Research Protocol

Full title:

Acute Coronary Syndrome rule-out strategies in the Emergency Department: An observational evaluation of current UK practice & clinical effectiveness

Short title:

ACS-ED

Chief Investigator:

Professor Edward Carlton

Sponsor:

North Bristol NHS Trust

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Contents

1. Key Contacts

Chief Investigator	Professor Edward Carlton
Co-Investigators	
Study Coordinator	Dr Fraser Birse and Alice Colombo
Sponsor	North Bristol NHS Trust This study will be internally reviewed and supported by the Royal College of Emergency Medicine Research Committee.
Funder(s)	Royal College of Emergency Medicine
Key Protocol Contributors	All co-investigators
Committees	Independent statistical review will be provided by Dr Camilla Sammut-Powell, a statistician at the University of Manchester.

2. Study Summary

Title	Acute Coronary Syndrome rule-out strategies in the Emergency Department: An observational evaluation of current UK practice & clinical effectiveness
Short Title	ACS-ED
Participants	Adults over the age of 18 presenting with chest pain who trigger testing to rule out a cardiac cause
Planned Study Period	March 13th – April 23rd 2023
Summary of research questions: In adults presenting with suspected cardiac chest pain, which ACS rule-out strategy leads to the shortest length of stay in the Emergency Department? In adults presenting with suspected cardiac chest pain, what is the index AMI rate and distribution of alternative diagnoses in the Emergency Department? In Emergency Departments across the UK, which ACS rule-out strategies are used?	

3. Plain English Summary

This study will examine Emergency Department (ED) rule-out strategies for patients presenting with suspected cardiac chest pain. We want to understand how the use of blood tests and strategies impact upon a patient's time in the ED. We will also collect data on the final diagnoses of patients presenting to the ED with suspected cardiac chest pain, whether that be cardiac or non-cardiac in origin.

4. List of Abbreviations

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
CRF	Case Report Forms
cTN	Cardiac Troponin
ECG	Electrocardiogram
ED	Emergency Department
HRA	Health Research Authority
MACE	Major Adverse Cardiovascular Events
NHS	National Health Service
NIHR	National Institute for Health Research
RCEM	Royal College of Emergency Medicine
STEMI	ST-Elevation Myocardial Infarction
TERN	Trainee Emergency Research Network

5. Background & Rationale

Non-traumatic chest pain, which includes those patients with suspected acute coronary syndrome (ACS), is one of the commonest presentations to the emergency department (ED) (1). ACS is only confirmed in around 15% of these patients (1) and can be a challenging diagnosis to confirm or exclude in the ED. Recent research has highlighted the limitations of clinical gestalt to either rule in or rule out the diagnosis (2,3). However, the ability of clinicians to differentiate chest pain patients with ACS and administer urgent treatment is vital. Consequently, a number of risk stratification strategies have been developed to facilitate objective and reproducible categorisation of a patient's likelihood of having ACS. These strategies vary in their components but generally incorporate patient symptoms, history and examination findings alongside biomarker levels and ECG findings. The aim of these risk stratification strategies is two-fold; to ‘rule-in’ those who may be undergoing ACS and to allow identification of low-risk patients who can be safely discharged home from the ED.

These scores and ‘rule-out’ strategies are in a continual state of development. With the accessibility of high sensitivity biomarker assays, many scores are recurrently updated or refined. In addition, the performance of these assays has prompted debate that risk scores add negligible information to clinical decision making and that we may be reaching a state where a single blood test might constitute an effective rule-out strategy (4,5). Both NICE (6) and the European Society of Cardiology (7) provide guidance on investigating ACS, but usage varies, with heterogenous practice

found across the United Kingdom (8). The usage of high-sensitivity troponin testing has been marked as a 2020/21 NHS CQUIN (9).

Discharging low risk patients has several downstream benefits, including reduction in patient burden (including medical investigations), reduced length of stay in the ED with subsequent mitigation of crowding, reduced frequency of hospital admission and reduced opportunity cost (10). Conversely, inadvertent discharge of patients with resulting ACS results in increased mortality and morbidity of patients. All risk-stratification tools are balanced in their desire to provide diagnostic accuracy alongside safe discharge.

Although there have been several studies comparing the clinical effectiveness of risk scores for ACS rule-out within the ED, the real-world variation in the use and adherence to rule-out pathways is poorly understood. In addition, there is limited data on the comparative clinical effectiveness of these pathways, or their diagnostic accuracy outside a research environment and the prevalence of alternative diagnoses in those presenting with suspected cardiac chest pain. To understand the size of the diagnostic dilemma of chest pain, we must try to establish the incidence of ACS and alternative diagnoses in those presenting to the ED with suspected cardiac chest pain.

