

The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department

S Goodacre, M Bradburn, P Fitzgerald,
E Cross, P Collinson, A Gray and AS Hall



May 2011
10.3310/hta15230

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk





How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

- fax (with **credit card details**)
- post (with **credit card details** or **cheque**)
- phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services'
(out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque

If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card

You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of HTA on DVD?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department

S Goodacre,^{1*} M Bradburn,¹ P Fitzgerald,¹
E Cross,¹ P Collinson,² A Gray³ and AS Hall⁴

¹School of Health and Related Research, University of Sheffield, Sheffield, UK

²St George's Hospital, London, UK

³Royal Infirmary of Edinburgh, Lothian Health Board, Edinburgh, UK

⁴Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, UK

*Corresponding author

Declared competing interests of authors: none

Published May 2011

DOI: 10.3310/hta15230

This report should be referenced as follows:

Goodacre S, Bradburn M, Fitzgerald P, Cross E, Collinson P, Gray A, *et al*. The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Health Technol Assess* 2011;**15**(23).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents*®/Clinical Medicine.

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 06/302/19. The contractual start date was in April 2007. The draft report began editorial review in January 2010 and was accepted for publication in October 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley CBE

Series Editors: Dr Martin Ashton-Key, Professor Aileen Clarke, Professor Chris Hyde, Dr Tom Marshall, Professor John Powell, Dr Rob Riemsma and Professor Ken Stein

Associate Editor: Dr Peter Davidson

Editorial Contact: edit@southampton.ac.uk

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

© Queen's Printer and Controller of HMSO 2011. This work was produced by Goodacre *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (<http://www.publicationethics.org/>).

This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department

S Goodacre,^{1*} M Bradburn,¹ P Fitzgerald,¹ E Cross,¹ P Collinson,²
A Gray³ and AS Hall⁴

¹School of Health and Related Research, University of Sheffield, Sheffield, UK

²St George's Hospital, London, UK

³Royal Infirmary of Edinburgh, Lothian Health Board, Edinburgh, UK

⁴Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, UK

*Corresponding author s.goodacre@sheffield.ac.uk

Objectives: To evaluate the clinical effectiveness and cost-effectiveness of using a point-of-care cardiac marker panel in patients presenting to the emergency department (ED) with suspected but not proven acute myocardial infarction (AMI).

Design: Multicentre pragmatic open randomised controlled trial and economic evaluation.

Setting: Six acute hospital EDs in the UK.

Participants: Adults presenting to hospital with chest pain due to suspected but not proven myocardial infarction, and no other potentially serious alternative pathology or comorbidity.

Interventions: Participants were allocated using an online randomisation system to receive either (1) diagnostic assessment using the point-of-care biochemical marker panel or (2) conventional diagnostic assessment without the panel. All tests and treatments other than the panel were provided at the discretion of the clinician.

Main outcome measures: The primary outcome was the proportion of patients successfully discharged home after ED assessment, defined as patients who had (1) either left the hospital or were awaiting transport home with a discharge decision having been made at 4 hours after initial presentation and (2) suffered no major adverse event (as defined below) during the following 3 months. Secondary outcomes included length of initial hospital stay and total inpatient days over 3 months, and major adverse events (death, non-fatal AMI, life-threatening arrhythmia, emergency revascularisation or hospitalisation for myocardial ischaemia). Economic analysis estimated mean costs and quality-adjusted life-years (QALYs), and then estimated the probability of cost-effectiveness assuming willingness to pay of £20,000 per QALY gained.

Results: We randomised 1132 participants to point of care and 1131 to standard care, and analysed 1125 and 1118, respectively [mean age 54.5 years, 1307/2243 (58%) male and 269/2243 (12%) with known coronary heart disease (CHD)]. In the point-of-care group 358/1125 (32%) were successfully discharged compared with 146/1118 (13%) in the standard-care group [odds ratio (OR) adjusted for age, gender and history of CHD 3.81; 95% confidence interval (CI) 3.01 to 4.82, $p < 0.001$]. Mean length of the initial hospital stay was 29.6 hours versus 31.8 hours (mean difference = 2.1 hours; 95% CI -3.7 to 8.0 hours,

$p=0.462$), while median length of initial hospital stay was 8.8 hours versus 14.2 hours ($p<0.001$). More patients in the point-of-care group had no inpatient days recorded during follow-up (54% vs 40%, $p<0.001$), but mean inpatient days did not differ between the two groups (1.8 vs 1.7, $p=0.815$). More patients in the point-of-care group were managed on coronary care [50/1125 (4%) vs 31/1118 (3%), $p=0.041$]. There were 36 (3%) patients with major adverse events in the point-of-care group and 26 (2%) in the standard-care group (adjusted OR 1.31; 95% CI 0.78 to 2.20, $p=0.313$). Mean costs per patient were £1217 with point-of-care versus £1006 with standard care ($p=0.056$), while mean QALYs were 0.158 versus 0.161 ($p=0.250$). The probability of standard care being dominant (i.e. cheaper and more effective) was 0.888.

Conclusions: Point-of-care testing increases the proportion of patients successfully discharged home and reduces the median (but not mean) length of hospital stay. It is more expensive than standard care and unlikely to be considered cost-effective.

Trial registration: Current Controlled Trials ISRCTN37823923.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 15, No. 23. See the HTA programme website for further project information.

Contents

List of abbreviations	vii
Executive summary	ix
1. Introduction	1
Diagnostic assessment of acute chest pain	1
The point-of-care cardiac marker panel	2
Research objectives	3
2. Methods	5
Study design	5
Setting	5
Participants	5
Recruitment and randomisation	6
Planned interventions	6
Point-of-care assays and analyser	7
The recommended point-of-care protocol	8
Standard care	9
Outcome measures	9
Assessment of outcomes	10
Proposed sample size	11
Statistical analysis	11
Economic evaluation	12
Economic analysis	12
Decision-analytic model	12
Ethical arrangements	13
Data management	14
Trial progress	14
Changes to protocol and other unanticipated events	16
Change of the point-of-care analyser	16
Recall of point-of-care testpaks	16
Amendment of the point-of-care protocol	16
Early termination of trial recruitment	16
3. Results	19
Screening, recruitment, randomisation and follow-up	19
Protocol violations	21
Baseline characteristics, emergency department findings and diagnosis	21
Blood testing	25
Primary efficacy	26
Secondary efficacy	30
Economic analysis	42
Decision-analytic modelling	49
Evaluation of GRACE and TIMI scores	50
4. Discussion	57
Effectiveness of point-of-care panel assessment	57

Cost-effectiveness of point-of-care panel assessment	58
Variation between the participating sites	59
Variation over time	60
Other studies of point-of-care cardiac markers	60
Strengths and weaknesses of the study	61
Implications for practice	63
Implications for future research	63
Analysis of GRACE and TIMI scores	64
5. Conclusions	65
Acknowledgements	67
References	71
Appendix 1 Point-of-care protocol	75
Appendix 2 Futility analysis	77
Appendix 3 Primary outcome details at each hospital	79
Appendix 4 Health economic parameter values used directly in model	83
Appendix 5 The RATPAC trial protocol	89
Health Technology Assessment programme	103

List of abbreviations

ACS	acute coronary syndrome
AMI	acute myocardial infarction
CABG	coronary artery bypass graft
CHD	coronary heart disease
CI	confidence interval
CK-MB	
(mass)	creatinine kinase MB (mass)
CTU	Clinical Trials Unit
CV	coefficient of variation
DMEC	Data Monitoring and Ethics Committee
ECG	electrocardiogram
ED	emergency department
EQ-5D	European Quality of Life-5 Dimensions
GCP	Good Clinical Practice
GP	general practitioner
GRACE	Global Registry of Acute Coronary Events (risk score)
GTN	glyceryl trinitrate
LREC	local research ethics committee
MI	myocardial infarction
MRC	Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NSTEMI	non-ST-elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
QALY	quality-adjusted life-year
RATPAC	Randomised Assessment of Treatment using Panel Assay of Cardiac markers
RCT	randomised controlled trial
SD	standard deviation
SE	standard error
STEMI	ST-elevation myocardial infarction
TIMI	thrombolysis in myocardial infarction (risk score)
TMG	Trial Management Group
TSC	Trial Steering Committee

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Patients with acute chest pain require rapid and accurate diagnostic assessment for acute myocardial infarction (AMI). Standard care currently involves hospital admission for measurement of troponin at least 12 hours after worst symptoms. As most patients do not ultimately have AMI this is inconvenient for patients and wastes health-care resources.

Point-of-care biomarker assessment with the combination of creatine kinase MB (mass) [CK-MB (mass)], myoglobin and troponin measured at presentation and 90 minutes later could potentially reduce the need for hospital admission and improve patient care. This combination has been shown to have high sensitivity for AMI, allowing earlier identification than laboratory testing and expedited decision-making. However, existing studies do not reliably tell us whether the panel would alter patient care, improve outcomes or reduce health service costs.

Objectives

We aimed to measure the effect of using a point-of-care cardiac marker panel upon successful discharge home after emergency department (ED) assessment, length of hospital stay, use of coronary care, cardiac tests and treatments, subsequent hospital attendance and/or admission, and major adverse events, and then estimate the cost-effectiveness of the point-of-care panel in terms of mean costs and quality-adjusted life-years (QALYs) accrued compared with standard care.

Methods

We undertook a multicentre pragmatic randomised controlled trial and economic evaluation of a point-of-care cardiac marker panel in the management of patients with acute chest pain in six EDs. We recruited people presenting to hospital with chest pain due to suspected but not proven AMI, and no other potentially serious alternative pathology or comorbidity. Participants were randomly allocated to receive either (1) diagnostic assessment using the point-of-care biochemical marker panel or (2) conventional diagnostic assessment without the panel. All tests and treatments other than the panel were provided at the discretion of the clinician. Data were collected from hospital records and a questionnaire mailed to participants at 1 and 3 months, measuring health and social care resource use, health utility [European Quality of Life-5 Dimensions (EQ-5D)] and satisfaction with care.

The primary outcome was the proportion of patients successfully discharged home after ED assessment, defined as patients who had (1) either left the hospital or were awaiting transport home with a discharge decision having been made at 4 hours after initial presentation and (2) suffered no adverse event (as defined below) during the following 3 months.

Secondary outcomes were (1) length of initial hospital stay and total inpatient days over 3 months; (2) health utility measured using the EQ-5D self-complete questionnaire at 1 and 3 months after attendance; (3) satisfaction with care measured at 1 month after attendance using an 11-question self-complete Likert-scale questionnaire; (4) the proportion of patients

admitted to the coronary care unit, receiving cardiac medications or cardiac interventions (such as angiography, percutaneous intervention or bypass grafting); (5) re-attendance at, and/or re-admission to, hospital and outpatient attendances over the following 3 months; (6) major adverse events (death, non-fatal AMI, life-threatening arrhythmia, emergency revascularisation or hospitalisation for myocardial ischaemia); and (7) the proportion of admitted patients ultimately diagnosed as having AMI by the universal definition.

We planned to recruit 1565 to each arm of the trial to give 80% power to detect a 5% absolute difference in the proportion of patients successfully discharged (55% vs 50%) and a 2% absolute difference in the major adverse event rate (2% vs 4%) at the two-sided significance level of 5%. We estimated that this could be achieved by six hospitals recruiting 550 patients each over 12 months, assuming that 70% of those eligible were recruited. Actual patient recruitment was slower than anticipated and varied between 300 and 400 patients per centre per year of recruitment, with 35% of eligible patients recruited instead of the 70% anticipated. After 1800 patients had been recruited, a futility analysis undertaken by the Data Monitoring Committee at the request of the funders suggested that there were grounds for termination on the basis of futility, with the trial having >99% conditional power to detect a 5% difference in the proportion successfully discharged and <10% power to detect a 2% difference in major adverse events. Recruitment was terminated with 2263 patients recruited.

An economic analysis was undertaken from a health and social care perspective using trial data to estimate the mean cost per patient of chest pain-related care and the mean number of QALYs accrued by patients in each arm of the trial up to 3 months after recruitment. A microcosting study of 30–40 participants at each site was used to obtain precise estimates of the costs of initial diagnostic assessment. The trial analysis was augmented with a decision-analytic model to explore the potential effect of differences in major adverse event rates upon long-term costs and outcomes.

Results

We recruited 2263 participants, of whom 2243 had usable data [mean age 54.5 years, 1307/2243 (58%) male and 269/2243 (12%) with known coronary heart disease (CHD)]. In the point-of-care group 358/1125 (32%) were successfully discharged compared with 146/1118 (13%) in the standard-care group [odds ratio (OR) adjusted for age, gender and history of CHD 3.81; 95% confidence interval (CI) 3.01 to 4.82, $p < 0.001$]. The effect on the primary outcome varied between hospitals with point-of-care panel assessment increasing successful discharges at four hospitals, having no effect at one and decreasing successful discharges at one. The ORs for successful discharge at individual hospitals varied from 0.12 (95% CI 0.01 to 1.03, $p = 0.054$) to 11.07 (95% CI 6.23 to 19.26, $p < 0.001$).

Mean length of the initial hospital stay was 29.6 hours in the point-of-care group versus 31.8 hours in the standard-care group (mean difference = 2.1 hours, 95% CI -3.7 to 8.0 hours, $p = 0.462$), while median length of initial hospital stay was 8.8 hours versus 14.2 hours ($p < 0.001$). More patients in the point-of-care group had no inpatient days recorded during follow-up (54% vs 40%, $p < 0.001$), but mean inpatient days did not differ between the two groups (1.8 vs 1.7, $p = 0.815$). More patients in the point-of-care group were managed on coronary care [50/1125 (4%) vs 31/1118 (3%), $p = 0.041$].

There were no significant differences between the groups in the proportions receiving glyceryl trinitrate, heparin, glycoprotein inhibitors, antacids or beta-blockers. More patients in the point-of-care group received clopidogrel (21% vs 16%, $p = 0.002$), while more patients in

the standard-care group received aspirin (60% vs 55%, $p=0.031$). There were no significant differences in the use of non-biomarker cardiac investigations, cardiac interventions, re-attendances or subsequent admissions, although there were non-significant trends towards increased use of cardiac interventions with point-of-care that influenced cost analysis. Patients in the point-of-care group were slightly more likely to have a chest pain-related outpatient review (21% vs 18%, $p=0.05$).

There were no significant differences in mean EQ-5D scores at 1 or 3 months (point-of-care 0.742 vs standard care 0.759 at 1 month, $p=0.614$, and 0.752 vs 0.759 at 3 months, $p=0.638$). Most patients were satisfied with most aspects of their care, with only a small proportion rating their care as poor. Point-of-care panel assessment was favoured in two of the 10 dimensions (urgency of assessment and personal interest in care) and in the question rating overall care.

There were 36 patients (3%) with major adverse events in the point-of-care group and 26 (2%) in the standard-care group (adjusted OR 1.31, 95% CI 0.78 to 2.20, $p=0.313$). The proportion of patients ultimately diagnosed as having AMI was 82/1125 (7.3%) in the point-of-care group and 76/1118 (6.8%) in the standard-care group ($p=0.650$).

Mean costs per patient were £1217 with point-of-care versus £1006 with standard care ($p=0.056$), while mean QALYs were 0.158 versus 0.161 ($p=0.250$). The probability of standard care being dominant (i.e. cheaper and more effective) was 0.888, whereas the probability of the point-of-care panel being dominant was 0.004.

Conclusions

Point-of-care panel assessment increases the proportion of patients successfully discharged home, leading to reduced median length of initial hospital stay, but no change in mean hospital stay or total inpatient days. Point-of-care panel assessment is associated with increased use of coronary care and may be associated with increased use of other interventions. Cost-effectiveness is mainly driven by differences in mean cost, with point estimates suggesting that point-of-care panel assessment is £211 per patient more expensive than standard care. It is unlikely to be considered cost-effective in the NHS, with a 0.888 probability that standard care is dominant.

Further research is required to identify factors that influence the effectiveness and cost-effectiveness of point-of-care panel assessment, explore alternative ways of managing patients with low-risk chest pain and evaluate new cardiac biomarkers.

Trial registration

This study is registered as ISRCTN37823923.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Introduction

Diagnostic assessment of acute chest pain

Chest pain is responsible for around 700,000 patient attendances per year in England and Wales, and around one-quarter of hospital admissions.¹ The main reason for attendance is the possibility of acute myocardial infarction (AMI). Patients with ST-elevation myocardial infarction (STEMI) can benefit from early coronary reperfusion using primary angioplasty or intravenous thrombolysis. Patients with non-ST-elevation myocardial infarction (NSTEMI), who are much more numerous than those with STEMI, benefit from hospital admission and treatment. The potential benefits of treatment for AMI have led to public awareness campaigns encouraging people with acute chest pain to call for emergency medical help and national guidelines recommending that patients with chest pain should call for an emergency ambulance to take them to a hospital emergency department (ED) rather than contact their general practitioner (GP).² Thus, ED attendances with chest pain are increasing.

Standard initial assessment of patients with acute chest pain consists of a clinical history and examination, 12-lead electrocardiogram (ECG) recording and a chest radiograph. On the basis of this assessment around 34% will have a clinical diagnosis of suspected acute coronary syndrome (ACS), 11% will have an ECG diagnosis of suspected acute coronary syndrome, 19% will have a clear diagnosis of benign non-cardiac chest pain (such as muscular pain) and 12% will have suspected serious non-cardiac chest pain (such as pulmonary embolus) or comorbidity (such as heart failure). The remaining 24% have no clear diagnosis but have a significant risk (5–10%) of undiagnosed AMI.¹

Acute myocardial infarction is usually diagnosed by serial cardiac biomarker testing ('cardiac enzymes') typically by measurement of troponin in the blood. A patient with ischaemic symptoms (such as chest pain) would be diagnosed as having AMI according to the universal definition for acute, evolving or recent AMI if a troponin level is recorded above the 99th percentile of the values for a reference control group.³ These patients are likely to benefit from hospital admission.⁴ Patients with no troponin elevation have a low risk of adverse outcome and are unlikely to benefit from hospital admission, unless they have a serious non-coronary cause for their pain (such as pulmonary embolus) or serious comorbidity (such as heart failure or arrhythmia). Rapid and accurate identification of patients with AMI is thus a hallmark of effective emergency care for chest pain.

Current recommendations suggest that patients with chest pain due to suspected, but not proven, AMI should receive diagnostic testing with a troponin sample taken 12 hours after symptom onset,⁵ 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 presenting to the ED with suspected AMI do not actually have subsequent confirmation of AMI, so their admission will ultimately prove avoidable. Economic analysis suggests that admitting patients for cardiac marker testing is not a cost-effective use of health service resources compared with early cardiac marker testing.⁶ Recent studies^{7,8} have suggested that new high-sensitivity

troponin assays may be able to rule out AMI earlier than 12 hours, although the effect of using these assays in practice has not yet been evaluated.

Evidence also suggests that these guidelines are often not followed in a busy emergency setting where acute beds are limited. Collinson *et al.*⁹ showed that 7% of patients discharged after ED assessment for acute chest pain had elevated troponin levels at follow-up 2 days later. Goodacre *et al.*¹⁰ showed that, in the standard-care arm of a randomised trial of a chest pain unit, 14% of patients with an elevated troponin level at 2-day follow-up had been sent home from the ED. A national survey of EDs¹¹ 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 undetected AMI.

The point-of-care cardiac marker panel

Rapid point-of-care testing using a panel of markers offers an alternative approach that may be more effective and cost-effective than current practice. This technology has two elements that offer putative benefits: (1) point-of-care testing to reduce the turnaround time to results being available and (2) the use of a combination of markers, including measurement of marker gradients, to optimise early sensitivity. This is based on the idea that other markers, such as myoglobin and creatine kinase MB (mass) [CK-MB (mass)], may start to rise earlier than cardiac troponin.

