ensure appropriate procedures are used for consent and follow-up.

6. References

1. Myocardial infarction redefined—A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *Eur Heart J* 2000;21:1502-1513.
2. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, and Nicholl J. The health care burden of acute chest pain. *Heart* 2005; 91:229-230.
3. Task Force on the Management of Acute Coronary Syndromes of the European Society for Cardiology. Management of acute coronary syndromes in patients presenting without ST elevation. *Eur Heart J* 2002;23:1809-40.
4. The National Service Framework for Coronary Heart Disease. Department of Health, 2000.
5. Goodacre S & Calvert N. Cost effectiveness of diagnostic strategies for patients with acute, undifferentiated chest pain. *Emerg Med J* 2003;20:429-433.
6. Collinson PO, Premachandram S, Hashemi K. Prospective audit of incidence of prognostically important myocardial damage in patients discharged from the emergency department. *BMJ* 2000;320:1702-5.
7. Goodacre S, Nicholl J, Dixon S et al. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004;328:254-7.
8. Goodacre S, Nicholl J, Beahan J, Quinney D & Capewell S. National survey of emergency department management of patients with acute, undifferentiated chest pain. *B J Cardiol* 2003;10:50-4.
9. Price CP. Point of care testing. *BMJ*2001;322:1285-1288.
10. Fesmire FM, Percy RF, Bardoner JB, Wharton DR, Calhoun FB. Serial creatinine kinase (CK) MB testing during the emergency department evaluation of chest pain: utility of a 2-hour deltaCK-MB of +1.6ng/ml. *Am Heart J* 1998;136:237-44.
11. Fesmire FM, Christensen RH, Focj EP, Feintuch TA. Delta creatinine kinase MB outperforms myoglobin at two hours during the emergency department identification and exclusion of troponin positive non-ST elevation acute coronary syndromes. *Ann Emerg Med* 2004;44:12-19.
12. Ebell MH, Flewelling D, Flynn CA. A systematic review of troponin T and I for diagnosing acute myocardial infarction. *J Fam Pract* 2000;49:550:556.
13. Balk EM, Ioannidis JPA, Salem D, Chew PW, Lau J. Accuracy of cardiac biomarkers to diagnose acute cardiac ischaemia in the emergency department: A meta-analysis. *Ann Emerg Med* 2001;37:478-494.
14. Craig J, Bradbury I, Collinson P et al. Health Technology Assessment Report Number 4: The organisation of troponin testing services in acute coronary syndromes. NHS Quality Improvement Scotland 2003.
15. McCord J, Nowak RM, McCullough PA et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation* 2001;104:1483-8.
16. Apple FS, Christensen RH, Valdes R et al. Simultaneous rapid measurement of whole blood myoglobin, creatinine kinase MB and cardiac troponin I by the Triage cardiac panel for detection of myocardial infarction. *Clin Chem* 1999;45:199-205.
17. Newby LK, Storrow AB, Gibler WB et al. Bedside multimarker testing for risk stratification in chest pain units: The CHECKMATE Study. *Circulation* 2001;103:1832-7.
18. Caragher TE, Fernandez BB, Jacobs FL & Barr LA. Evaluation of quantitative cardiac biomarker point of care testing in the emergency department. *J Emerg Med* 2002;22:1-7.
19. Ng SM, Krishnaswamy P, Morissey R et al. Ninety-minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol* 2001;88:611-7.
20. Rocke LGR et al. Chest pain observation units - are they really necessary? <http://bmj.bmjournals.com/cgi/eletters/328/7434/254#49899>

21. Collinson PO, John C, Lynch S et al. A prospective randomised controlled trial of point-of-care testing on the coronary care unit. *Ann Clin Biochem* 2004;41:397-404.
22. Kendall J, Reeves B & Clancy M. Point of care testing: randomised controlled trial of clinical outcomes. *BMJ* 1998;316:1052-7.
23. Griffs JC. Diagnosis and Treatment of ACS in the ED: The Impact of Rapid Bedside cTnl Testing on Outcomes. <http://clinicaltrials.gov/ct/show/NCT00222352>
24. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). *Lancet* 2002;360:711-15.
25. **Panteghini M, Pagani F, Yeo KT, Apple FS, Christenson RH, Dati F et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem* 2004;50:327-32.**
26. Antman EM, Cohen M, Berninck PJ et al. The TIMI risk score for unstable angina / non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-842.
27. Eagle KA, Lim MJ, Babbous OH et al. A validated prediction model for all forms of acute coronary syndrome. *JAMA* 2004;291:2727-2733.
28. Goodacre S, Mason S, Arnold J & Angelini K. Psychological morbidity and health-related quality of life of patients assessed on a chest pain observation unit. *Ann Emerg Med* 2001;38:369-376.
29. Conway Morris A, Caesar D, Gray S and Gray A. The TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. *Heart* (2006);92:1333-1334
30. Keating L, Bengier J, Beetham R, Bateman S, Veysey S, Kendall J, Pullinger R. The PRIMA Study: Presentation IMA in the emergency department. *Emerg Med J* 2006 (In press).
31. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, Cook J, Glick H, Liljas B, Petitti D, Reed S. Good research practices for cost-effectiveness analysis alongside clinical trials: The ISPOR RCT-CEA Task Force Report. *Value in Health* 2005;8:521-533.
32. National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal. London: NICE, April 2004.
33. Netten, A. and Curtis, L. Unit Costs of Health and Social Care 2004. University of Kent, Personal Social Services Research Unit.
34. NHS Reference Costs 2005. <http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en>
35. Fenwick E, Claxton K, Sculpher M. Representing Uncertainty: The role of cost effectiveness acceptability curves. *Health Economics Letters* 2001;10:779-787.
36. Schafer J. Analysis of Incomplete Multivariate data. Chapman & Hall/CRC 2000
37. Rubin D. Multiple imputation for nonresponse in surveys. New York: J Wiley & Sons 1987.
38. Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. *Value in Health* 2005;8:1-2.
39. The ESCAPE multicentre trial of the role of chest pain units in the NHS (NHS Service Delivery and Organisation Programme), www.shef.ac.uk/~scharr/escape
40. Collinson PO, Gaze DC, Bainbridge K, Morris F, Morris B, Price A & Goodacre S. Utility of admission cardiac troponin and ischaemia modified albumin (IMA) measurements for rapid evaluation and rule out of suspected acute myocardial infarction in the emergency department. *Emerg Med J* 2006;23: 256-261.
41. The 3CPO Trial (NHS Health Technology Assessment Programme), www.shef.ac.uk/trial3cpo
42. Hall A, Barth J, Hassan T, Farrin A. H-FABP (Heart-type Fatty Acid Binding Protein) and other markers in early diagnosis and risk stratification in suspected acute coronary syndrome – the FAB study. 2006, unpublished.
43. Tsang DM, Owen AM, Collinson PO, Barth JH. Surveys on the use of cardiac markers in the United Kingdom. *Ann Clin Biochem* 2003;40:138-142.

7. CONSORT diagram