In 2017, The James Lind/Emergency Medicine Research Priority Setting Partnership named research into the effects of implementing new techniques in assessing patients with chest pain in practice amongst the top 10 research questions of priority in EM, in addition to their use alongside shared decision making (11). This study aims to directly address this research priority. Finally, NHS England have chosen the adoption of high sensitivity troponins as a key technology that NHS Trusts will be incentivised to adopt via the “Innovation and Technology Payment” scheme (12).

6. Research questions and aims

The research questions this study will answer are:

1. In adults presenting with suspected cardiac chest pain, which ACS rule-out strategy leads to the shortest length of stay in the ED?

2. In adults presenting with suspected cardiac chest pain, what is the index AMI rate and distribution of alternative diagnoses in the ED?
3. In Emergency Departments across the UK, which ACS rule-out strategies are used?

Our overall aim is to establish the clinical effectiveness of different ACS investigation strategies across EDs in the UK, the epidemiology of ACS across the UK, and the different investigation strategies these EDs use.

7. Study Design

This study is a prospective multi-centre observational study that will be conducted over a ten-week period starting on the 13th of March 2023. Patients will be actively recruited for 7 days during a 6-week recruitment window with sites to determine their own 7-day recruitment period during this window. Consecutive patients presenting to EDs with suspected cardiac chest pain who trigger ACS rule-in or rule-out testing will be screened and invited to opt-out by trained clinicians or research nurses for inclusion. A cross-sectional survey will also be administered to all recruiting hospitals collecting data on their local ACS rule-out strategies.

Patients will be identified prospectively but, depending on resources, data may be collected retrospectively. Demographic data and pathway specific parameters will be collected at the point of clinical review on a paper or digitised Case Report Forms (CRF). Research nurse or clinician follow up using clinical notes or electronic health records will be conducted to document reference standard ED diagnosis and clinical outcome including AMI.

Patient data collected will focus on pathway performance, including patient demographics, length of stay in hospital, ED disposition and discharge diagnosis. Data will be collected separately from each site about their use of biochemical assays, reference ranges, use of ACS rule-out strategy and pathway for investigation of these patients.

7.1. Detailed plan of investigation

7.2. Recruitment

Research in an emergent setting is challenging due to high clinical workload and the high proportion of eligible patients presenting out of hours. Clinicians have additional levels of clinical demand during night shifts and research teams are often not available to support recruitment. The diurnal variation in patients presenting with ACS is well-recognised in the literature (13,14), so consecutive recruitment over a continuous 24-hour period is vital to ensure a representative, generalisable sample and avoid recruitment bias. Data collection will be performed by clinicians or research teams where these are present. In order to maximise the generalisability of the study but minimize the administrative burden, we will use an opt-out consent process to facilitate recruitment into the trial.

7.3. Consent

This study involves no change in clinical care and no study specific interventions for participants. It carries minimal clinical risk. We will be collecting routinely collected data and wish to maximise recruitment in order to produce a study with maximal generalisability, so will not approach individual participants for written consent. We will adopt a layered/tiered approach using an opt-out strategy, as supported by the Health Research Authority (HRA) (15).

We will offer the following two approaches to patients dependent on recruiting site preference:

Approach 1 – On-site opt-out

We will display relevant materials in the appropriate areas of every participating ED, describing the study and providing assurance that clinical care will not be affected in any way.

We will offer information leaflets with a description of the study and identified point of site contact for every patient enrolled to the study. Staff in the ED will be available on request, to speak to any participant or their next of kin. We will ensure anonymized record of all patients provided with opt out materials, such that we can cross check at multiple occasions (including follow up) that they have not recorded a wish to opt out.

Approach 2 – Mailed opt-out

Patients will be informed of their inclusion in the study via the delivery of a study pack containing information about the study and how to 'opt-out'. This will be mailed to the patient's home address one week after attendance. Patients identified as admitted to hospital at this point will be approached by the hospital study team.

These two strategies, targeted to the individual, are considered to constitute active recruitment as per paragraph 22 of the NIHR Clinical Research Network (CRN) Recruitment Policy Document (16). These methodologies for consent have been used internationally and within the UK, with "on-site opt-out" methodology being used for the PAT-POPS study (17) and "mailed opt-out" used by the AHEAD study group (18).

From previous experience in certain regions some research & development teams prefer prospective recruitment and consent. For these hospitals we offer an alternate approach more in keeping with traditional models of recruiting a patient to a research study, although expect that not many sites will adopt this model.