Point-of-care testing involves using an analyser in the ED for marker assays. The analyser needs to be operated quickly and reliably by clinical staff. It can then allow rapid provision of marker results with short turnaround times to guide decision-making. Several randomised controlled trials (RCTs) have compared point-of-care tests with the same test performed on a laboratory analyser to determine whether use of point-of-care testing reduces turnaround times and changes practice. Collinson *et al.*¹² showed that the use of point-of-care troponin testing on a coronary care unit led to reduced length of coronary care unit stay and overall hospital stay. Renaud *et al.*¹³ showed that point-of-care troponin testing in an ED reduced time to anti-ischaemic therapy and physician notification of troponin results, but did not change ED length of stay or patient outcomes. Ryan *et al.*¹⁴ evaluated point-of-care troponin testing in four EDs and found that the effect varied between settings, with length of stay in the ED being increased in one hospital and decreased in another. Kendall *et al.*¹⁵ evaluated a variety of point-of-care tests in an ED and found that point-of-care testing reduced turnaround times and times to decisions being made, but did not influence clinical outcomes or length of stay. Overall, therefore, there is reasonable evidence that point-of-care testing reduces turnaround times and possibly also times to decisions being made, but no consistent evidence of an effect on length of stay. One crucial component may be the need to incorporate point-of-care testing within a decision-making protocol.

Combining markers in a panel aims to overcome the limitations of individual markers. Different cardiac markers have optimal sensitivity for AMI at different times after symptom onset.^{16,17} Combining markers to form a panel that is positive if any one marker is positive should optimise sensitivity and ensure that fewer cases of AMI are missed. Measuring the gradient rise of markers between baseline (when the patient arrives at hospital) and a specified time later (typically 90 minutes) has been shown to improve early sensitivity^{18,19} and can also improve specificity if only the gradient rise (rather than the absolute value) is considered positive.

Most studies of point-of-care cardiac marker panels have evaluated the combination of CK-MB (mass), myoglobin and troponin I measured at presentation and 90 minutes later. These have

shown that the panel has high sensitivity and can accurately rule out AMI by 90 minutes after presentation.^{20–27} This results in earlier identification of AMI than with laboratory testing²² and expedited decision-making with turnaround times reduced by 55%.²³ Meanwhile, comparison of patient management with the panel with previous practice showed a 40% reduction in coronary care unit admissions.²⁴

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 lead to changes in practice only if clinicians act upon the additional diagnostic information. The before and after study by Ng *et al.*²⁴ may be confounded by changes in coronary care referrals over time and, originating from the USA where coronary care usage is much higher than in the UK, may not be applicable to the UK NHS. To date, there have been no randomised trials comparing marker panels with routine practice.

Existing data therefore suggest that point-of-care cardiac markers can accelerate decision-making in the ED and that a panel of markers consisting of troponin, CK-MB (mass) and myoglobin, measured at baseline and 90 minutes later, can accurately identify patients with AMI. This strategy could allow rapid and accurate diagnosis in the ED or clinical decision unit, facilitating hospital admission for those with AMI and discharge home for those without. However, such a strategy needs to be evaluated in practice and compared with current management before it can be recommended for widespread adoption throughout the NHS. Evaluation allows us to determine whether clinical decision-making is changed by using the point-of-care panel, whether hospital admissions are actually reduced in practice, whether reduced hospital admissions save sufficient health service costs to compensate for the additional costs of point-of-care testing and whether patient outcomes are improved. In addition, advances in assay methodology for troponin suggest that troponin alone may be used to rule in and rule out AMI soon after presentation, and marker panels may be unnecessary.²⁸ This has also not been tested in a randomised controlled manner.

Research objectives

We aimed to measure the effect of using a point-of-care cardiac marker panel upon the following outcomes in patients presenting to the ED with suspected but not proven AMI:

1. the proportion of patients successfully discharged home after ED 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.

In addition, we planned to undertake secondary analysis of the data of the Randomised Assessment of Treatment using Panel Assay of Cardiac markers (RATPAC) trial to evaluate the TIMI (thrombolysis in myocardial infarction)²⁹ and GRACE (Global Registry of Acute Coronary Events)³⁰ clinical prediction scores and store blood samples taken from participants in the intervention arm to evaluate potential new or alternative markers. The results of the evaluation of TIMI and GRACE scores are presented in this report. Funding has been sought to undertake secondary blood sample analysis.

Chapter 2

Methods

Study design

We undertook a multicentre pragmatic RCT and economic evaluation of a point-of-care cardiac marker panel in the management of patients with suspected, but not proven, AMI in six EDs in the UK.

Setting

The participating hospitals were Barnsley District General Hospital, Derriford Hospital in Plymouth, Edinburgh Royal Infirmary, Frenchay Hospital in Bristol, Leeds General Infirmary and Leicester Royal Infirmary. They were selected to provide a range of different settings that reflected the variation in current NHS practice and the variation in facilities available to manage patients with acute chest pain. *Table 1* outlines the characteristics of the participating centres.

Participants

We recruited people presenting to the ED 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. All patients with chest pain were considered for participation but then excluded if they met any of the following criteria:

1. Diagnostic ECG changes for AMI or high-risk acute coronary syndrome (> 1 mm ST deviation or > 3 mm inverted T waves). These patients are at high risk of adverse outcome and require inpatient care even if marker tests are negative.
2. Known coronary heart disease (CHD) 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.

TABLE 1 Characteristics of the participating centres

	Annual ED attendances: 1 April 2008 to 31 March 2009	No. of acute medical beds ^a	ED facilities	On-site cardiology services
Barnsley	71,678	462	—	CCU, rapid access clinic
Derriford	85,341	240	CDU	CCU, angioplasty, cardiac surgery, rapid access clinic
Edinburgh	105,378	843 ^b	—	CCU, angioplasty, cardiac surgery, rapid access clinic
Frenchay	62,823	461	CDU	CCU, angioplasty
Leeds	109,362	491	CDU	CCU, angioplasty, cardiac surgery, rapid access clinic
Leicester	156,053	290	—	CCU, rapid access clinic

CCU, coronary care unit; CDU, clinical decision unit.

^a Excluding escalation beds.

^b Breakdown for medical beds not available, so all acute beds reported.

3. Proven or suspected serious non-coronary pathology (e.g. pulmonary embolus) that requires inpatient care even if AMI is ruled out.
4. Comorbidity or social problems that require hospital admission even if AMI can be ruled out.
5. An obvious non-cardiac morbidity (e.g. pneumothorax or muscular pain) in a patient in whom AMI can be excluded as a possible cause without resorting to further diagnostic testing.
6. Presentation more than 12 hours after the most significant episode of pain, in which case a single troponin measurement would clearly be more appropriate than point-of-care panel assessment.
7. Previous participation in the RATPAC trial.
8. Inability to understand the trial information owing to cognitive impairment.
9. Non-English-speaking patients for whom translation facilities were not available.

For every fourth week of trial recruitment the research nurse at each hospital examined ED attendance lists to identify patients attending with chest pain and record basic demographic details and reasons for exclusion. The huge number of attendances with chest pain meant that undertaking this process throughout the whole trial would have produced an excessive workload, whereas monitoring every fourth week achieved the aim of reporting sample selection within acceptable use of resources.

Recruitment and randomisation

Research nurses and ED staff identified eligible patients, provided trial information and obtained written consent. Participants were then randomly allocated to receive either (1) diagnostic assessment using the point-of-care biochemical marker panel or (2) conventional diagnostic assessment without the panel.

The Nottingham Clinical Trials Unit (CTU) generated a simple randomisation sequence, stratified by centre, which was not revealed to any person involved in patient recruitment. Recruiting doctors and research nurses accessed a secure website provided by Nottingham CTU and entered participant details. The CTU revealed the participant's allocated treatment group to the ED only after the participant's details were entered, written consent was confirmed and the participant irrevocably entered into the trial.

Planned interventions

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 assessment with the point-of-care panel. The use of all other tests and treatments, and decision-making in the ED, was at the discretion of the attending clinician.

The point-of-care cardiac marker panel comprised CK-MB (mass), myoglobin and troponin I, measured at presentation and 90 minutes later, using the Siemens Stratus® CS Analyser (Dade Behring, Milton Keynes, UK). Clinical staff were trained to use the test and given guidance in

interpretation of the results. We provided a recommended protocol that advised a first panel test immediately after initial ED assessment and a second panel test 90 minutes later, and then advised hospital admission or discharge on the basis of point-of-care results (*Appendix 1*). Decisions were ultimately at the discretion of clinical staff. We did not police the use of the point-of-care protocol to ensure that it was being followed.

Other than obtaining consent, collecting data and random allocation to use of the point-of-care test, the only change to routine practice was that we asked clinical staff to take an additional sample of blood for storage (without repeating venepuncture) each time a point-of-care blood sample was required. The additional blood sample taken after point-of-care testing was transported to the hospital laboratory to be centrifuged and the serum separated and then frozen. Batches of frozen samples were then transported quarterly to St George's Hospital for longer-term storage and future secondary analysis of new biomarker assays.

The RATPAC trial was a pragmatic trial, intended to determine whether point-of-care panel assessment should be standard practice for patients presenting to the ED with suspected AMI. It was designed to compare two pragmatic alternatives (management with and without point-of-care panel assessment) under routine conditions to determine whether use of the test changes costs or outcomes. This pragmatic design had the following implications:

1. There was no attempt to blind clinical staff, patients or carers to the allocated treatment group after randomisation.
2. The point-of-care test was provided with a recommended protocol for use but management decisions were ultimately at the discretion of the clinical staff.
3. All other diagnostic tests and the use of laboratory blood tests in the control group were at the discretion of the clinical staff. Blood samples were taken only for the purposes of clinical management. We did not take blood samples at additional time points to evaluate theoretical management strategies or to evaluate the accuracy of diagnostic assessments. The blood samples taken for storage and future analysis were taken at the same time as the point-of-care samples used for clinical care and did not require additional venepuncture.

Point-of-care assays and analyser

Cardiac troponin I, CK-MB (mass) and myoglobin were measured by point-of-care testing in the ED on the Stratus CS Analyser. The original project protocol planned to use the Biosite Triage[®] analyser (Biosite, San Diego, CA, USA), as this was the most widely used analyser at the time of protocol development. However, as protocol development continued it became apparent that new-generation high-sensitivity troponin assays, as well as point-of-care analysers with high-sensitivity troponin assays, were becoming available.³¹ Discussions with experts in the field revealed reservations about the analytical performance of the Biosite system, particularly the analytical sensitivity of its troponin assay. In view of this, and the need to ensure the future generalisability and the development towards more sensitive troponin assays, it was deemed prudent to use a more sensitive system in the trial. Recent publications^{7,8} have since confirmed the potential of high-sensitivity troponin assays to improve early assessment.

The Stratus CS Analyser was selected on the basis of having most data as an instrument suitable both for the emergency laboratory and for use as a point-of-care instrument,^{32–34} as well as a troponin assay with performance characteristics close to current recommendations for analytical goals. It has the advantage that it can measure troponin, myoglobin and CK-MB (mass) on the same sample.³⁵ In addition, it has the health and safety advantages of using a closed system that does not require the operator to open the blood tube and pipette the sample on to a test strip.

Blood is drawn directly into a Vacutainer tube (a standard no-touch aseptic blood-sampling system) using lithium heparin as an anticoagulant. The tube is then inverted twice to mix the blood and anticoagulant. It is then ready for analysis. The sample is introduced directly into the machine, the sample door closed and analysis is fully automatic.

The analytical characteristics of the assays were as follows. Cardiac troponin I: detection limit 0.02 µg/l, analytical range 0.02–50 µg/l, interassay coefficient of variation (CV) 4.3–5.1% (0.03–0.22 µg/l). The 99th centile of the assay is 0.07 µg/l. Myoglobin: detection limit 1 µg/l, analytical range 1–900 µg/l, interassay CV 1.9–12.7% (56–308 µg/l); 95% reference interval, males 21–98 µg/ml, females 19–56 µg/l, combined 20–82 µg/l. CK-MB (mass): detection limit 0.3 µg/l, analytical range 0.3–150 µg/l, interassay CV 0.15–1.27% (3.7–39.3 µg/l); 95% reference interval 0.6–3.5 µg/l.

The recommended point-of-care protocol

The point-of-care protocol is outlined in *Appendix 1*. The sample(s) were deemed positive and hospital admission advised if any of the following were met:

1. any CK-MB (mass) exceeded 5 µg/l
2. the CK-MB (mass) gradient exceeded 1.6 µg/l
3. the myoglobin gradient increase exceeded 25% of the baseline value
4. troponin exceeded 0.02 µg/l.

The CK-MB (mass) gradient is based on data from Fesmire *et al.*,^{18,19} suggesting that this value allows optimisation of both sensitivity and specificity. The myoglobin gradient was used alone because absolute myoglobin levels have very poor specificity, whereas using only the gradient rise maintains the value of early sensitivity without compromising specificity.

The Stratus CS Analyser is able to detect troponin levels in the range of 0.03–0.07 µg/l even though this is below the 99th centile of normal, which is conventionally used as a diagnostic threshold. Our understanding of the significance of very low troponin levels developed during the trial and is continuing to develop now (indeed we anticipate that secondary analysis of RATPAC blood samples will provide a further contribution). At the start of the trial we decided to err on the side of caution and recommended that any detectable troponin above 0.02 µg/l should be considered positive in case it represented the start of a significant rise. However, it became apparent from emerging data that levels between 0.03 and 0.07 µg/l do not typically represent an early troponin rise and where they do this is evident upon measuring the difference between baseline and 90-minute values. We therefore amended the guidance to recommend that the tests only be considered positive on the troponin assay if:

- any troponin level exceeded 0.07 µg/l
- or
- the initial troponin is below 0.03 µg/l and the second sample is above 0.02 µg/l.

The new guidance was disseminated and implemented between December 2008 and February 2009.

Standard care

The standard-care group were managed without point-of-care panel assessment according to existing guidance for management of low-risk chest pain due to suspected ACS at each of the participating hospitals. We deliberately selected a variety of hospitals that were operating a range of different strategies and had a variety of different facilities available for chest pain management. *Table 2* summarises the location of care and biomarker(s) used for low-risk patients in each hospital. Patients were referred to the cardiology team if biomarkers were positive and discharged (with or without exercise treadmill testing) if negative.

Outcome measures

The primary outcome was the proportion of patients successfully discharged home after ED assessment. To be considered successfully discharged the patient had to have both (1) left the hospital or be awaiting transport home with a discharge decision having been made at 4 hours after initial presentation and (2) suffered no major adverse event (as defined below) during the following 3 months.

Secondary outcomes were:

1. Health utility measured using the European Quality of Life-5 Dimensions (EQ-5D) self-complete questionnaire at 1 and 3 months after attendance.
2. Satisfaction with care measured at 1 month after attendance using a modified Group Health Association of America questionnaire that had been used successfully in previous studies of diagnostic strategies for acute chest pain.^{10,36}
3. The proportion of patients admitted to the coronary care unit, receiving cardiac medications (aspirin, heparin, clopidogrel or glycoprotein IIb/IIIa inhibitors) or receiving cardiac interventions [angiography, percutaneous coronary intervention (PCI) or bypass grafting].
4. Length of initial hospital stay and total inpatient days over 3 months.

TABLE 2 Existing management strategies for low-risk chest pain

	Location	Troponin assay	Troponin threshold used (µg/l)	Laboratory analyser	Timing of troponin (hours) ^a	Other biomarkers
Barnsley	Inpatient ward	Siemens Centaur Troponin I Ultra	<0.20	Siemens Centaur XP	12	
Derriford	CDU	Roche Troponin T	<0.01	Roche Modular E170	6	
Edinburgh	Medical Assessment Unit	Abbott STAT Troponin I	<0.05 ^b	Architect i2000SR	12	Creatine kinase
Frenchay	CDU	Beckman Coulter Access Accu Troponin I	<0.06	Beckman Coulter Access 2	12	
Leeds	CDU	Siemens Centaur Troponin I Ultra	<0.05	Siemens Centaur XP	12	
Leicester	Inpatient ward	Siemens Centaur Troponin I Ultra	<0.06	Siemens Centaur XP	12	Creatine kinase

CDU, clinical decision unit.

^a Timing after onset of worst symptoms.

^b Changed from <0.2 µg/l on 21 January 2009.

5. Re-attendance at and/or re-admission to hospital and outpatient attendances over the following 3 months.
6. Adverse events (death, non-fatal AMI, life-threatening arrhythmia, emergency revascularisation or hospitalisation for myocardial ischaemia).
7. The proportion of admitted patients ultimately diagnosed as having AMI by the universal definition.³

We 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 suffered an adverse event after discharge were not classified as a successful discharge home because they may have benefited from hospital admission. We also recorded the proportion of admitted patients who were ultimately diagnosed as having AMI to provide a measure of the appropriateness of admissions.

Assessment of outcomes

Recruiting staff recorded baseline data (including the variables required to calculate the TIMI or GRACE score), the results of initial assessment (including any biochemical cardiac tests) and admission or discharge from the ED. Research nurses then used ED 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 3 months. Time and date of discharge for the initial admission were recorded as precisely as possible using computer records, case notes and contact with hospital staff. The total number of inpatient days over 3 months was recorded using hospital notes. An inpatient day was defined as being an overnight stay.

Research nurses checked patient status (dead or alive) at 1 and 3 months, using hospital information systems. Deceased patients were assumed to have a score of zero on EQ-5D and were excluded from other patient-based assessments. Participants who were not recorded as dead were mailed a questionnaire at 1 and 3 months from the University of Sheffield to identify adverse events and hospital attendances, health and social care resource use, and measure EQ-5D and satisfaction with care (satisfaction at 1 month only). Our previous study suggested a 70–80% response rate to this questionnaire.^{10,37}

A single reviewer (SG) blinded to treatment group classified all ED re-attendances, subsequent hospital admissions and outpatient reviews as either potentially chest pain related (including non-cardiac conditions that could have initially presented as chest pain) or clearly non-chest pain related (such as limb injuries).

The initial working diagnosis and final diagnosis were recorded and categorised by the research nurse, based upon the diagnosis recorded in the notes by the most senior clinician at the end of initial ED assessment and at the end of hospital admission, respectively. Patients were classified as having AMI on the basis of the presence of a rise in their troponin level above the diagnostic threshold of the relevant assay and absence of a final diagnosis of an alternative condition (such as sepsis or pulmonary embolism) that could have produced a troponin elevation. Patients with a troponin rise consistent with AMI and final diagnosis of ACS or 'other AMI' were classified as having AMI. Patients with no troponin rise and a final diagnosis that was not ACS or 'other AMI' were classified as not having AMI. A single reviewer blinded to treatment group reviewed the initial and next-day ECGs of patients with a final diagnosis of ACS and no troponin rise

and categorised these patients as having AMI if an ECG showed ST elevation and coronary reperfusion was performed, otherwise they were categorised as having no AMI. Two independent reviewers blinded to treatment group reviewed case details of all patients with a troponin rise and a final diagnosis other than ACS or 'other AMI', and all patients with a troponin rise that was inconsistent with AMI (e.g. if a positive troponin was shortly followed by a negative troponin result). Each decided whether AMI was the most likely diagnosis. Disagreements were resolved by discussion and patients classified as having AMI or no AMI.

Proposed sample size

We planned to recruit 3130 participants to the trial. A previous randomised trial in this patient group suggested that around 50% of the control group would be successfully discharged.¹⁰ With 1565 evaluable subjects in each arm of the trial we expected to have 80% power to detect a 5% absolute difference in the primary outcome (50% vs 55%) at the two-sided significance level of 5%. The same sample size provided 80% power to detect a 2% absolute difference (2% vs 4%) in major adverse events (death, non-fatal AMI, life-threatening arrhythmia, emergency revascularisation or hospitalisation for myocardial ischaemia), again at the two-sided 5% level of significance.

We estimated that we would require six hospitals to recruit for 12 months each to achieve the sample size of 3130, assuming that we recruited 70% of those eligible. Previous studies of this specific patient group undertaken by our team had shown that recruitment of 550 suitable patients per year is attainable at a typical hospital.^{10,37–39}

Previous studies had also shown a response rate of 70–80% for postal questionnaires,^{10,37} 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.