Approach 3 (Alternate Consent)

Alternatively, consent can be sought for inclusion in this study prior to discharge. Patient will be engaged while in the ED with signs and posters about the study. Patient meeting inclusion criteria will be given information leaflet about the study and opportunity to discuss about the study with a member of the study team if available or at a later time. Patient discharged from ED prior to consent will be contacted by telephone to get consent with option to give consent over the phone or through an emailed or posted opt out consent model as above. If no communication is received within a week to decline or withdraw consent, participants anonymised data will be uploaded to the secure encrypted database.

7.4. Withdrawal

Participants will be allowed to withdraw from the study at any point. We will not collect any further data from these participants; due to the opt-out methodology, any patient who expresses a wish to withdraw from the study will have any collected data deleted.

7.5. Inclusion & exclusion criteria

Inclusion:

- Age 18 years or older
- Presenting with chest pain who trigger testing to rule-in or rule-out a cardiac cause

Exclusion:

- Patients who lack capacity
- Patients with another medical condition requiring hospital admission
- Prisoner presenting to ED
- Non-English speaker where translation unable to be offered
- Clear non-ACS cause at presentation

7.6. Definitions

Acute coronary syndromes include unstable angina and acute myocardial infarction (AMI). AMI is defined as per the Fourth Universal Definition of Myocardial Infarction (19), namely:

- Acute myocardial injury with clinical evidence of acute myocardial ischaemia with detection of a rise and/or fall of cardiac troponin (cTn) values with at least one value above the 99th percentile upper reference limit and at least one of the following:
    - Symptoms of myocardial ischaemia
    - New ischaemic ECG changes
    - Development of pathological Q waves on ECG

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
- Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ECG changes before cTn values become available.

7.7. Outcomes

Primary outcomes

- Index AMI rate
- Length of stay in ED +/- observation ward
- ACS risk stratification strategy used, and patient risk category

Secondary outcomes

- Time to be seen by treating clinician
- ED disposition
- Discharge diagnosis

4. This will be one of: Diagnosis at the point of emergency department discharge for those not admitted to an inpatient area OR discharge diagnosis from an inpatient area for those admitted and then subsequently discharged within 28 days from presentation OR working diagnosis if still admitted at 28 days from presentation

7.8. Outcome Adjudication

Primary outcomes such as ‘index AMI rate’, ‘discharge diagnosis’, and ‘patient risk category’ using each site’s local risk stratification strategy will be determined through local analysis of case report files (incorporating ECG findings & biochemical results) and the Emergency Care Data Set (ECDS) data where necessary. ‘ACS risk stratification strategy’ at each site will be classified by the ACS ED steering group. The other outcomes are data points that will not require further adjudication.

8. Statistical Analysis Plan

We will use descriptive statistics with measures of variation to describe the epidemiology, current rule-out strategies and adherence to these strategies for patients presenting with chest pain to the ED. Funnel plots will be used to assess for site variation and inconsistency between different rule-out strategies. Our application includes funding for a statistician who will be employed to develop a more in-depth statistical analysis plan.

8.1. Sample size calculation

This is a pragmatic real-world evaluation, with an aim to recruit from approximately 100 centres over 7 days, in line with previous successful TERN studies. Chest pain is thought to represent 6% of attendances to EDs in the UK (1). To date, the rate of AMI is estimated between 10 to 19% in those presenting with chest pain to the ED. In a type 1 ED receiving 100,000 presentations per annum, this equates to approximately ten to twenty patients presenting with chest pain requiring ACS rule-out each day. Of the 192 type 1 EDs in the United Kingdom, a previous TERN study was able to recruit from approximately 100 centres. A similar study recruiting on a similar scale over a 7-day period would be expected to recruit 10,500 patients, of which over 1500 would receive an acute diagnosis of acute myocardial infarction.

9. Study Management & Administration

9.1. Timeline

The project will commence in March 2022 with application for ethical approval, NIHR portfolio adoption and necessary site approvals. It is anticipated recruitment will start in March 2023. The study will open for recruitment on 13th March 2023 at 00:00 and close for recruitment on 23rd of April 2023 at 23:59. During this 6-week window sites will choose a one week period during which to complete 7 days of consecutive recruitment. i. Data collection, clean-up and management will close at 23:59 on the 21st of May. The end of the study will be at 23:59 on the 21st of May.

9.2. Administration

The survey will be administered via the online platform REDCap (20,21). This electronic data capture platform is fully compliant with Good Clinical Practice, 21 CFR Part 11, GDPR, 20 ISO 27001 and ISO 9001.14. It has stringent data security procedures and uses private servers. Data will be held securely on secure online server hosted by the University of Bristol, UK.

9.3. Data management & record-keeping

Local data will be collected & stored according to local research ethics requirements. Anonymised individual case-report files (CRF) data will be uploaded as non-identifiable data to a recognised and GCP/GDPR approved online data storage platform for clinical research (REDCAP), by an appropriately Good Clinical Practice-trained medical practitioner or research nurse. Local centres will be involved with ensuring appropriate research governance, source data validation, oversight, and support. Patient identifiable data will be encrypted, and password protected, accessible only to certain members of the study team. Research data will only be downloaded for the purpose of statistical analysis, and will be downloaded onto a secure, firewall & password protected computer system. Patient identifiable data will never be downloaded or transferred along with research data.

9.4. Data storage

Data will be stored electronically for 5 years by the University of Bristol.

9.5. Regional & local collaborator involvement

Overall responsibility and oversight for the study will be provided by the study Chief InvestigatorEC. The co-investigators and study coordinator will assist with the day-to-day management of the study, data collection, data analysis and write-up. Questions from participants regarding the study will be directed to the study coordinator in the first instance.

10. Ethical & Regulatory Issues

10.1. Study conduct

The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and other applicable guidance.

The study will not commence until all regulatory approvals are in place, which will include HRA Approval, REC Approval and confirmation from local R&D that each Trust has capacity and capability to carry out the research.

10.2. Monitoring & audit

The study will be subject to the standard procedures for monitoring and auditing of studies by the sponsor. Any changes to the protocol will be agreed with the sponsor prior to submission to NHS Research Ethics Committee (REC) for review except for where urgent safety measures apply. All staff working in the study will have completed appropriate study training to undertake the duties delegated to them by the Principal Investigator. Evidence of up to date GCP training and a signature on the delegation log will be required from the Principal Investigator only. This is the approach previously approved for use in other TERN low risk observational studies where successful consecutive 24-hour recruitment has also relied on staff working a full shift pattern rota.

10.3. Protocol deviations

The study will be subject to the standard procedures for monitoring and auditing of studies by the sponsor. Any changes to the protocol will be agreed with the sponsor prior to submission to NHS Research Ethics Committee (REC) for review except for where urgent safety measures apply. All staff working in the study will have completed appropriate training to undertake the duties delegated to them by the Principal Investigator such an ICH-GCP.

10.4. Ethical Approval

Ethical approval will be sought from a local ethics committee and regulatory approval will be sought from the Health Regulation Authority (HRA) and Health and Care Research Wales (HCRW).

10.5. Confidentiality

Data will be stored on a secure server for clinical research as previously detailed. Local centres will be consulted to ensure appropriate research governance, source data validation, oversight, and support. Patient identifiable data will be encrypted and password protected, and accessible only to certain members of the study team at their own site. Research data will only be downloaded for the purpose of statistical analysis, and will be downloaded onto a secure, firewall & password protected computer system. Patient identifiable data will never be downloaded or transferred along with research data.

10.6. PPI & Stakeholder Engagement

Whilst there has not been direct patient & public involvement in the design of this study, the James Lind Alliance / Emergency Medicine Research Priority Setting Partnership named research into the effects of implementing new technique in assessing patients with chest pain amongst its top ten research priorities (11).

11. Dissemination of Results & Publication Policy

The results from this study will be submitted for publication in leading journals and to national conferences for presentation. TERN's work with RCEMLearning has generated a focal point for knowledge dissemination in the UK. Using social media, TERN's e-mail list, TERN will publish a multitude of blogs, infographics and podcasts to supplement our publication, which will be hosted on RCEMLearning.

11.1 Anticipated impact

There are a number of ACS-rule out pathways in clinical practice, with varying degrees of sensitivity & specificity (3), and practice is heterogenous across the United Kingdom (10). There is little research into which strategy is the most efficient

for an ED. This study could identify outliers and thus lead to a change in working practices. The James Lind Alliance Priority Setting Partnership classified the assessment of chest pain as a top ten priority, and research in this area has the capacity to implement widescale changes (11).

12. Funding & Competing Interests

12.1. Funding

Funding for the project has been obtained from the Royal College of Emergency Medicine for the following costs:

Funding	Year 1 £	Total £
Staff	2000	2000
Meeting Costs	1000	1000
Consumables	714	714
Sponsorship / Management Costs	700	700
Online data collection tool	750	750
Sub-total	5164	5164
Indirect costs (40% of staff costs)	0	0
Grand total	5164	5164

The Survey platform is provided courtesy of University of Bristol. The chief investigator is directly funded as a research fellow by the Royal College of Emergency Medicine.

12.2. Sponsor

North Bristol NHS Trust will be the sponsor.

12.3. Competing Interests

The study coordinator (FB) and chief investigator (EC) both receive funding from the Royal College of Emergency Medicine, whom the grant is provided by.

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