Statistical analysis

We planned to analyse the primary outcome through logistic regression, fitting concurrently with intervention group the effect of centre and appropriate baseline measures (including age, gender and past history of CHD), to present adjusted odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). A similar analysis was used for adverse events. Primary analysis was on an intention-to-treat basis. Secondary analysis excluded those who were not managed according to their allocated strategy.

We undertook a descriptive assessment to explore whether use of biochemical cardiac markers or admission rates changed 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.

For each patient, GRACE and TIMI scores were calculated. Two approaches were undertaken for calculating each score: one using the first available troponin sample and the second using the highest troponin level taken during the initial hospital stay. Some patients did not have all of the data items that were required to permit calculation of the score so two analyses were undertaken: one including only cases with complete data, the other including all cases with imputation to complete the data set. Imputation involved assuming that missing variables would be negative or, where appropriate, the mean value for the RATPAC population (e.g. continuous variables used in the GRACE score). We evaluated the predictive value of GRACE and TIMI by calculating the

proportion with an adverse outcome at 1 and 3 months in each quintile of GRACE score and each TIMI category. We then calculated the area under the receiver-operator characteristic curve (*c*-statistic) for each score.

Economic evaluation

Economic evaluation was undertaken alongside the trial using recommended practice.⁴⁰ In addition, a cost-effectiveness model was developed to duplicate the trial results (as a way of validation) and extrapolate the results to longer follow-up periods. The NHS perspective was undertaken and other methods were in line with National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Guidelines.⁴¹

Resource use data were collected for all patients covering the length of time in the ED, the use of diagnostic tests, admissions, re-admissions, outpatient reviews and cardiac procedures. Cost and outcome data were collected using patient notes and self-completed questionnaires as described previously. A small microcosting study of 30–40 patients was carried out at each site, gathering data on staff times relating to the care of patients. ED cost per minute was based on a study previously undertaken by the investigators,¹⁰ and amended using the microcosting data from this study. Panel costs were based on purchase price, and the remaining costs were valued using national unit costs.^{42,43} Total NHS costs up to 3 months after initial attendance were calculated. Quality-adjusted life-years (QALYs) were calculated by the trapezium rule using the EQ-5D tariff values at all follow-up points.

Economic analysis

Both cost and QALY analysis compared bootstrap estimates of the mean cost per patient of the two groups. Cost-effectiveness analysis estimated the incremental cost per QALY of using point-of-care cardiac marker testing compared with management without point-of-care panel assessment. Results were plotted on the cost-effectiveness plane and then transformed into cost-effectiveness acceptability curves with their associated frontier.⁴⁴ A sensitivity analysis was undertaken to include production losses as reported by the patient.

We anticipated that some of the resource use and QALY data would be incomplete (missing). Thus, in order to maximise the information collected from the trial, we imputed missing values using multiple imputation within STATA (StataCorp LP, College Station, TX, USA).⁴⁵ 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 an unbiased representation of uncertainty.⁴⁶ Thus, an additional set of results is available from the imputed cost and QALY data.

Decision-analytic model

We constructed a decision-analytic model to describe the care observed in the trial, and likely care pathways subsequent to it. This allowed us to systematically investigate the impact of subsequent costs, quality of life and survival. These values were initially based on population norms, but then replaced with literature review estimates where appropriate. Finally, they were replaced by RATPAC trial estimates where required. The decision-analytic model was probabilistic, but with conventional sensitivity analysis used to assess the impact of structural uncertainties.⁴⁷

The main purpose of the decision-analytic model was to explore the potential impact of changes in the major adverse event rate upon cost-effectiveness. We anticipated that the trial would have adequate power to detect economically important differences in resource use and EQ-5D, but would only have limited power to detect differences in major adverse events. It was therefore possible that an intervention could be apparently cost-effective (in terms of reducing costs and increasing health utility), while being associated with a statistically non-significant increase in adverse events. The decision-analytic model was intended to explore whether uncertainty around the effect of the intervention upon the major adverse event rate could influence the potential cost-effectiveness of the intervention.

The decision-analytic model used trial data to estimate costs and QALYs up to 3 months. Beyond this, we used lifetime cost and QALY estimates from a previous economic analysis of a similar population.⁴⁸ The mean lifetime cost of care for a patient with CHD was estimated to be £10,079 [standard error (SE) = £2200] and mean QALYs accrued were estimated to be 6.829 (SE = 0.34), while estimates of £0 and 20 QALYs [standard deviation (SD) = 5] were used for patients without CHD. Trial data were used to estimate the rates of death and non-fatal AMI by 3 months after management with the point-of-care panel and standard care. We then assumed that those who had died by 3 months would accrue no further costs or QALYs, while those who survived with non-fatal AMI would accrue costs and QALYs associated with CHD. Probabilistic sensitivity analysis was then used to estimate the mean lifetime costs and QALYs of patients in the two arms of the trial.

The decision-analytic model was developed and implemented in an EXCEL (Microsoft Corporation, Redmond, WA, USA) spreadsheet, which included a VISUAL BASIC macro to implement the replication of outcomes from the model. The results presented were based on 10,000 outcome simulations. The pathways through the model described (1) the choice of diagnostic tool, using either point-of-care tests or standard-care approaches; (2) the disposal from the ED, either to admission or to discharge; (3) possible interventions or care once a positive diagnosis of ACS (and therefore admission) was made, including coronary artery bypass graft (CABG), PCI, thrombolysis, hospital stay with no intervention or thrombolysis treatment, and discharge without intervention in the case of a negative updated diagnosis, or death from ACS while in hospital; and (4) possible ACS events after discharge without diagnosis from the ED, which resulted in subsequent admission and treatment according to the treatments outlined in (3). Costs were accrued as simulated patients passed through the various stages in the model, and benefits were accrued at the end of each passage. Once discharged, either from ED or after admission, costs were assumed to be unaffected by the choice of diagnostic technique, and therefore costs of follow-up care or intervention were combined across both arms.

Ethical arrangements

All participants were asked to provide written, informed consent. Although participants were recruited in an emergency setting and there was only 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) ensured that eligible patients would not be incapacitated by their medical condition. We did not therefore make provision for recruitment of incapacitated patients by personal or professional legal representatives.

Ethical approval was granted by Leeds East Research Ethics Committee and review provided by the local research ethics committee (LREC) at each participating centre. The trial was conducted in accordance with Medical Research Council (MRC) *Guidelines for Good Clinical Practice in Clinical Trials*.⁴⁹ The University of Sheffield was the sponsor for the trial. The Trial Steering

Committee (TSC) consisted of the Chief Investigator (SG), one of the co-applicants (PC), an independent chair (MF), two independent members (SH, JK) and a consumer representative (EH). We also invited a representative of the funder to join the committee but this was declined. The Data Monitoring and Ethics Committee (DMEC) consisted of an independent statistician (HT), emergency physician (WT) and cardiologist (JG), who were asked to review trial data at regular intervals and implement stopping rules in accordance with MRC guidance. The Trial Management Group (TMG) consisted of the Chief Investigator, co-applicants, Principal Investigator at each site, project manager, statistician, health economist and research nurses.

Data management

Trial data were collected on the case report form and follow-up form and then entered by the research nurses into an online database provided on a secure central server by the Sheffield CTU. The system had a full electronic audit trail. Quality control procedures were applied to validate the trial data. The project manager undertook quarterly data monitoring visits to each site, at which a random sample of data forms were checked for errors and validated against source documents. Any errors, protocol deviations or violations were reviewed with the research nurse and Principal Investigator and documented in the site files and master file. Central monitoring involved flagging discrepant or questionable data. Error reports were generated where data clarification was required. Monthly outputs were generated for the TMG and TSC summarising baseline characteristics of patients recruited, follow-up rates, data completion and adverse events by study site, but not study group. Outcome data summaries were provided for closed meetings of the DMEC. All activities were performed in accordance with Sheffield CTU standard operating procedures.

Trial progress

The project started on 1 April 2007. We planned to recruit staff and gain ethical and local governance approvals in months 1–6, recruit patients in months 7–18 and complete follow-up, data analysis, writing-up and dissemination in months 19–24. Actual trial progress was slower than anticipated: staff recruitment, ethics and regulatory approvals took up to 12 months to complete, patient recruitment was slower than expected, and the trial was terminated before the target of 3130 patients was recruited. The Gantt chart in *Figure 1* outlines the planned and actual trial progress.

Table 3 shows the timing of processes at the six participating centres.

The reasons for the set-up phase being longer than expected are as follows:

1. The process of drawing up contracts between the sponsor (the University of Sheffield) and the six participating hospitals took longer than expected.
2. Local ethics and regulatory approvals could not be processed at some sites until contracting had been completed.
3. The time taken to provide local ethics and, in particular, governance approvals varied between hospitals.
4. In addition to trial training, some of the participating hospitals required all staff involved in the trial, including recruiting doctors, to have received formal training in Good Clinical Practice (GCP), even though the RATPAC trial was not a trial of an investigational medicinal product.

Month of project	1–3	4–6	7–9	10–12	13–15	16–18	19–21	22–24	25–27	28–30	31–33
Dates	Apr– June 2007	Jul– Sep 2007	Oct– Dec 2007	Jan– Mar 2008	Apr– June 2008	Jul– Sep 2008	Oct– Dec 2008	Jan– Mar 2009	Apr– June 2009	Jul– Sep 2009	Oct– Dec 2009
Planned											
Staff recruiting, ethics and regulatory approvals	XXX	XXX									
Patient recruitment			XXX	XXX	XXX	XXX	XXX				
Follow-up			XX	XXX	XXX	XXX	XXX				
Analysis and writing-up								XXX			
Actual											
Staff recruiting, ethics and regulatory approvals	XXX	XXX	XXX	XXX							
Patient recruitment				X	XXX	XXX	XXX	XXX	XX		
Follow-up					XXX	XXX	XXX	XXX	XXX	XX	
Analysis and writing-up										X	XX

FIGURE 1 Gantt chart of trial timetable and progress.

TABLE 3 Set-up process at each site

Site	Contract signed with Sheffield	Memorandum of Understanding signed with Siemens	Approved by LREC	Approved by Hospital Research Office	Research nurse appointed	Recruitment started
Barnsley	6 August 2007	14 September 2007	7 June 2007	22 May 2007	1 October 2007	30 January 2008
Derriford	22 November 2007	3 January 2008	5 July 2007	4 January 2008	26 November 2007	25 February 2008
Edinburgh	28 August 2007	4 December 2007	11 June 2007	15 June 2007	14 January 2008	2 April 2008
Frenchay	22 November 2007	23 October 2007	18 July 2007	28 November 2007	9 January 2008	31 March 2008
Leeds	9 September 2007	17 September 2007	5 July 2007	18 June 2007	3 March 2008 ^a	16 April 2008
Leicester	1 October 2007	5 October 2007	25 June 2007	19 September 2008	14 January 2008	25 March 2008

^a Research nurse initially appointed 1 October 2007, but resigned before recruitment started.

Patient recruitment was slower than anticipated and varied between 300 and 400 patients per centre per year of recruitment, compared with the expected 550 per centre per year. Details of patient recruitment are reported below (see *Results*) but it appeared that failure to achieve the expected recruitment rate was due to failure to recruit the expected proportion of eligible patients rather than any lack of eligible patients. Overall 35% (604/1719 – see *Table 4*) of eligible patients were recruited instead of the 70% anticipated. The following factors are likely to have accounted for this difference:

1. The requirement for GCP training resulted in doctors being unwilling to assist with trial recruitment. This varied between centres, depending upon the local regulatory requirements. In one centre the need for all doctors to receive formal GCP training resulted in most patients being recruited by research nurses. This centre recruited the lowest proportion of eligible patients (19%).
2. Service commitments, particularly the target of discharging 98% of patients from the ED within 4 hours of arrival, discouraged ED staff from recruiting patients during busy times.
3. The recall of point-of-care testpaks (described below) may have reduced the confidence of ED staff in the technology and thus their willingness to recruit patients to the trial.

Changes to protocol and other unanticipated events

A number of unanticipated events occurred during the trial, two of which resulted in changes to the protocol. Most of the unanticipated events related to the intervention being evaluated. Point-of-care cardiac markers are a developing technology and clinicians are learning more about the technology as it is implemented. Even mature technologies can be subject to unanticipated problems, especially if used by a wide range of staff in a variety of settings.

The unanticipated events were:

1. change of the point-of-care analyser
2. recall of point-of-care testpaks
3. amendment of the point-of-care protocol
4. early termination of trial recruitment.

The first and third of these resulted in changes to the protocol. In addition, we became aware that we had not included life-threatening arrhythmia as a major adverse event in the trial protocol, although it was included as such in the case report form. We therefore amended the protocol to include life-threatening arrhythmia as a major adverse event.

Change of the point-of-care analyser

This occurred during protocol development and before the trial started. Details and the reasons for this are outlined above (see *Point-of-care assays and analyser*).

Recall of point-of-care testpaks

Siemens informed the RATPAC research team on 4 July 2008 of the need to recall point-of-care assays for troponin I because of a faulty batch that could have produced low false-positive levels. All six sites were affected, resulting in a suspension of recruitment at all sites for up to 1 week between 4 and 14 July 2008 until new assays were delivered. A meeting was held with Siemens and the biochemical expert on the Research Team (PC) to address concerns. It was concluded that quality assurance was tight, particularly with high-risk tests, so this would be a rare rather than a common occurrence. It was also discussed in length at a TMG meeting in July 2008. It was agreed that patients with a potentially false-positive point-of-care troponin result would have received appropriate follow-up based on their 12-hour troponin level and clinical condition, and therefore no additional intervention was required.

Amendment of the point-of-care protocol

Details and the reasons for this are outlined above (see *The recommended point-of-care protocol*).

Early termination of trial recruitment

Owing to the set-up delays and slower than anticipated recruitment, a request for additional funding was submitted to allow completion of the trial. The DMEC undertook a futility analysis (*Appendix 2*). This showed that the conditional power for the primary outcome recalculated

using data to May 2009 was >99.9% and the conditional power against major cardiac events was <10%. In the light of this analysis, the trial funder declined the request for additional funding, based on clear efficacy (primary outcome) and futility (major cardiac events), and, consequently, trial recruitment was terminated on 2 June 2009, with a total of 2263 patients recruited. The findings reported here represent those as accrued at the point at which this decision to halt the trial was taken.

Chapter 3

Results

Screening, recruitment, randomisation and follow-up

Patients were recruited between 30 January 2008 and 2 June 2009. *Table 4* summarises the process of screening and recruitment at each centre. All hospitals stopped recruitment on 2 June 2009 but the staggered start meant that some recruited for more days than others. Overall, 2263 patients were recruited over a total of 2658 hospital-days (0.9 patients per day). The total at each site ranged from 327 to 469, and the recruitment rate ranged from 0.7 to 1.1 per day.

TABLE 4 Screening and recruitment

	All centres	Barnsley	Derriford	Edinburgh	Frenchay	Leeds	Leicester
Recruitment							
No. of days recruiting	2658	490	464	427	429	413	435
No. of patients recruited	2263	327	328	457	469	353	329
No. of patients recruited/day	0.9	0.7	0.7	1.1	1.1	0.9	0.8
Screening^a							
No. of days screening	667	124	135	106	102	92	108
No. of patients screened	9109	1164	1632	1769	662	1760	2122
No. of patients screened/day	13.7	9.4	12.1	16.7	6.5	19.1	19.6
No. (%) of patients recruited	604 (7)	83 (7)	93 (6)	123 (7)	111 (17)	90 (5)	104 (5)
No. (%) of patients not recruited	8505 (93)	1081 (93)	1539 (94)	1646 (93)	551 (83)	1670 (95)	2018 (95)
Reason for non-recruitment [n, (%)]							
Diagnostic ECG changes	1295 (14)	74 (6)	153 (9)	221 (12)	137 (21)	401 (23)	309 (15)
Known CHD with prolonged/ recurrent episodes	1378 (15)	232 (20)	456 (28)	271 (15)	58 (9)	150 (9)	211 (10)
Proven/suspected serious non- coronary pathology	724 (8)	54 (5)	186 (11)	60 (3)	37 (6)	219 (12)	168 (8)
Comorbidity or social problems requiring admission	414 (5)	9 (<1)	70 (4)	223 (13)	5 (<1)	70 (4)	37 (2)
Obvious non-cardiac	2506 (28)	407 (35)	369 (23)	488 (28)	210 (32)	431 (24)	601 (28)
Presented > 12 hours after most significant pain	465 (5)	13 (1)	45 (3)	182 (10)	10 (2)	53 (3)	162 (8)
Previous participant	21 (<1)	1 (<1)	3 (<1)	3 (<1)	2 (<1)	8 (<1)	4 (<1)
Unable to understand trial information	109 (1)	16 (1)	23 (1)	26 (1)	9 (1)	3 (<1)	32 (2)
Non-English speaking	29 (<1)	2 (<1)	7 (<1)	7 (<1)	4 (<1)	0	9 (<1)
Refused consent	40 (<1)	2 (<1)	4 (<1)	8 (<1)	1 (<1)	8 (<1)	17 (<1)
Eligible but recruitment not sought	1115 (12)	265 (23)	171 (10)	60 (3)	37 (6)	148 (8)	434 (20)
Prisoner	8 (<1)	0	1 (<1)	2 (<1)	0	4 (<1)	1 (<1)
Other	161 (2)	6 (<1)	14 (<1)	29 (2)	20 (3)	60 (3)	32 (2)
Unknown	240 (3)	0	37 (2)	66 (4)	21 (3)	115 (7)	1 (<1)

a Screening was undertaken only on every fourth week of the trial.

Research nurses screened 9109 chest pain attendances on a total of 667 hospital-days during the trial (13.7 patients per hospital per day). Overall, 1719/9109 (19%) were eligible for recruitment (2.6 per hospital per day), of whom 604/1719 (35%) were recruited. The proportion of eligible patients recruited varied across the sites from 19% to 75%.

The proportions excluded for each exclusion criterion were as follows: 14% had ECG changes, 15% had known CHD with prolonged or recurrent pain, 8% had suspected serious non-CHD pathology, 5% had comorbidities or social problems, 28% had obvious non-cardiac pain, 5% presented > 12 hours since their worst pain, < 1% had previously participated in the trial, 2% were unable to understand the trial information owing to cognitive impairment or being non-English speaking, 2% had other exclusion criteria, 3% had an unknown reason for exclusion and < 1% declined consent. These proportions varied across the sites. We were unable to verify whether this was due to differences in coding and classification, or differences in population characteristics.

Figure 2 shows the flow of patients through the trial after recruitment and Table 5 shows withdrawals and losses to follow-up. We intended to follow up patients who were recruited in error, provided they did not withdraw their consent, so that all consented patients could be analysed as randomised. However, six patients (three in each group) were not followed up after being recruited in error for specific reasons necessitating their exclusion (prisoners, who were defined as 'vulnerable groups', $n = 3$; clinician error, $n = 2$; and recruitment when the trial was suspended, $n = 1$). In the point-of-care group seven patients withdrew or were lost to follow-up before any outcomes were recorded, and a further 18 withdrew or were lost to follow-up by the end of the trial. These numbers were 13 and 10, respectively, in the standard-care group. Questionnaire response rates were slightly higher in the point-of-care group: 75% at 30 days and 69% at 90 days, as opposed to 71% and 66%, respectively, for the standard-care group.

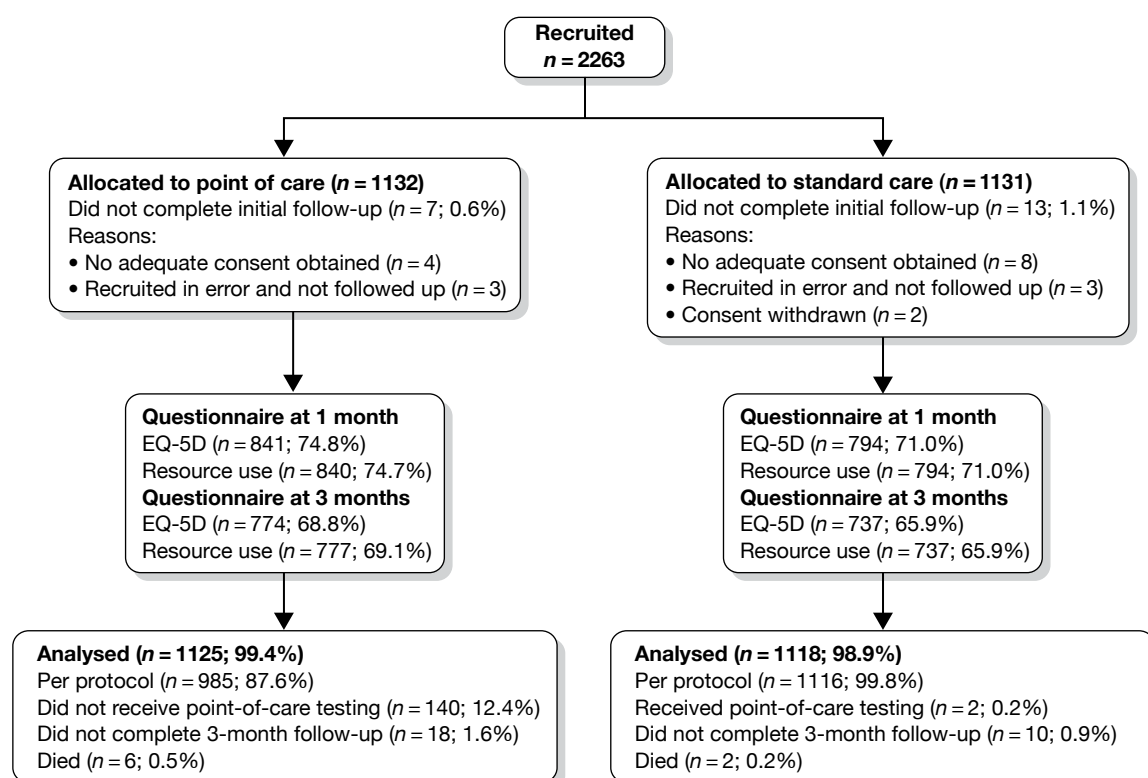


FIGURE 2 CONSORT chart showing flow of patients after recruitment.

TABLE 5 Analysis sets and study completion (all randomised patients)

	PoC (n= 1132)	SC (n= 1131)	Total (n= 2263)
Analysis population [n (%)]			
Full analysis set	1125 (99)	1118 (99)	2243 (99)
Failed to complete initial follow-up [n (%)]			
No adequate consent obtained	4 (< 1)	8 (1)	12 (1)
Withdrew consent before 4 hours	0	2 (< 1)	2 (< 1)
Recruited in error and not followed up	3 (< 1)	3 (< 1)	6 (< 1)
Failed to complete 3-month follow-up ^a	18 (2)	10 (1)	28 (1)
Incomplete questionnaire data^b [n (%)]			
No EQ-5D questionnaire at 1 month	284 (25.2)	324 (29.0)	608 (27.1)
No EQ-5D questionnaire at 3 months	351 (31.2)	381 (34.1)	732 (32.6)
No resource use questionnaire at 1 month	285 (25.3)	324 (29.0)	609 (27.2)
No resource use questionnaire at 3 months	348 (30.9)	381 (34.1)	729 (32.5)
No patient resource use questionnaires	284 (25.2)	322 (28.8)	606 (27.0)

PoC, point of care; SC, standard care.

a No details recorded for at least one major adverse event.

b Denominator is patients in the full analysis set.

Research nurses checked whether patients had been appropriately recruited and the results are shown in *Table 6*. In addition to the six patients who were randomised in error and not followed up (reported above), a total of 23 patients (1%) were inappropriately recruited: 12 in the point-of-care group and 11 in the standard-care group. These cases were followed up and analysed as planned on an intention-to-treat basis.

Protocol violations

Some 140 patients (12.4%) in the point-of-care group did not receive testing as recommended in the protocol, i.e. two panels consisting of CK-MB (mass), myoglobin and troponin (or one panel if the first troponin was positive). Of these, 34 did not receive any point-of-care testing at all, typically because of machine failure or inability to use the machine, while the remainder had fewer tests than recommended in the protocol. Two patients (0.2%) in the standard-care group received point-of-care testing.

Baseline characteristics, emergency department findings and diagnosis

Table 7 shows the characteristics and demographics of the recruited patients. The characteristics were as anticipated, with a mean age of 54.5 years, more men than women, and 12% with a past history of CHD.

Table 8 shows the presenting characteristics of the patients. The median duration between the onset of worst pain and arrival at hospital was just over 2 hours, excluding the 1% who suffered their worst pain after hospital arrival. There were no marked differences between the study groups in the nature or duration of pain, or the associated features.

TABLE 6 Inappropriate recruitment

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)
Number inappropriately randomised [<i>n</i> (%)]	12 (1)	11 (1)	23 (1)
Reason [<i>n</i> (%)]			
Diagnostic ECG changes	2 (<1)	0	2 (<1)
Known CHD with prolonged/recurrent episodes	3 (<1)	5 (<1)	8 (<1)
Proven/suspected serious non-coronary pathology	1 (<1)	1 (<1)	2 (<1)
Comorbidity or social problems requiring admission	0	1 (<1)	1 (<1)
Obvious non-cardiac	2 (<1)	1 (<1)	3 (<1)
Presented > 12 hours after most significant pain	1 (<1)	2 (<1)	3 (<1)
Other	3 (<1)	1 (<1)	4 (<1)

PoC, point of care; SC, standard care.

TABLE 7 Patient demographics and characteristics

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)
Age (years)			
<i>n</i>	1125	1118	2243
Mean (SD)	54.5 (13.8)	54.6 (14.4)	54.5 (14.1)
Median (IQR)	53.4 (44–64)	53.1 (44–64)	53.2 (44–64)
Minimum, maximum	22, 93	23, 96	22, 96
Gender [<i>n</i> (%)]			
Male	683 (61)	624 (56)	1307 (58)
Female	442 (39)	494 (44)	936 (42)
Centre [<i>n</i> (%)]			
Barnsley	162 (14)	164 (15)	326 (15)
Derriford	164 (15)	164 (15)	328 (15)
Edinburgh	228 (20)	224 (20)	452 (20)
Frenchay	233 (21)	231 (21)	464 (21)
Leeds	173 (15)	171 (15)	344 (15)
Leicester	165 (15)	164 (15)	329 (15)
Past history of CHD [<i>n</i> (%)]			
<i>n</i>	1117	1110	2227
No	985 (88)	973 (88)	1958 (88)
Yes	132 (12)	137 (12)	269 (12)
Previous MI	60 (5)	65 (6)	125 (6)
Angina with positive diagnostic test	46 (4)	53 (5)	99 (4)
Previous CABG	12 (1)	15 (1)	27 (1)
Previous angioplasty	37 (3)	34 (3)	71 (3)
Stenosis > 50% on angiography	14 (1)	12 (1)	26 (1)
Unproven clinical label of CHD	36 (3)	31 (3)	67 (3)
Other	12 (1)	10 (1)	22 (1)

TABLE 7 Patient demographics and characteristics (*continued*)

	PoC (n= 1125)	SC (n= 1118)	Total (n= 2243)
Risk factors [n (%)]			
Diabetes	86 (8)	92 (8)	178 (8)
Hypertension	376 (34)	361 (33)	737 (33)
Hyperlipidaemia	271 (26)	282 (27)	553 (27)
Present smoker	310 (28)	316 (29)	626 (28)
Ex-smoker – last 10 years	144 (13)	129 (12)	273 (13)
Cocaine abuse	6 (1)	10 (1)	16 (1)
First-degree relative with angina/MI, onset age <60 years	344 (33)	352 (34)	696 (33)
Use of aspirin in previous 7 days	207 (19)	215 (20)	422 (19)
> One episode rest angina in <24 hours	75 (7)	74 (7)	149 (7)
Source of referral [n (%)]			
n	1123	1115	2238
Referred by GP	188 (17)	189 (17)	377 (17)
Called emergency ambulance	481 (43)	510 (46)	991 (44)
Self-referred	419 (37)	375 (34)	794 (35)
Other	35 (3)	41 (4)	76 (3)

IQR, interquartile range; PoC, point of care; SC, standard care.

TABLE 8 Pain at presentation

	PoC (n= 1125)	SC (n= 1118)	Total (n= 2243)
Worst pain onset [n (%)]			
n	1115	1103	2218
Before attendance	1102 (99)	1090 (99)	2192 (99)
After attendance	13 (1)	13 (1)	26 (1)
Duration between onset of worst pain and arrival at hospital (minutes)^a			
n	1102	1090	2192
Mean (SD)	241.3 (503.9)	218.9 (325.1)	230.2 (424.6)
Median (IQR)	129.5 (79–240)	128.5 (80–256)	129.0 (80–246)
Duration of longest episode of worst pain (minutes)			
n	1083	1062	2145
Mean (SD)	97.1 (133.3)	98.7 (127.2)	97.9 (130.3)
Median (IQR)	60.0 (20–120)	50.0 (20–120)	50.0 (20–120)
Type of pain [n (%)]			
n	1098	1081	2179
Continuous	815 (74)	848 (78)	1663 (76)
Intermittent	283 (26)	233 (22)	516 (24)
n	1034	1018	2052
Single episode	672 (65)	695 (68)	1367 (67)
Multiple episodes	362 (35)	323 (32)	685 (33)

continued

TABLE 8 Pain at presentation (*continued*)

	PoC (<i>n</i> =1125)	SC (<i>n</i> =1118)	Total (<i>n</i> =2243)
Main chest pain [n (%)]			
<i>n</i>	1114	1099	2213
Indigestion/burning (<i>n</i> , %)	81 (7)	73 (7)	154 (7)
Stabbing/sharp (<i>n</i> , %)	219 (20)	240 (22)	459 (21)
Aching/dull (<i>n</i> , %)	273 (25)	294 (27)	567 (26)
Gripping/crushing/heavy (<i>n</i> , %)	416 (37)	378 (34)	794 (36)
Non-specific/other (<i>n</i> , %)	125 (11)	114 (10)	239 (11)
Main site [n (%)]			
<i>n</i>	1124	1114	2238
Central (<i>n</i> , %)	743 (66)	721 (65)	1464 (65)
Left chest (<i>n</i> , %)	285 (25)	288 (26)	573 (26)
Right chest (<i>n</i> , %)	24 (2)	26 (2)	50 (2)
Upper abdomen/epigastrium (<i>n</i> , %)	47 (4)	49 (4)	96 (4)
Other (<i>n</i> , %)	25 (2)	30 (3)	55 (2)
Radiation^b [n (%)]			
None	481 (43)	466 (42)	947 (43)
Left arm	365 (33)	384 (35)	749 (34)
Right arm	97 (9)	99 (9)	196 (9)
Neck	141 (13)	150 (14)	291 (13)
Jaw	71 (6)	97 (9)	168 (8)
Back	179 (16)	159 (14)	338 (15)
Other	97 (9)	90 (8)	187 (8)
Associated features^b [n (%)]			
Nausea	362 (33)	374 (34)	736 (34)
Vomiting	62 (6)	67 (6)	129 (6)
Dyspnoea	492 (45)	487 (44)	979 (45)
Sweating	503 (46)	470 (43)	973 (44)
Dyspepsia	83 (8)	67 (6)	150 (7)
Other	161 (15)	181 (17)	342 (16)

PoC, point of care; SC, standard care.

a Patients with worst pain prior to arrival.

b All that apply.

Table 9 shows the initial ECG and examination findings. A small proportion of patients had ST-segment deviations or T-wave inversions, although these were not deemed to be characteristic of myocardial ischaemia by the research nurse or recruiting doctor.

Table 10 shows the events in the ED, working diagnosis after initial assessment, the next-day ECG findings and final diagnosis. The proportions in each category differed between the final and initial diagnosis in both groups. More patients had a non-specific or other final diagnosis, and fewer had a final diagnosis of angina or ACS.

TABLE 9 Examinations in ED

	PoC (n= 1125)	SC (n= 1118)	Total (n= 2243)
First ECG in ED [n (%)]			
Normal	765 (68)	779 (70)	1544 (69)
T-wave inversion	79 (7)	74 (7)	153 (7)
ST depression	17 (2)	18 (2)	35 (2)
ST elevation	8 (1)	8 (1)	16 (1)
Bundle branch block	24 (2)	30 (3)	54 (2)
Other	205 (18)	179 (16)	384 (17)
Unknown/missing	27 (2)	30 (3)	55 (2)
Pulse (bpm)^a			
n	1120	1118	2238
Mean (SD)	76.6 (15.2)	76.2 (15.0)	76.4 (15.1)
Median (IQR)	75.0 (66–85)	75.0 (65–86)	75.0 (65–85)
Diastolic blood pressure (mmHg)			
n	1117	1116	2233
Mean (SD)	80.3 (14.0)	80.1 (14.7)	80.2 (14.3)
Median (IQR)	80.0 (71–90)	80.0 (70–90)	80.0 (71–90)
Systolic blood pressure (mmHg)			
n	1117	1117	2234
Mean (SD)	140.0 (22.9)	140.8 (22.5)	140.4 (22.7)
Median (IQR)	138.0 (124–154)	138.0 (125–155)	138.0 (125–154)
Killip class [n (%)]			
Class I	1020 (91)	1020 (91)	2040 (91)
Class II	8 (1)	5 (<1)	13 (1)
Class III	0	0	0
Class IV	1 (<1)	0	1 (<1)
Missing	96 (9)	93 (8)	189 (8)

bpm, beats per minute; PoC, point of care; SC, standard care.

a First reading taken in ED.

Blood testing

Table 11 shows the number and proportion of the point-of-care group who received each test, the number and proportion with a positive test, and the mean (median) time from worst symptoms to sampling. Most positive cases arose from the first troponin sample, although about one-quarter arose from the second sample.

Table 12 shows the number and proportion of patients in each study group receiving each laboratory blood test. Although most patients in the point-of-care group had negative point-of-care tests, a substantial proportion went on to have laboratory testing with troponin I or T. In the standard-care group around 90% received laboratory testing with troponin I or T. Other cardiac biomarkers were rarely used.

TABLE 10 Events in ED and clinical diagnoses

	PoC (n= 1125)	SC (n= 1118)	Total (n= 2243)
Events in ED^a [n (%)]			
Cardiac arrhythmia	8 (1)	8 (1)	16 (1)
Further pain requiring treatment	106 (11)	101 (10)	207 (11)
New ECG changes	8 (1)	21 (2)	29 (1)
Other symptoms requiring admission	26 (3)	20 (2)	46 (2)
Other events	35 (4)	26 (3)	61 (3)
Working diagnosis after initial assessment [n (%)]			
Non-specific	233 (21)	219 (20)	452 (20)
Anxiety	51 (5)	49 (4)	100 (4)
Angina no ACS	173 (15)	178 (16)	351 (16)
ACS	334 (30)	332 (30)	666 (30)
Gastro-oesophageal	117 (10)	115 (10)	232 (10)
Musculoskeletal	108 (10)	102 (9)	210 (9)
Other	86 (8)	93 (8)	179 (8)
Unknown/missing	23 (2)	30 (3)	53 (2)
Next-day ECG [n (%)]			
Normal	162 (14)	199 (18)	361 (16)
T-wave inversion	31 (3)	23 (2)	54 (2)
ST depression	1 (<1)	2 (<1)	3 (<1)
ST elevation	5 (<1)	3 (<1)	8 (<1)
Bundle branch block	6 (1)	8 (1)	14 (1)
Other abnormality	46 (4)	65 (6)	111 (5)
Not applicable	633 (56)	432 (39)	1065 (47)
Unknown/missing	35 (3)	66 (6)	101 (5)
Final diagnosis [n (%)]			
Non-specific	366 (33)	336 (30)	702 (31)
Anxiety	36 (3)	23 (2)	59 (3)
Angina no ACS	89 (8)	63 (6)	152 (7)
ACS	87 (8)	72 (6)	159 (7)
Gastro-oesophageal	126 (11)	136 (12)	262 (12)
Musculoskeletal	143 (13)	169 (15)	312 (14)
Other	215 (19)	252 (23)	467 (21)
Unknown/missing	63 (6)	67 (6)	130 (6)

PoC, point of care; SC, standard care.

a All that apply.

Primary efficacy

Table 13 shows the results for the primary outcome, i.e. successful discharge home. This was defined as having left the hospital or as a decision to discharge made 4 hours after initial presentation, and no adverse event over the following 3 months. Some 509 patients were defined as discharged at initial presentation: 453 had left the hospital by 4 hours and 56 had a decision to discharge. However, five of these patients had a major adverse event over the following 3 months, so 504 were defined as being successfully discharged home.

TABLE 11 Use and results of point-of-care tests

	Sample 1	Sample 2
<i>n</i> (%) with troponin result	1076 (95.6)	842 (74.8)
<i>n</i> (%) with troponin > 0.02 µg/l	272 (25.5)	150 (17.8)
<i>n</i> (%) with troponin > 0.07 µg/l	113 (10.5)	28 (3.3)
<i>n</i> (%) with myoglobin result	1078 (95.6)	840 (74.7)
<i>n</i> (%) with myoglobin gradient > 25%	—	67 (6.2)
<i>n</i> (%) with CK-MB (mass) result	1076 (95.6)	841 (74.8)
<i>n</i> (%) with both CK-MB (mass) result > 5 µg/l	—	17 (2.0)
<i>n</i> (%) with CK-MB (mass) gradient > 1.6 µg/l	—	2 (0.2)
Mean (median) time from worst symptoms to test (hours)	6.6 (4.1)	7.6 (5.7)

TABLE 12 Use of laboratory blood tests

	PoC	SC
<i>n</i> (%) with at least one laboratory troponin (I or T)	661 (58.8)	992 (88.7)
<i>n</i> (%) with at least one laboratory CK	177 (15.7)	155 (13.9)
<i>n</i> (%) with at least one laboratory CK-MB (mass)	1 (< 1)	1 (< 1)
<i>n</i> (%) with at least one LDH	1 (< 1)	0
<i>n</i> (%) with at least one laboratory myoglobin	9 (< 1)	9 (< 1)

LDH, laboratory lactate dehydrogenase; PoC, point of care; SC, standard care.

TABLE 13 Successful discharge home (primary outcome)

	PoC [<i>n</i> (%)]	SC [<i>n</i> (%)]	Total [<i>n</i> (%)]
Successfully discharged	358 (32)	146 (13)	504 (22)
Not successfully discharged	767 (68)	972 (87)	1739 (78)
Reason for no successful discharge			
In hospital 4 hours after arrival and no decision has been made to discharge	763 (68)	971 (87)	1734 (77)
Initially discharged but re-attended with major adverse event	4 (< 1)	1 (< 1)	5 (< 1)
Discharge success by initial status			
Initially discharged	362 (32)	147 (13)	509 (23)
Not in hospital at 4 hours	319 (28)	134 (12)	453 (20)
In hospital at 4 hours; decision made to discharge	43 (4)	13 (1)	56 (2)

PoC, point of care; SC, standard care.

The primary efficacy analyses were adjusted, as planned, for hospital, age, gender and known CHD. Patients in the point-of-care group were significantly more likely to be successfully discharged home (OR = 3.81, 95% CI 3.01 to 4.82, $p < 0.001$).

Variation between sites

Table 14 shows the results for each individual hospital. Full details are supplied in Appendix 3. There was marked variation in the primary outcome across the six hospitals. Point-of-care panel

TABLE 14 Primary outcome by study centre

	PoC [n (%)]	SC [n (%)]	OR ^a (95% CI)	RD ^b (95% CI)	p-value
Overall	358/1125 (32)	146/1118 (13)	3.81 (3.01 to 4.82)	18.7 (15.4 to 22.1)	<0.001
Barnsley	110/162 (68)	43/164 (26)	6.97 (4.18 to 11.63)	41.3 (31.4 to 51.1)	<0.001
Derriford	43/164 (26)	21/164 (13)	2.48 (1.37 to 4.49)	13.4 (5.0 to 21.9)	0.003
Edinburgh	104/228 (46)	16/224 (7)	11.07 (6.23 to 19.66)	38.4 (31.1 to 45.6)	<0.001
Frenchay	50/233 (21)	9/231 (4)	7.03 (3.35 to 14.75)	17.4 (11.6 to 23.2)	<0.001
Leeds	1/173 (1)	8/171 (5)	0.12 (0.01 to 1.03)	-4.0 (-7.2 to -0.7)	0.054
Leicester	50/165 (30)	49/164 (30)	1.11 (0.66 to 1.84)	0.4 (-9.5 to 10.3)	0.699

PoC, point of care; RD, risk difference; SC, standard care.

a Adjusted for age, gender and known CHD. Overall result is also adjusted for centre. The p-value corresponds to adjusted OR.

b Absolute risk difference.

assessment was associated with substantial increases in successful discharge rates at Barnsley and Edinburgh, modest increases at Derriford and Frenchay, and no increase at Leeds or Leicester.

Figure 3 shows how the proportion of patients in hospital varies with time from arrival and Figure 4 shows this for each individual hospital. Overall, point-of-care panel assessment is associated with fewer patients being in hospital between 4 and 24 hours after arrival. However, there was again variation between the hospitals. Point-of-care panel assessment was associated with markedly fewer patients being in hospital up to 24 hours at Barnsley and Edinburgh. At Derriford the difference in proportion in hospital was apparent only between 4 and 8 hours. At Frenchay the difference was marked up to 12 hours, but after 12 hours the proportion of patients in hospital was greater in the point-of-care group. At Leeds the difference between the groups did not emerge until 6 hours after attendance, but between 6 and 24 hours point-of-care panel assessment was associated with markedly fewer patients being in hospital. Finally, at Leicester there was no difference in the proportions in hospital up to 12 hours and only slightly fewer patients in hospital in the point-of-care group from 12 to 36 hours.

These differences probably reflect differences in standard care practice or the facilities for patients with chest pain at the hospitals. Standard care at Derriford was based on a troponin level measured 6 hours after arrival in hospital. This explains why the effect of point-of-care panel assessment at Derriford was limited to the 4- to 8-hour window. At Leeds all patients with chest pain are admitted to a clinical decision unit where diagnosis and management are undertaken without the pressure of the 4-hour target. This probably explains why the effect of point-of-care panel assessment was delayed at Leeds until 6 hours after arrival. At Leicester the point-of-care tests did not seem to alter decision-making with regards to hospital admission.

Per-protocol analysis

Table 15 shows the results of per-protocol analysis, with the 140 point-of-care patients who did not receive testing according to the protocol and the two standard-care patients who received point-of-care testing excluded. Exclusion of these patients does not markedly change the proportions in each group who are successfully discharged.

Variation over time

We analysed the primary outcome by each quarter-year to determine if the proportion successfully discharged varied over time due to clinical staff becoming more familiar with the intervention or changing management in the standard-care group. We also analysed the proportion of patients in the point-of-care group who did not receive testing according to

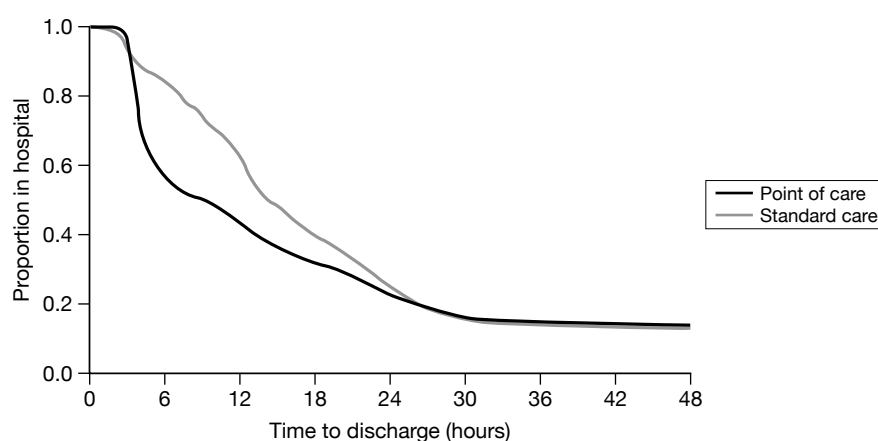


FIGURE 3 Duration from arrival to discharge from hospital (all centres).

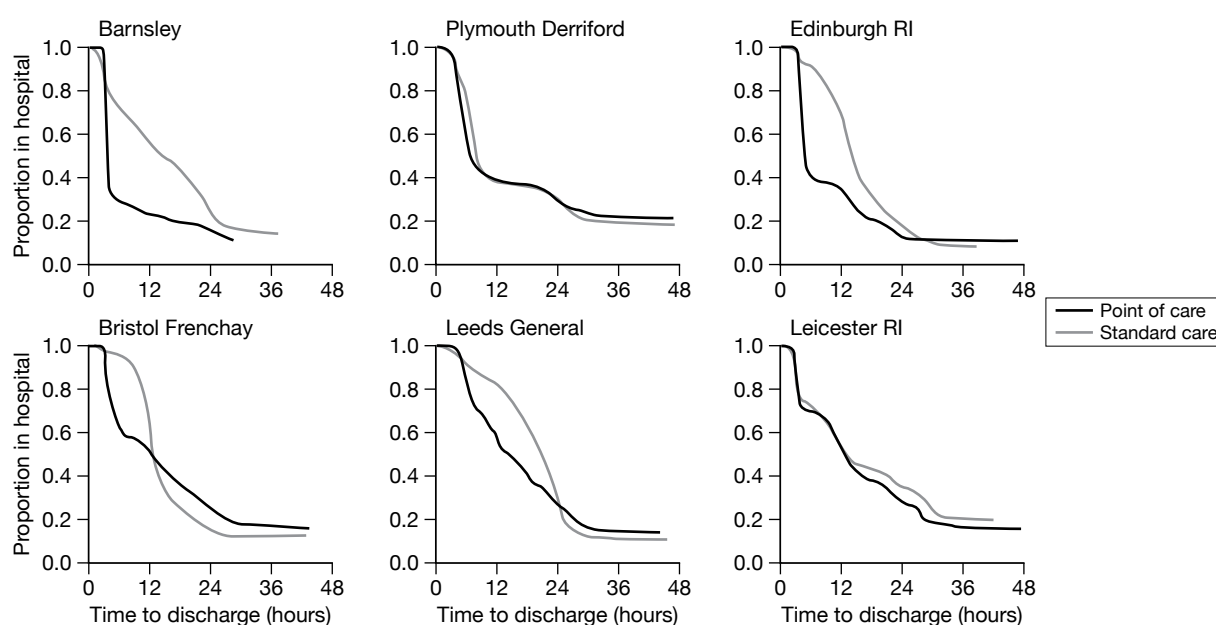


FIGURE 4 Duration from arrival to discharge from hospital (individual centres).

the recommended protocol to determine whether increased familiarity over time led to fewer protocol deviations. The results are outlined in *Table 16*. The proportion successfully discharged in the point-of-care group appears to dip in the middle of the trial and then rise again at the end, whereas the proportion successfully discharged in the standard-care group appears to progressively fall throughout the trial. The proportion of patients in the point-of-care group who did not receive testing according to the recommended protocol remained relatively constant.

We compared the primary efficacy analysis before and after the amendment to the troponin threshold in the point-of-care protocol. Before the amendment the proportion successfully discharged in the point-of-care group was 210/729 (29%) compared with 107/721 (15%) in the standard-care group (adjusted OR = 2.79, 95% CI 2.09 to 3.72). After the amendment the proportion successfully discharged in the point-of-care group was 148/396 (37%) compared with 39/397 (10%) in the standard-care group (adjusted OR = 5.61, 95% CI 3.79 to 8.31, $p < 0.001$). Hence, it appeared that the effect of point-of-care panel assessment increased after amendment of

TABLE 15 Primary outcome: per-protocol analysis

	PoC [n (%)]	SC [n (%)]	Total [n (%)]
Successfully discharged	326 (33)	145 (13)	471 (22)
Not successfully discharged	659 (67)	971 (87)	1630 (78)
Reason for no successful discharge			
In hospital 4 hours after arrival and no decision has been made to discharge	655 (66)	970 (87)	1625 (77)
Initially discharged but re-attended with major adverse event	4 (<1)	1 (<1)	5 (<1)
Discharge success by initial status			
Initially discharged	330 (34)	146 (13)	476 (23)
Not in hospital at 4 hours	292 (30)	133 (12)	425 (20)
In hospital at 4 hours, decision made to discharge	38 (4)	13 (1)	51 (2)

PoC, point of care; SC, standard care.

TABLE 16 Primary outcome and point-of-care protocol deviations: by quarter

Quarter	PoC protocol deviations [n (%)]	PoC successfully discharged [n (%)]	SC successfully discharged [n (%)]
January to March 2008	3/34 (9)	13/34 (38)	10/33 (30)
April to June 2008	41/286 (14)	93/286 (33)	42/286 (15)
July to September 2008	33/199 (17)	57/199 (29)	30/195 (15)
October to December 2008	24/239 (10)	64/239 (27)	27/235 (11)
January to March 2009	22/195 (10)	77/195 (35)	24/222 (11)
April to June 2009	17/150 (11)	54/150 (36)	13/147 (9)

PoC, point of care; SC, standard care.

the protocol, although some of this may be attributable to a lower successful discharge rate in the standard-care group.

Secondary efficacy

Length and location of hospital stay

The mean length of the initial hospital stay was 29.6 hours in the point-of-care group and 31.8 hours in the standard-care group [mean difference = 2.1 hours, 95% CI -3.7 to 8.0 hours, $p = 0.462$ (t -test)]. The median length of initial hospital stay was markedly shorter for both groups, reflecting the positively skewed nature of length-of-stay data: 8.8 hours for the point-of-care group and 14.2 hours for the standard-care group ($p < 0.001$, equality-of-medians test). The two groups had significantly different distributions of length of stay ($p < 0.001$, Mann-Whitney U -test). Point-of-care panel assessment was therefore associated with reduced probability of hospital admission and shorter median length of stay, but there was no significant difference in mean length of stay.

Table 17 shows the total number of days spent in hospital over the 3-month follow-up and the number of days spent in coronary care or intensive care, including the initial hospital admission. We did not record fractions of days spent in hospital for this analysis and recorded an inpatient day only if the patient stayed overnight. Hence, a proportion of patients were recorded as having no inpatient days if their initial hospital visit did not result in an overnight stay and they were not admitted on a subsequent occasion. More patients in the point-of-care group had no inpatient days recorded during follow-up (54% vs 40%, $p < 0.001$). This reflected the difference in the proportion of patients in Figure 5 who were no longer in hospital 12 hours after attendance, as patients who are discharged before 12 hours and are not re-admitted are likely to be recorded as having no inpatient days over follow-up.

Despite this difference in the proportion with no inpatient days, there was no difference in the mean days per patient or the total inpatient days in the two groups. Figure 5 compares histograms for total days spent in hospital in the two groups to show why this was. The difference between the two groups in the proportions of patients having no inpatient stay was reflected in the difference in proportions having one inpatient day. So point-of-care panel assessment saved one inpatient day in about 14%. However, a few patients in both groups had a very high number of inpatient days (over 30). There were a few more of these in the point-of-care group, and enough to contribute disproportionately to the mean and total inpatient days for the group. Hence, point-of-care panel assessment reduced the proportion of patients completely avoiding admission but did not reduce overall inpatient days. Point-of-care panel assessment was also associated with a higher use of coronary care over follow-up (4% vs 3%, $p = 0.041$), although only a small minority of patients received any coronary care or intensive care.

TABLE 17 Inpatient care at 3 months

	PoC (n = 1125)	SC (n = 1118)	Total (n = 2243)	Percentage difference (95% CI)	p-value
Days in hospital at any location					
n (%) with at least one day	518 (46.0)	670 (59.9)	1188 (53.0)	-13.9 (-18.0 to -9.8)	<0.001
Mean days per patient	1.8	1.7	1.7		0.815
Total days (all patients)	1961	1908	3869		
Days in coronary care					
n (%) with at least one day	50 (4.4)	31 (2.8)	81 (3.6)	1.7 (0.1 to 3.2)	0.041
Mean days per patient	0.17	0.09	0.13		0.033
Total days (all patients)	190	105	295		
Days in intensive care					
n (%) with at least one day	8 (<1)	3 (<1)	11 (<1)	0.4 (-0.2 to 1.0)	0.225
Mean days per patient	0.08	0.01	0.04		0.259
Total days (all patients)	76	14	90		

PoC, point of care; SC, standard care.

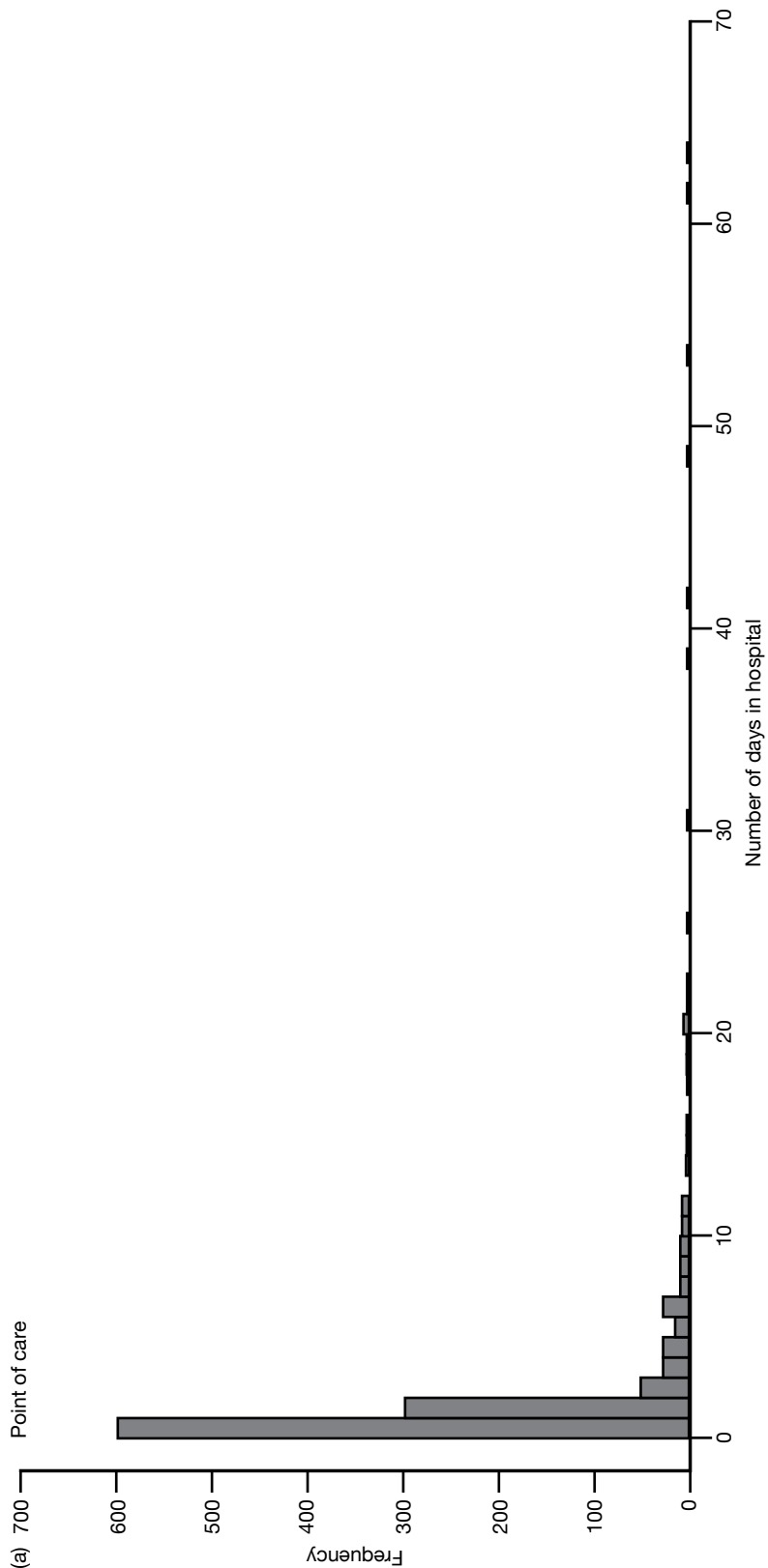


FIGURE 5 Histograms of number of inpatient days.

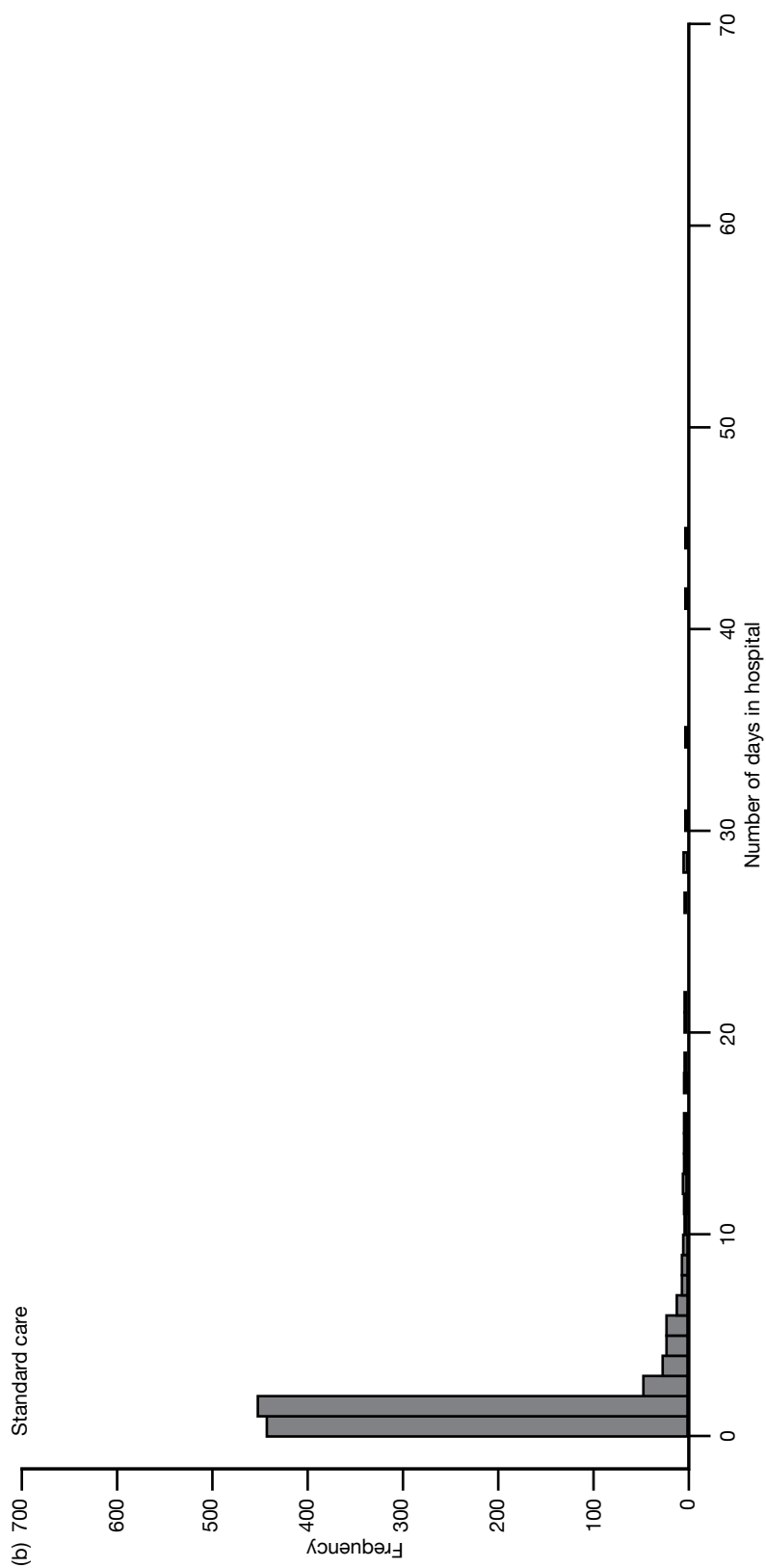


FIGURE 5 Histograms of number of inpatient days. (continued)

Initial care in the first 24 hours

Table 18 shows the proportion of patients in each group receiving various elements of care in the first 24 hours after arrival. Only a small proportion in each group was admitted from the ED on to coronary care, but twice as many were admitted to coronary care in the point-of-care group (4% vs 2%, $p=0.001$). There were no significant differences between point-of-care and standard care in the proportions receiving glyceryl trinitrate (GTN), heparin, glycoprotein inhibitors, antacids or beta-blockers. More patients in the point-of-care group received clopidogrel (21% vs 16%, $p=0.002$), while more patients in the standard-care group received aspirin (60% vs 55%, $p=0.031$). There were non-significant trends towards greater use of angiography and PCI in the point-of-care group and greater use of analgesia in the standard-care group.

Interventions, re-attendances, re-admissions, investigations and outpatient reviews up to 3 months

Table 19 shows the proportion of patients receiving cardiac interventions in each study group over the 3-month follow-up period, including during the initial hospital admission. Very few patients received cardiac interventions and there were no significant differences between the study groups.

Table 20 shows the proportion of patients in each group with any ED attendance, the proportion with a potentially chest pain-related attendance, the proportion with any subsequent hospital admission (i.e. any admission other than that arising from their initial visit) and the proportion with a potentially chest pain-related hospital admission over the follow-up 3 months. There were no significant differences between the two groups in any of these outcomes.

Table 21 shows the proportion of patients in each group receiving each investigation over the 3-month follow-up. Most patients did not receive any of these investigations. There were no differences between the two groups in the proportions receiving any of the investigations.

Table 22 shows the proportion of patients in each group who received outpatient follow-up (any or potentially chest pain related). Patients in the point-of-care group were slightly more likely to have a chest pain-related outpatient review (21% vs 18%, $p=0.05$).

TABLE 18 Initial care in the first 24 hours

	PoC ($n=1125$) [n (%)]	SC ($n=1118$) [n (%)]	Total ($n=2243$) [n (%)]	p -value
Admitted to coronary care	50 (4)	21 (2)	71 (3)	0.001
Received GTN	446 (40)	460 (42)	906 (41)	0.327
Received heparin	206 (18)	186 (17)	392 (18)	0.381
Received glycoprotein inhibitors	8 (1)	7 (1)	15 (1)	0.822
Received antacid	90 (8)	108 (10)	198 (9)	0.128
Received angiography	16 (1)	8 (1)	24 (1)	0.105
Received aspirin	618 (55)	663 (60)	1281 (58)	0.031
Received beta-blocker	108 (10)	105 (10)	213 (10)	0.967
Received clopidogrel	237 (21)	176 (16)	413 (19)	0.002
Received analgesic	373 (34)	407 (37)	780 (36)	0.058
Received any other drugs	316 (29)	340 (31)	656 (30)	0.150
Received angioplasty/stent	11 (1)	4 (<1)	15 (1)	0.073

PoC, point of care; SC, standard care.

TABLE 19 Cardiac interventions at 3 months

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)	<i>p</i> -value
<i>n</i> (%) needing thrombolysis	1 (<1)	2 (<1)	3 (<1)	0.624
<i>n</i> (%) needing PCI	29 (3)	29 (3)	58 (3)	1.000
<i>n</i> (%) needing emergency PCI	7 (1)	12 (1)	19 (1)	0.260
<i>n</i> (%) needing CABG	11 (1)	5 (<1)	16 (1)	0.209

PoC, point of care; SC, standard care.

TABLE 20 Re-attendances at ED and hospital at 3 months

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)	<i>p</i> -value
<i>n</i> (%) of ED attendances	140 (12)	138 (12)	278 (12)	0.949
<i>n</i> (%) of chest pain-related ED attendances	107 (10)	103 (9)	210 (9)	0.828
<i>n</i> (%) of subsequent hospital admissions	117 (10)	122 (11)	239 (11)	0.732
<i>n</i> (%) of subsequent chest pain-related admissions	84 (7)	99 (9)	183 (8)	0.247

PoC, point of care; SC, standard care.

TABLE 21 Investigations at 3 months

	PoC (<i>n</i> = 1125) [<i>n</i> (%)]	SC (<i>n</i> = 1118) [<i>n</i> (%)]	<i>p</i> -value
Exercise treadmill test	231 (20.5)	226 (20.2)	0.893
Echocardiography	73 (6.5)	60 (5.4)	0.300
Radionuclide scan	36 (3.2)	33 (3.0)	0.827
24-hour tape	12 (1.1)	19 (1.7)	0.270
Coronary angiography	81 (7.2)	78 (7.0)	0.901
Abdominal ultrasound	13 (1.2)	20 (1.8)	0.284
Upper gastrointestinal endoscopy	9 (0.8)	17 (1.5)	0.162
Other test	20 (1.8)	17 (1.5)	0.755

PoC, point of care; SC, standard care.

TABLE 22 Attendances as outpatients at 3 months

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)	<i>p</i> -value
<i>n</i> (%) with any outpatient attendance	334 (30)	322 (29)	656 (29)	0.676
<i>n</i> (%) with a chest pain-related outpatient attendance	241 (21)	202 (18)	443 (20)	0.050

PoC, point of care; SC, standard care.

Patient-reported use of health services

Tables 23 and 24 show the number and proportion of patients in each group who reported having used various health services over the previous month in their 1- and 3-month resource use questionnaires. The only significant difference was in the proportion admitted to hospital. There may have been some confusion in responses to this question, with some patients reporting the initial hospital admission while others reported only subsequent admissions.

TABLE 23 Patient-reported health service use at 1 month

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)	<i>p</i> -value
Questionnaires returned [<i>n</i> (%)]	841 (74.8)	795 (71.1)	1636 (72.9)	
<i>n</i> (%) using telephone health advice	232/760 (31)	221/711 (31)	453/1471 (31)	0.821
<i>n</i> (%) using GP surgery consultations	555/799 (69)	537/758 (71)	1092/1557 (70)	0.580
<i>n</i> (%) using GP home visits	45/749 (6)	43/702 (6)	88/1451 (6)	1.000
<i>n</i> (%) using nurse home visits	44/756 (6)	46/698 (7)	90/1454 (6)	0.587
<i>n</i> (%) using social worker visits	14/751 (2)	18/698 (3)	32/1449 (2)	0.376
<i>n</i> (%) attending ED	282/765 (37)	280/728 (38)	562/1493 (38)	0.557
<i>n</i> (%) attending outpatients	334/778 (43)	277/726 (38)	611/1504 (41)	0.066
<i>n</i> (%) using other health services	83/733 (11)	76/660 (12)	159/1393 (11)	0.933
<i>n</i> (%) admitted to hospital	182/832 (22)	208/786 (26)	390/1618 (24)	0.032
<i>n</i> (%) operated on	33/829 (4)	32/784 (4)	65/1613 (4)	1.000
<i>n</i> (%) having ECG	224/813 (28)	228/765 (30)	452/1578 (29)	0.344
<i>n</i> (%) having exercise stress test	184/818 (22)	157/769 (20)	341/1587 (21)	0.328
<i>n</i> (%) having heart monitor	43/806 (5)	58/757 (8)	101/1563 (6)	0.064
<i>n</i> (%) having abdominal ultrasound	59/806 (7)	54/746 (7)	113/1552 (7)	1.000
<i>n</i> (%) having coronary angiography	91/813 (11)	79/756 (10)	170/1569 (11)	0.685

PoC, point of care; SC, standard care.

TABLE 24 Patient-reported health service use at 3 months

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)	<i>p</i> -value
Questionnaires returned [<i>n</i> (%)]	787 (70.0)	745 (66.6)	1532 (68.3)	
<i>n</i> (%) using telephone health advice	151/661 (23)	145/633 (23)	296/1294 (23)	1.000
<i>n</i> (%) using GP surgery consultations	512/746 (69)	457/701 (65)	969/1447 (67)	0.180
<i>n</i> (%) using GP home visits	27/646 (4)	40/626 (6)	67/1272 (5)	0.080
<i>n</i> (%) using nurse home visits	32/645 (5)	39/622 (6)	71/1267 (6)	0.330
<i>n</i> (%) using social worker visits	12/642 (2)	21/621 (3)	33/1263 (3)	0.112
<i>n</i> (%) attending ED	106/659 (16)	112/635 (18)	218/1294 (17)	0.459
<i>n</i> (%) attending outpatients	281/693 (41)	265/661 (40)	546/1354 (40)	0.868
<i>n</i> (%) using other health services	84/625 (13)	80/598 (13)	164/1223 (13)	1.000
<i>n</i> (%) admitted to hospitals	76/779 (10)	79/742 (11)	155/1521 (10)	0.611
<i>n</i> (%) operated on	27/772 (3)	21/734 (3)	48/1506 (3)	0.558
<i>n</i> (%) having ECG	97/762 (13)	74/720 (10)	171/1482 (12)	0.144
<i>n</i> (%) having exercise stress test	83/761 (11)	71/724 (10)	154/1485 (10)	0.497
<i>n</i> (%) having heart monitor	32/760 (4)	28/712 (4)	60/1472 (4)	0.794
<i>n</i> (%) having abdominal ultrasound	45/758 (6)	42/716 (6)	87/1474 (6)	1.000
<i>n</i> (%) having coronary angiography	39/755 (5)	31/717 (4)	70/1472 (5)	0.465

PoC, point of care; SC, standard care.

Patient-reported time taken off work

Tables 25 and 26 show the number and proportion of patients in each group who reported at 1 and 3 months that they had taken time off work during the last month, had not taken time off, were retired and were not in paid employment. They also show the median (IQR) number of days taken off. Around one-half of those in paid employment had taken time off during the

TABLE 25 Patient-reported time taken off work at 1 month

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)	<i>p</i> -value
Questionnaires returned [<i>n</i> (%)]	841 (74.8)	795 (71.1)	1636 (72.9)	0.841
<i>n</i> (%) taken time off	226 (27)	215 (28)	441 (27)	
<i>n</i> (%) not taken time off	227 (27)	222 (28)	449 (28)	
<i>n</i> (%) retired	107 (13)	65 (8)	172 (11)	
<i>n</i> (%) not in paid employment	267 (32)	279 (36)	546 (34)	0.29
Median (IQR) days off	8.0 (3–20)	10.0 (4–20)	10.0 (3–20)	

PoC, point of care; SC, standard care.

TABLE 26 Patient-reported time taken off work at 3 months

	PoC (<i>n</i> = 1125)	SC (<i>n</i> = 1118)	Total (<i>n</i> = 2243)	<i>p</i> -value
Questionnaires returned [<i>n</i> (%)]	787 (70.0)	745 (66.6)	1532 (68.3)	0.498
<i>n</i> (%) taken time off	136 (17)	123 (17)	259 (17)	
<i>n</i> (%) not taken time off	275 (35)	278 (38)	553 (37)	
<i>n</i> (%) retired	89 (11)	61 (8)	150 (10)	
<i>n</i> (%) not in paid employment	279 (36)	271 (37)	550 (36)	0.399
Median (IQR) of days off	11.0 (4–40)	9.0 (3–35)	10.0 (3–40)	

PoC, point of care; SC, standard care.

first month and around one-third had taken time off during the third month. There were no differences in time taken off work between the two groups.

Health utility

Table 27 compares mean EQ-5D scores at 1 and 3 months between the point-of-care and standard-care groups. There were no significant differences in mean EQ-5D scores at either time point.

Patient satisfaction

Table 28 shows the proportion of responses in each category for each question of the patient satisfaction questionnaire. Most patients were satisfied with most aspects of their care, with only a small proportion rating their care as poor. The exception was the question on advice about ways to avoid illness and stay healthy, where 19% rated their care as poor and only 14% rated it as excellent.

Patients receiving point-of-care panel assessment were generally more likely to rate their care as excellent or very good, while those receiving standard care were more likely to rate their care as good, fair or poor. However, this trend was clearly significant only on the final question of overall satisfaction with the service received, whilst being borderline significant for questions relating to the urgency of assessment, explanations given and personal interest shown in the patient and his or her medical problems.

Table 29 shows the characteristics of responders and non-responders in the two groups. At both 1 and 3 months the responders were older and more likely to be female.

TABLE 27 EQ-5D health utility

	PoC (<i>n</i> =1125)	SC (<i>n</i> =1118)	Total (<i>n</i> =2243)	Difference between means (95% CI)	<i>p</i> -value
1 month					
<i>n</i> (%) of responses	825 (73.3)	770 (68.9)	1595 (71.1)		
Mean (SD)	0.742 (0.289)	0.759 (0.267)	0.750 (0.279)	−0.017 (−0.04 to 0.01)	0.614
Median (IQR)	0.796 (0.69–1.00)	0.796 (0.69–1.00)	0.796 (0.69–1.00)		
3 months					
<i>n</i> (%) of responses	756 (67.2)	717 (64.1)	1473 (65.7)		
Mean (SD)	0.752 (0.291)	0.759 (0.279)	0.755 (0.285)	−0.007 (−0.03 to 0.02)	0.638
Median (IQR)	0.796 (0.69–1.00)	0.796 (0.69–1.00)	0.796 (0.69–1.00)		

PoC, point of care; SC, standard care.

TABLE 28 Patient satisfaction with care: how would you rate the following?

	PoC (<i>n</i> =1125)	SC (<i>n</i> =1118)	Total (<i>n</i> =2243)
<i>n</i> (%) of questionnaires returned	841 (74.8)	796 (71.2)	1637 (73.0)
<i>The urgency with which you were assessed</i>			
<i>n</i>	838	791	1629
Poor	10 (1)	16 (2)	26 (2)
Fair	40 (5)	51 (6)	91 (6)
Good	132 (16)	160 (20)	292 (18)
Very good	317 (38)	257 (32)	574 (35)
Excellent	339 (40)	307 (39)	646 (40)
<i>p</i> -value			0.038
<i>The thoroughness of your assessment</i>			
<i>n</i>	837	791	1628
Poor	9 (1)	10 (1)	19 (1)
Fair	41 (5)	37 (5)	78 (5)
Good	140 (17)	162 (20)	302 (19)
Very good	325 (39)	295 (37)	620 (38)
Excellent	322 (38)	287 (36)	609 (37)
<i>p</i> -value			0.163
<i>Explanations given to you about medical procedures and tests</i>			
<i>n</i>	837	789	1626
Poor	19 (2)	20 (3)	39 (2)
Fair	55 (7)	57 (7)	112 (7)
Good	167 (20)	177 (22)	344 (21)
Very good	315 (38)	301 (38)	616 (38)
Excellent	281 (34)	234 (30)	515 (32)
<i>p</i> -value			0.066

TABLE 28 Patient satisfaction with care: how would you rate the following? (*continued*)

	PoC (n= 1125)	SC (n= 1118)	Total (n= 2243)
<i>Attention given to what you have to say</i>			
<i>n</i>	837	792	1629
Poor	24 (3)	21 (3)	45 (3)
Fair	62 (7)	67 (8)	129 (8)
Good	207 (25)	193 (24)	400 (25)
Very good	346 (41)	317 (40)	663 (41)
Excellent	198 (24)	194 (24)	392 (24)
<i>p</i> -value			0.996
<i>Advice you got about ways to avoid illness and stay healthy</i>			
<i>n</i>	831	776	1607
Poor	151 (18)	161 (21)	312 (19)
Fair	142 (17)	121 (16)	263 (16)
Good	210 (25)	192 (25)	402 (25)
Very good	209 (25)	197 (25)	406 (25)
Excellent	119 (14)	105 (14)	224 (14)
<i>p</i> -value			0.487
<i>Friendliness and courtesy shown to you by hospital staff</i>			
<i>n</i>	839	790	1629
Poor	7 (1)	8 (1)	15 (1)
Fair	39 (5)	28 (4)	67 (4)
Good	121 (14)	141 (18)	262 (16)
Very good	307 (37)	272 (34)	579 (36)
Excellent	365 (44)	341 (43)	706 (43)
<i>p</i> -value			0.605
<i>Personal interest in you and your medical problems</i>			
<i>n</i>	837	788	1625
Poor	24 (3)	26 (3)	50 (3)
Fair	77 (9)	89 (11)	166 (10)
Good	204 (24)	206 (26)	410 (25)
Very good	308 (37)	281 (36)	589 (36)
Excellent	224 (27)	186 (24)	410 (25)
<i>p</i> -value			0.044
<i>Respect shown to you, and attention to your privacy</i>			
<i>n</i>	837	788	1625
Poor	20 (2)	21 (3)	41 (3)
Fair	65 (8)	67 (9)	132 (8)
Good	174 (21)	179 (23)	353 (22)
Very good	338 (40)	276 (35)	614 (38)
Excellent	240 (29)	245 (31)	485 (30)
<i>p</i> -value			0.870

continued

TABLE 28 Patient satisfaction with care: how would you rate the following? (*continued*)

	PoC (n= 1125)	SC (n= 1118)	Total (n= 2243)
<i>Reassurance and support offered to you by hospital staff</i>			
<i>n</i>	836	787	1623
Poor	31 (4)	33 (4)	64 (4)
Fair	79 (9)	81 (10)	160 (10)
Good	207 (25)	182 (23)	389 (24)
Very good	288 (34)	275 (35)	563 (35)
Excellent	231 (28)	216 (27)	447 (28)
<i>p</i> -value			0.870
<i>Amount of time the hospital staff gave you</i>			
<i>n</i>	839	789	1628
Poor	32 (4)	28 (4)	60 (4)
Fair	108 (13)	127 (16)	235 (14)
Good	246 (29)	230 (29)	476 (29)
Very good	278 (33)	247 (31)	525 (32)
Excellent	175 (21)	157 (20)	332 (20)
<i>p</i> -value			0.210
<i>Overall, how satisfied are you with the service you received?</i>			
<i>n</i>	839	788	1627
Poor	20 (2)	22 (3)	42 (3)
Fair	51 (6)	68 (9)	119 (7)
Good	153 (18)	172 (22)	325 (20)
Very good	326 (39)	284 (36)	610 (37)
Excellent	289 (34)	242 (31)	531 (33)
<i>p</i> -value			0.008

PoC, point of care; SC, standard care.

Adverse events

Table 30 shows the number of major adverse events in each study group up to 3 months. The causes of death were MI (two cases), cancer (two cases), multiorgan failure, pneumonia and unknown (two cases). Adverse event rates were very low, with an overall death rate of 3.6 per thousand, non-fatal MI rate of 4.5 per thousand and emergency revascularisation rate of 10.7 per thousand. The analyses were adjusted as planned for age, gender and known CHD. There were no significant differences in adverse event rates between the two groups.

As shown in Table 13 (primary efficacy), five of the adverse events occurred in patients who were discharged after initial assessment. As these could potentially represent episodes of suboptimal care, these are described in Table 31.

The proportion of admitted patients ultimately diagnosed as having myocardial infarction

Overall 158/2243 (7%) patients were diagnosed as having AMI during their initial presentation: 157 were diagnosed on the basis of a troponin rise and one developed ST elevation and received immediate reperfusion.

TABLE 29 Characteristics of responders and non-responders to EQ-5D questionnaire

	PoC (n= 1125)		SC (n= 1118)	
	Responders (n= 825)	Non-responders (n= 300)	Responders (n= 771)	Non-responders (n= 347)
1 month				
Age (years) [mean (SD)]	56.7 (13.1)	48.5 (14.0)	57.1 (13.9)	48.9 (13.8)
<i>Gender</i>				
Male [n (%)]	468 (56.7)	215 (71.7)	410 (53.2)	214 (61.7)
Female [n (%)]	357 (43.3)	85 (28.3)	361 (46.8)	133 (38.3)
<i>Previous CHD</i>				
Yes [n (%)]	50 (6.1)	10 (3.4)	45 (5.9)	20 (5.8)
No [n (%)]	767 (93.9)	288 (96.6)	719 (94.1)	324 (94.9)
3 months				
Age (years) [mean (SD)]	57.1 (13.3)	49.0 (13.2)	58.1 (13.7)	48.1 (13.3)
<i>Gender</i>				
Male [n (%)]	439 (57.2)	244 (68.2)	386 (53.3)	238 (60.4)
Female [n (%)]	328 (42.8)	114 (31.8)	338 (46.7)	156 (39.6)
<i>Previous CHD</i>				
Yes [n (%)]	49 (6.5)	11 (3.1)	43 (6.0)	22 (5.6)
No [n (%)]	710 (93.5)	345 (96.9)	675 (94.0)	368 (94.4)

PoC, point of care; SC, standard care.

TABLE 30 Major adverse events

	PoC (n= 1125) [n (%)]	SC (n= 1118) [n (%)]	Total (n= 2243) [n (%)]	OR (95% CI) ^a	p-value ^a
Any event	36 (3)	26 (2)	62 (3)	1.31 (0.78 to 2.20)	0.313
Death	6 (1)	2 (<1)	8 (<1)	3.4 (0.7 to 17.3)	0.142
Non-fatal AMI	5 (<1)	5 (<1)	10 (<1)	0.9 (0.3 to 3.2)	0.903
Hospitalisation for ACS without AMI	18 (2)	9 (1)	27 (1)	1.8 (0.8 to 4.1)	0.149
Life-threatening arrhythmia	6 (1)	2 (<1)	8 (<1)	3.2 (0.6 to 15.9)	0.160
Emergency revascularisation	10 (1)	14 (1)	24 (1)	0.7 (0.3 to 1.5)	0.324

PoC, point of care; SC, standard care.

^a Adjusted for age, gender and known CHD.

The proportion diagnosed with AMI was slightly higher in the point-of-care group [82/1125 (7.3%) vs 76/1118 (6.8%)] but this was not statistically significant ($p = 0.650$).

The proportion of admitted patients diagnosed with AMI was 82/763 in the point-of-care group and 75/971 in the standard-care group (10.7% vs 7.7%, $p = 0.029$), suggesting that point-of-care panel assessment was associated with a higher proportion of admitted patients having AMI. This reflects a difference in the denominator between these two proportions, rather than the

TABLE 31 Adverse events occurring in patients discharged after initial assessment

Age and gender	Study group	Testing at initial presentation	Working diagnosis	Adverse event
43, female	Point of care	PoC tests negative, taken 505 and 600 minutes after worst pain	Musculoskeletal pain	Hospitalisation for ACS 50 days later
63, male	Point of care	PoC tests negative, taken 721 and 824 minutes after worst pain	Musculoskeletal pain	Hospitalisation for ACS 1 day later
64, female	Standard care	Troponin negative 1606 minutes after worst pain	Angina, no ACS	Non-fatal AMI 32 days later
78, female	Point of care	PoC tests negative, taken 800 and 900 minutes after worst pain	Gastro-oesophageal pain	Died from metastatic pancreatic carcinoma 75 days later
78, male	Point of care	CK-MB and myoglobin negative, troponin 0.06 µg/l and 0.07 µg/l at 909 and 1005 minutes after worst pain	Angina, no ACS	Life-threatening arrhythmia (supraventricular tachycardia) 48 days later

PoC, point of care.

numerator, i.e. point-of-care was associated with fewer admissions rather than more diagnosis of AMI.

Economic analysis

Tables 32 and 33 show the unit costs used in the main analysis and the microcosting, respectively.

Table 34 shows the unit costs used to estimate the cost per patient of providing point-of-care panel assessment. The total cost per patient of point-of-care panel assessment was estimated as the sum of a number of components: the cost of the machine and of periodic maintenance, the cost of calibration and quality control during testing, and the annual testing rate for the machine. Information was provided by Siemens Healthcare Diagnostics. Machine and maintenance costs were annualised to the index year (2009). The cost applied to the analyses reported here is that for an annual rate of 1500 full panels (£21.33 per panel). It is worth noting that the relationship between cost and annual rate of testing is known with certainty only for the rates reported in Table 34.

Data were collected from 246 patients for the microcosting study. The average age of this sample was 54 years, 52% were male (slightly lower than the overall percentage: 58% – Table 7) and 12% had a history of CHD. The results are shown in Table 35. The point-of-care panel assessment added £38.13 per patient managed in this arm of the trial. Staff costs were £11.55 higher in the point-of-care group, reflecting the increased level of staff involvement required to deliver the intervention. Overall, the microcosting study showed that point-of-care panel assessment added £53.16 to the costs of ED management.

Table 36 shows the number of patients in each group receiving other interventions during their initial assessment, the number of interventions received and the cost per patient of providing these interventions. The small differences noted in the use of aspirin and clopidogrel between the two groups did not produce a significant difference in the cost per patient of medications. The standard-care group received more laboratory blood tests, leading to an excess cost of £9.42 per patient compared with the point-of-care group. The standard-care group also received more ECGs than the point-of-care group, although this resulted in only a small (£1.95) additional cost per patient. More patients in the point-of-care group received angiography or PCI, but the

TABLE 32 Unit costs used in the economic evaluation

Trial costs	Cost (£)/event	Source ^a	
PoC panel assessment	See Table 34		
Cardiac interventions (adjusted for cost of mean length of stay – see below)			
CABG	6806.86	HRG code	Average of EA14Z–EA16Z
PCI for stenting	2012.97	HRG code	Average of EA31Z–EA32Z
Thrombolysis	780.00	BNF ⁵⁰	Alteplase: accelerated regimen, 15 mg IV injection + 50 mg IV infusion (30 minutes) + 35 mg IV infusion (1 hour)
Diagnostic procedures			
Angiogram	129.96	HRG code	Average of RA16Z–RA18Z – contrast fluoroscopy procedures
Radionuclide scan	221.32	HRG code	Average of RA35Z–RA39Z – nuclear medicine
Exercise treadmill test	116.04	HRG code	EA47Z – ECG monitoring and stress testing
ECG	116.04	HRG code	EA47Z – ECG monitoring and stress testing
24-hour monitoring test	116.04	HRG code	EA47Z – ECG monitoring and stress testing
Echocardiogram	176.39	HRG code	EA46Z – simple echocardiogram
Transoesophageal echocardiogram	104.69	HRG code	EA45Z – complex echocardiogram
Abdominal ultrasound	57.42	HRG code	AVERAGE of RA23Z–RA24Z, across both outpatient and admitted care
Upper gastrointestinal endoscopy	258.62	HRG code	FZ03A – diagnostic and intermediate procedures on the upper gastrointestinal tract 19 years and over
MRI scan	198.53	HRG code	Average of RA01Z–RA03Z
Outpatient clinic/centre visits			
Cardiology – first attendance	160.08	HRG code	320 – cardiology clinic (assume consultant led)
Cardiology – follow-up visit	70.83	HRG code	320 – cardiology clinic (assume non-consultant led)
Cardiac surgery – first attendance	270.45	HRG code	172 – cardiac surgery (assume consultant led)
Cardiac surgery – follow-up attendance	272.85	HRG code	172 – cardiac surgery (assume non-consultant led)
Cardiothoracic surgery – first attendance	202.27	HRG code	170 – cardiothoracic surgery (assume consultant led)
Cardiothoracic surgery – follow-up attendance	215.03	HRG code	170 – cardiothoracic surgery (assume non-consultant led)
Cardiac rehabilitation	195	HRG code	average of VB38Z – rehabilitation for AMI and other cardiac disorders (across levels 1 and 2)
Rapid-access chest pain clinic	569.78	£458 (from Goodacre <i>et al.</i> ⁵¹) inflated according to Hospital & Community Health Services (pay and prices index) ⁵²	
Hospital cost per day			
Coronary care	1115.78	HRG code	Average of XC01Z–XC07Z – adult critical care (cardiac ICU)
Intensive care	1410.54	HRG code	Average of XC01Z–XC07Z – adult critical care (ITU)
Medical assessment unit	276.21	HRG code	VEB10Z Actual or suspected MI – observation ward – inflated according to Hospital & Community Health Services (pay and prices index) ⁵²
Clinical ward	276.21	Assumed same as observation ward	
Community health-care costs			
GP – surgery (17.2 minutes' contact)	52.00	8.8b GP ⁵² (p. 109)	
GP – home visit (23.4 minutes)	58.00	8.8b GP ⁵² (p. 109)	
Nurse – home visit (quarter hour)	21.65	8.4 nurse specialist (community) ⁵²	
Social worker visit (1 hour)	28.46	9.2 social worker (adult) ⁵²	

HRG, Healthcare Resource Group; ITU, Intensive Therapy Unit; IV, intravenous; MRI, magnetic resonance imaging; PoC, point of care.

a Unless specified, source is National Schedule of Reference Costs 2007/08 – NHS Trusts.

TABLE 33 Unit costs used in costing ED staff costs for the initial episode

Resource	Cost (£)	Source ⁵²
Consultant	163	13.4 Consultant: medical (all duties/patient contact)
Trainee specialist doctor, year 4	52	13.3 Specialty doctor (40-hour week)
Trainee specialist doctor, year 3	51	13.3 Specialty doctor (40-hour week)
Trainee specialist doctor, year 2	49	13.3 Specialty doctor (40-hour week)
Trainee specialist doctor, year 1	47	13.3 Specialty doctor (40-hour week)
Staff grade	60	Staff grade (Table 3, p, 169)
Senior house officer	32	13.2 Foundation house officer 2 (56-hour week)
House officer	27	13.1 Foundation house officer 1 (56-hour week)
Nursing director (band 8/9)	85	Table 2, p, 168 (band 8b) (patient contact)
Nurse manager (band 7)	74	12.1 Nurse team manager (patient contact)
Nurse team leader (band 6)	65	12.2 Nurse team leader (patient contact)
Staff nurse (band 5)	47	12.3 Nurse, 24-hour ward/RN (patient contact)
Clinical/health-care assistant	23	12.5 Clinical support worker (patient contact)

RN, research nurse.

TABLE 34 Point-of-care testing unit costs

Cost component	Cost (£)
Panel costs (includes reagent, machine and maintenance)	
Based on 1500 full panels ^a	20.54
Based on 3000 full panels ^a	15.70
Based on 3000 troponin-only panels ^a	5.70
Calibration and quality control for full panel (per annum) ^b	1426
Calibration and quality control for troponin only panel (per annum) ^b	1397
Total cost per panel	
Based on 1500 full panels	21.33
Based on 3000 full panels	16.18
Based on 3000 troponin-only panels	6.17

a Costs provided by Hilda Crockett, Marketing Manager Point of Care, Siemens Healthcare Diagnostics.

b Based on 5-minute daily systems check, twice-weekly 15-minute quality control check and 5 minutes per reagent calibration check every 60 days, and Agenda for Change Grade 6 staff member (£29 per hour).

TABLE 35 Emergency department economic microcosting study costs

Item cost	PoC (£) (n=122)	SC (£) (n=124)
Staff costs ^a	60.76	49.21
PoC tests (£21.33/panel)	38.13 ^b	0
ED overheads (£5.38/hour)	20.81	17.32
Total costs		
Mean	119.70	66.54
Minimum	52.04	26.41
Maximum	268.46	151.81

PoC, point of care; SC, standard care.

a Source: RATPAC microcosting study.

b Based on n=119 – three patients had no test panels (21 had only one).

TABLE 36 Other resource use at initial assessment, by treatment group

Resource item	No. of patients		Frequencies		Cost (£)		<i>p</i> -value ^b
	PoC	SC	PoC ^a	SC ^a	PoC ^a	SC ^a	
Medications	827	891	2086	2112	5.56	5.21	0.703
Laboratory tests	1071	1075	2079	2546	28.58	38.00	<0.001
ECGs	1125	1118	1411	1484	33.44	35.39	<0.001
Angiograms	16	8	16	8	1.85	0.92	0.104
ED stay ^c	598	446	–	–	40.36	34.53	<0.001

PoC, point of care; SC, standard care.

a SC: *n* = 1118, PoC: *n* = 1125.

b For *t*-test.

c Pro rata cost of hospital ward for patients not admitted.

differences in mean cost per patient attributable to these two interventions were not statistically significant. A cost for ED stay for discharged patients was estimated on a pro rata basis using the ward cost for a day (£276.21) for patients who were discharged from the ED without any subsequent hospital admission. This cost was higher by £5.83 for patients discharged from the point-of-care group, who spent about a half-hour longer in the ED.

Table 37 shows resource use after the initial assessment. Items of resource use were costed only if they were chest pain related and could be matched with an appropriate unit cost. This explains why the numbers in this table for some items are slightly lower than corresponding data in the main outcomes analysis (Tables 16–21). Patients in the point-of-care group received more coronary care and intensive care, while patients in the standard-care group received more general inpatient care. None of these resulted in significant differences in mean cost, although the differences in the point estimates for costs relating to coronary care and intensive care were marked, with point-of-care panel assessment being associated with an additional £70.77 and £62.58 per patient, respectively. Patients in the point-of-care group received more outpatient follow-up. Standard care is associated with more nurse home visits and social work visits, but with relatively small differences in mean cost per patient.

Table 38 shows resource use and costs for community health service support use when missing values for each item are imputed by the mean cost for the corresponding treatment arm. Note that this approach usually underestimates the variability in the data so that *p*-values are slightly underestimated.

Table 39 shows the mean cost per patient by treatment group at each site and across all sites. Inferential analyses were conducted on imputed data; totals based on complete case means are included for comparison. Across all sites the mean cost per patient was higher in the point-of-care group by £211.22 in the imputed analysis (*p* = 0.056). Mean differences at individual sites ranged from £214.49 less in the point-of-care group at Leeds to £646.57 more in the point-of-care group at Edinburgh, with only the difference at Edinburgh being statistically significant (*p* = 0.025). An ANOVA test across centres (based on permuted test summed across the imputed data sets) yielded a *p*-value of 0.0803.

Tables 40 and 41 show the mean EQ-5D scores at 30 and 90 days using complete cases only (i.e. only those with data at both time points) and with imputation of missing values. There was no significant difference at either time point. Imputation did not markedly change the mean scores in either group at either time point.

TABLE 37 Non-ED resource use and costs, by treatment group

Item ^a	Resource use				Cost (£)		
	PoC		SC		PoC	SC	<i>p</i> -value ^b
	Patients	Frequency	Patients	Frequency			
Coronary care days	47	176	31	104	174.56	103.79	0.064
Intensive care days	7	64	3	14	80.24	17.66	0.352
Other inpatient days	429	1353	564	1467	330.96	362.43	0.420
Outpatient attendances	191	222	155	183	35.18	27.67	0.045
Diagnostic tests (non-laboratory)	344	450	327	430	51.41	49.28	0.573
Interventions	47	54	38	40	149.83	91.25	0.061
Post-discharge events (ED attendances)	100	140	104	155	13.30	14.82	0.507
<i>Community health support^c</i>							
GP surgery visits	562/626	1977	519/666	1816	154.36	150.85	0.646
GP home visits	44/553	98	47/535	109	10.28	11.82	0.602
Nurse home visits	44/554	128	46/529	262	5.00	10.72	0.046
Social worker visits	14/549	45	26/529	164	2.33	8.82	0.091

PoC, point of care; SC, standard care.

a Costs of informal care excluded as it is outside the perspective of the study.

b The *p*-value for *t*-test [permutation (non-parametric) tests also conducted and qualitative results coincide].

c Complete case analysis: fraction is number of patients with events over number with completed items.

TABLE 38 Non-hospital resource use: mean imputation analysis

Item	Resource use				Cost (£)		
	PoC		SC		PoC	SC	<i>p</i> -value ^a
	Patients	Frequency	Patients	Frequency			
GP surgery visits	1125	2668	1118	2440	123.32	113.48	0.065
GP home visits	1125	166	1118	186	8.56	9.64	0.497
Nurse home visits	1125	206	1118	400	3.96	7.75	0.008
Social worker visits	1125	77	1118	226	1.95	5.75	0.040
Work time lost (days)	1125		1118		7.58	8.28	0.3776 ^b

PoC, point of care; SC, standard care.

a The *p*-value for *t*-test [permutation (non-parametric) tests also conducted and qualitative results coincide] unless specified.

b The *p*-value for permutation of *t*-test.

Table 42 shows the total QALYs accrued (the difference) over 3 months at each site for both treatment groups. Data are reported assuming that EQ-5D was zero at baseline, although means for any baseline score between 0 and 1 can be estimated by adding a constant $k/24$, where k is the baseline EQ-5D score of interest. As 3 months is approximately one-quarter of a year, the maximum possible number of QALYs accrued is 0.25 (assuming EQ-5D was 1 at baseline). In practice, there is very little difference between treatment arms evident (a difference of 0.00273 is equivalent to 1 day), and there were no significant differences in QALYs accrued at any site or across all sites.

TABLE 39 Total costs, by treatment group and site

	PoC (£)		SC (£)		Difference (95% CI)	p-value
	n	Mean	n	Mean		
Barnsley	162	1058.33	164	923.13	135.20 (-306.97 to 598.44)	0.538
Derriford	164	1466.81	164	1307.95	158.86 (-326.84 to 679.23)	0.529
Edinburgh	228	1356.35	224	709.78	646.57 (73.12 to 1612.71)	0.025
Frenchay	233	1162.53	231	1058.33	104.20 (-288.11 to 511.34)	0.625
Leeds	173	785.00	171	999.49	-214.49 (-657.10 to 132.56)	0.345
Leicester	165	1495.54	164	1115.41	380.13 (-181.53 to 914.82)	0.148
Total (imputed data)	1125	1217.14	1,118	1005.91	211.23 (-16.53 to 442.90)	0.056
Total (complete case means)		1216.18		1008.94	207.24 (2.98 to 431.62)	0.047

PoC, point of care; SC, standard care.

TABLE 40 European Quality of Life-5 Dimensions scores: complete case analysis

	PoC		SC		p-value ^a
	n	Mean	n	Mean	
Score at 1 month	697	0.747	650	0.761	0.369
Score at 3 months	697	0.753	650	0.759	0.710

PoC, point of care; SC, standard care.

a The p-value for t-test [permutation (non-parametric) tests also conducted and qualitative results coincide].

TABLE 41 European Quality of Life-5 Dimensions scores: imputed data sets analysis

Item	PoC		SC		p-value ^a
	n	Mean	n	Mean	
Score at 1 month	1125	0.753	1118	0.769	0.158
Score at 3 months	1125	0.764	1118	0.772	0.433

PoC, point of care; SC, standard care.

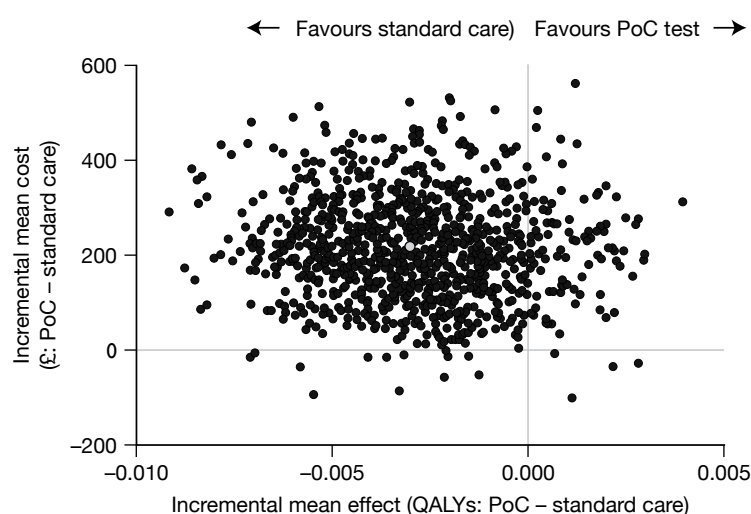
a The p-value for t-test [permutation (non-parametric) tests also conducted and qualitative results coincide].

The cost-effectiveness plane based on the resampled cost-effectiveness data points for the point-of-care test strategy (*Figure 6*, with mean values shown by grey target) shows that, owing to the negative sign of the incremental QALYs, there is a high probability that the strategy is dominated

TABLE 42 Total QALYs, by treatment group and site

	PoC		SC		Difference (95% CI)	p-value
	n	Mean	n	Mean		
Barnsley	162	0.153	164	0.157	−0.004 (−0.016 to 0.010)	0.621
Derriford	164	0.158	164	0.156	0.002 (−0.011 to 0.013)	0.743
Edinburgh	228	0.158	224	0.162	−0.004 (−0.014 to 0.006)	0.529
Frenchay	233	0.157	234	0.163	−0.006 (−0.016 to 0.004)	0.267
Leeds	173	0.162	171	0.162	0.000 (−0.010 to 0.011)	0.687
Leicester	165	0.158	164	0.163	−0.005 (−0.015 to 0.006)	0.401
Total	1125	0.158	1118	0.161	−0.003 (−0.007 to 0.002)	0.250

PoC, point of care; SC, standard care.

**FIGURE 6** Cost-effectiveness plane for point-of-care treatment strategy.

(empirical probability 0.888). Conversely, the probability of the point-of-care test strategy being cost-effective at £20,000 per QALY is (understandably) very low (0.004).

Cost-effectiveness results are presented in *Table 43*. Empirical probabilities of a policy being dominated [i.e. has higher cost and is less effective than the index (standard care) policy], and of being cost-effective (i.e. having an incremental cost-effectiveness ratio no larger than £20,000 when the policy is more effective), are also presented.

Table 43 also shows the results of two analyses used to explore whether the findings were robust to two important assumptions. First, we explored whether a cheaper point-of-care test could be

TABLE 43 Cost and QALYs incremental differences

Policy	Incremental means		Probability of	
	Cost (£)	QALYs	Being dominated	Cost-effectiveness at £20,000 per QALY
SC	0	0	—	—
PoC	211.22	−0.0028154	0.888	0.004
PoC test using a single troponin test	179.26	−0.0028154	0.869	0.006
PoC costs excluding intensive care	153.59	−0.0028154	0.876	0.006

PoC, point of care; SC, standard care.

cost-effective by assuming that the test performance for a single troponin test, which at £6.17 incurs the lowest feasible point-of-care test cost, is the same as that of the trial strategy. In this scenario only costs would be affected, and test costs are reduced from £38.13 to £6.17, so that the mean cost difference would reduce to £179.26. Despite this, the probability of the point-of-care strategy being cost-effective remained low. Second, we explored whether excluding intensive care costs would alter the findings. Intensive care costs are only weakly related to the intervention and one patient in the point-of-care group had spent 52 days on intensive care, incurring substantial costs and increasing the variance of cost estimates. The results show that excluding intensive care costs reduced the mean cost per patient of point-of-care but did not markedly alter the probability that this strategy would be cost-effective.

These sensitivity analyses do not vary the results of the base case (i.e. trial) cost-effectiveness analysis, which might be expected as the alternative scenarios affect only costs.

Figure 7 shows estimated 95% confidence ellipses, assuming bivariate normality, of incremental costs and QALYs, for each of the hospital sites. Note that the plots are based on smaller sample sizes than the overall result and this is reflected in the higher variability. The plots generally reflect the overall result, and highlight, for example, the greater incremental cost variability of Edinburgh (where the patient with the long intensive care stay was recruited) and the possibility that, for Derriford or Leeds, the strategy may have a reasonable probability of being cost-effective.

Decision-analytic modelling

The parameters used in the model are shown in *Appendix 4*. The probabilistic analyses based on the decision-analytic model yielded a mean difference in costs (point of care minus standard care) of £169 (empirical 95% CI −£1229 to £1658) and in QALYs of −0.002 (95% CI −0.108 to 0.104), which correspond reasonably with the trial-based results, particularly in the light of the simplifications outlined above (see *Methods*). The estimated probability that point-of-care panel assessment is cost-effective for a willingness to pay of £20,000 per QALY under these circumstances was 0.223. The model extrapolated to lifetime survival resulted in a mean cost difference of £329 (95% CI −£1312 to £2028) and corresponding value for QALYs of −0.087 (95% CI −12.3 to 12.2) accrued over a lifetime. The probability of cost-effectiveness of point-of-care panel assessment based on lifetime survival was estimated at 0.336.

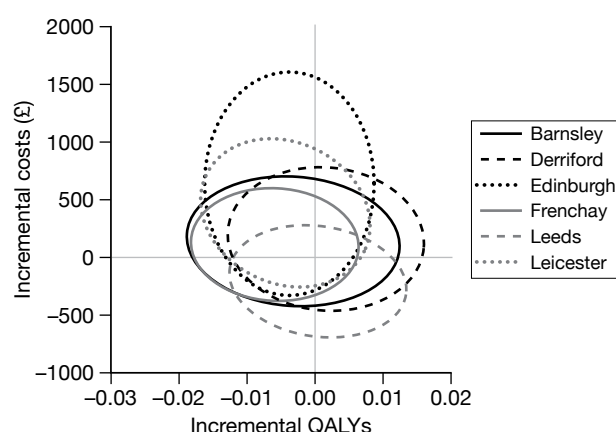


FIGURE 7 Cost-effectiveness plane for point-of-care treatment strategy, by site.

Evaluation of GRACE and TIMI scores

Table 44 shows the number and proportion of patients with and without a major adverse event up to 1 month in each quintile of the GRACE score and each category of the TIMI score. *Table 45* shows the same data for major adverse events up to 3 months. The proportion with a major adverse event at either 1 month or 3 months increases progressively with increasing quintiles of GRACE score regardless of the method used to incorporate troponin or the method used to analyse the data. The relationship between TIMI score and proportion with a major adverse event is not as clear, especially at 1 month. Patients with a TIMI score of 2 had the highest rate of major adverse events by 1 month.

Table 46 reports the area under the receiver-operator characteristic curve for GRACE and TIMI scores for predicting major adverse events up to 1 month and 3 months, and *Figure 8* shows the curves. As before, these are presented for both methods of incorporating the troponin measurement and both methods of analysing the data. The method of analysis made little difference but the use of any troponin measurement resulted in consistently higher discriminant value than the use of the first troponin only. Both scores tended to predict events slightly better over the longer follow-up period. Overall, GRACE had better discriminant value for predicting adverse events than TIMI, although neither score predicted events with the kind of accuracy required to be clinically useful (i.e. with an area under the receiver-operator characteristic curve greater than 0.8). The area under the receiver-operator characteristic curve for age alone as a predictor was 0.66 for major adverse events up to 1 month and 0.69 for events up to 3 months. Hence, knowing the TIMI score appears to be no better than knowing the patient's age for predicting subsequent major adverse events in this cohort.

TABLE 44 Major adverse events up to 1 month by GRACE and TIMI score

Score	No. of patients	Major adverse event [<i>n</i> (%)]	No major adverse event [<i>n</i> (%)]
GRACE score			
<i>Complete case analysis</i>			
Any troponin positive			
< 60	280	0	280 (100.0)
60–79	402	5 (1.2)	397 (98.8)
80–89	251	3 (1.2)	248 (98.8)
90–109	384	11 (2.9)	373 (97.1)
> 109	422	19 (4.5)	403 (95.5)
First troponin positive			
< 60	304	1 (0.3)	303 (99.7)
60–79	429	4 (0.9)	425 (99.1)
80–89	260	5 (1.9)	255 (98.1)
90–109	363	11 (3.0)	352 (97.0)
> 109	392	17 (4.3)	375 (95.7)
<i>Imputed analysis</i>			
Any troponin positive			
< 60	389	0	389 (100.0)
60–79	520	5 (1.0)	515 (99.0)
80–89	327	5 (1.5)	322 (98.5)
90–109	477	13 (2.7)	464 (97.3)
> 109	530	20 (3.8)	510 (96.2)
First troponin positive			
< 60	414	1 (0.2)	413 (99.8)
60–79	547	4 (0.7)	543 (99.3)
80–89	338	7 (2.1)	331 (97.9)
90–109	459	13 (2.8)	446 (97.2)
> 109	485	18 (3.7)	467 (96.3)
TIMI score			
<i>Complete case analysis</i>			
Any troponin positive			
0	764	5 (0.7)	759 (99.3)
1	565	14 (2.5)	551 (97.5)
2	314	13 (4.1)	301 (95.9)
3	106	4 (3.8)	102 (96.2)
4 or 5	33	1 (3.0)	32 (97.0)
First troponin positive			
0	839	6 (0.7)	833 (99.3)
1	531	15 (2.8)	516 (97.2)
2	305	13 (4.3)	292 (95.7)
3	89	2 (2.2)	87 (97.8)
4 or 5	31	1 (3.2)	30 (96.8)

continued

TABLE 44 Major adverse events up to 1 month by GRACE and TIMI score (*continued*)

Score	No. of patients	Major adverse event [<i>n</i> (%)]	No major adverse event [<i>n</i> (%)]
<i>Imputed analysis</i>			
Any troponin positive			
0	969	6 (0.6)	963 (99.4)
1	695	15 (2.2)	680 (97.8)
2	403	16 (4.0)	387 (96.0)
3	138	5 (3.6)	133 (96.4)
4 or 5	38	1 (2.6)	37 (97.4)
First troponin positive			
0	1046	8 (0.8)	1038 (99.2)
1	656	15 (2.3)	641 (97.7)
2	386	16 (4.1)	370 (95.9)
3	120	3 (2.5)	117 (97.5)
4 or 5	35	1 (2.9)	34 (97.1)

TABLE 45 Major adverse events up to 3 months by GRACE and TIMI score

Score	No. of patients	Major adverse event [<i>n</i> (%)]	No major adverse event [<i>n</i> (%)]
GRACE score			
<i>Complete case analysis</i>			
Any troponin positive			
<60	280	0	280 (100.0)
60–79	402	7 (1.7)	395 (98.3)
80–89	251	7 (2.8)	244 (97.2)
90–109	384	12 (3.1)	372 (96.9)
>109	422	29 (6.9)	393 (93.1)
First troponin positive			
<60	304	1 (0.3)	303 (99.7)
60–79	429	6 (1.4)	423 (98.6)
80–89	260	9 (3.5)	251 (96.5)
90–109	363	12 (3.3)	351 (96.7)
>109	392	27 (6.9)	365 (93.1)
<i>Imputed analysis</i>			
Any troponin positive			
<60	389	0	389 (100.0)
60–79	520	7 (1.3)	513 (98.7)
80–89	327	10 (3.1)	317 (96.9)
90–109	477	14 (2.9)	463 (97.1)
>109	530	31 (5.8)	499 (94.2)
First troponin positive			
<60	414	1 (0.2)	413 (99.8)
60–79	547	6 (1.1)	541 (98.9)
80–89	338	12 (3.6)	326 (96.4)
90–109	459	15 (3.3)	444 (96.7)
>109	485	28 (5.8)	457 (94.2)

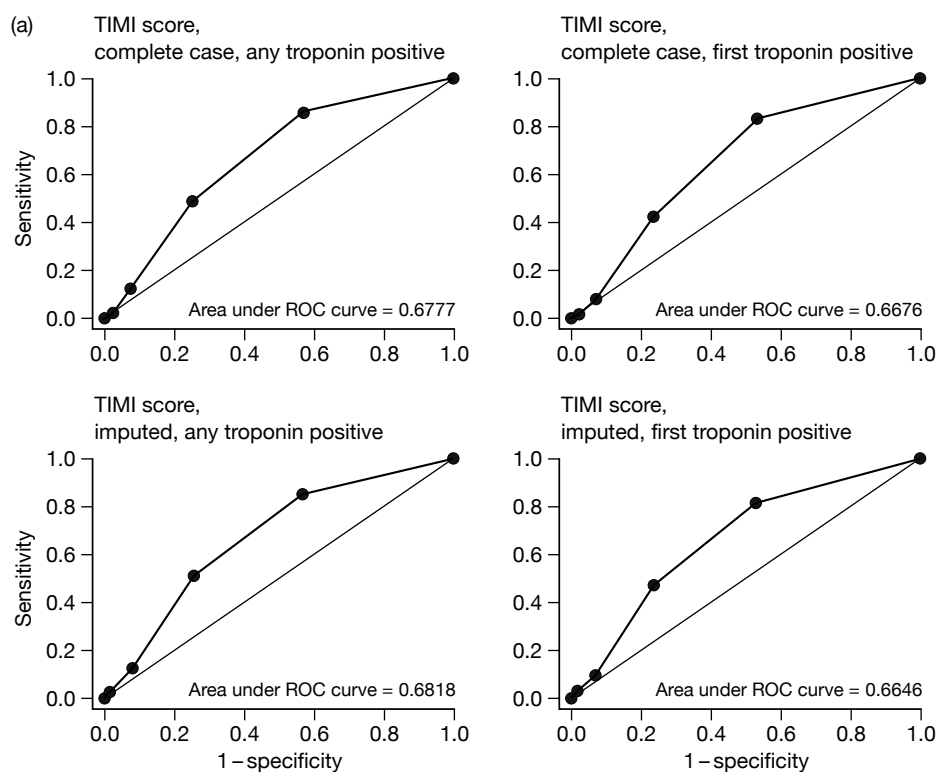
TABLE 45 Major adverse events up to 3 months by GRACE and TIMI score (*continued*)

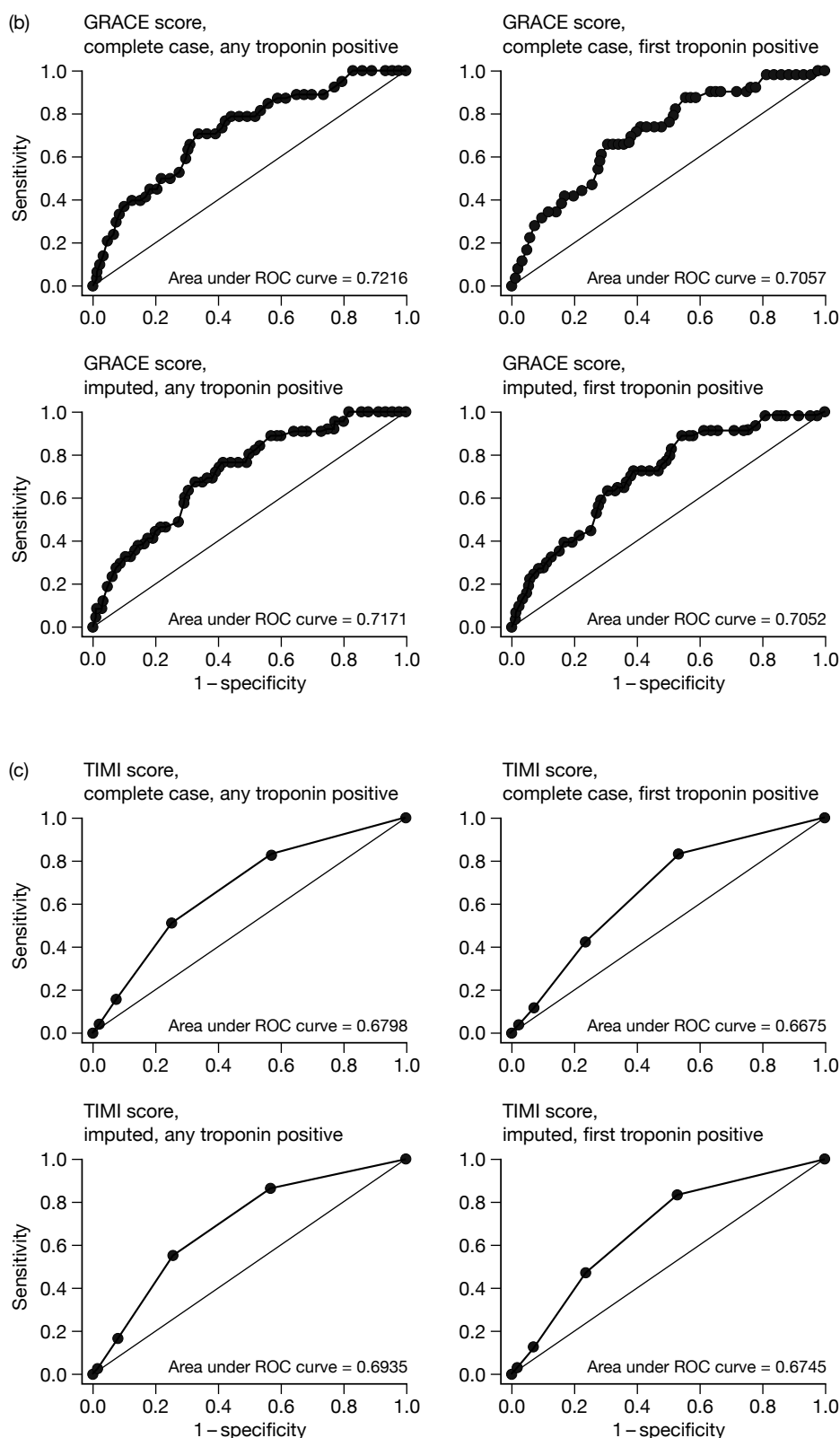
Score	No. of patients	Major adverse event [<i>n</i> (%)]	No major adverse event [<i>n</i> (%)]
<i>TIMI score</i>			
<i>Complete case analysis</i>			
Any troponin positive			
0	764	8 (1.0)	756 (99.0)
1	565	17 (3.0)	548 (97.0)
2	314	18 (5.7)	296 (94.3)
3	106	6 (5.7)	100 (94.3)
4 or 5	33	2 (6.1)	31 (93.9)
First troponin positive			
0	839	9 (1.1)	830 (98.9)
1	531	20 (3.8)	511 (96.2)
2	305	16 (5.2)	289 (94.8)
3	89	4 (4.5)	85 (95.5)
4 or 5	31	2 (6.5)	29 (93.5)
<i>Imputed analysis</i>			
Any troponin positive			
0	969	9 (0.9)	960 (99.1)
1	695	19 (2.7)	676 (97.3)
2	403	24 (6.0)	379 (94.0)
3	138	8 (5.8)	130 (94.2)
4 or 5	38	2 (5.3)	36 (94.7)
Troponin positive			
0	1046	11 (1.1)	1035 (98.9)
1	656	22 (3.4)	634 (96.6)
2	386	21 (5.4)	365 (94.6)
3	120	6 (5.0)	114 (95.0)
4 or 5	35	2 (5.7)	33 (94.3)

TABLE 46 Receiver-operator characteristic curve analysis of GRACE and TIMI scores

			Area under the ROC curve	95% CI	
				Lower	Upper
1 month					
GRACE score	Complete case analysis	Any troponin positive	0.722	0.700	0.743
		First troponin positive	0.706	0.683	0.727
	Imputed analysis	Any troponin positive	0.717	0.698	0.735
		First troponin positive	0.705	0.686	0.724
TIMI score	Complete case analysis	Any troponin positive	0.678	0.656	0.700
		First troponin positive	0.668	0.645	0.689
	Imputed analysis	Any troponin positive	0.682	0.662	0.701
		First troponin positive	0.665	0.645	0.684
3 months					
GRACE score	Complete case analysis	Any troponin positive	0.731	0.709	0.752
		First troponin positive	0.721	0.699	0.742
	Imputed analysis	Any troponin positive	0.726	0.707	0.745
		First troponin positive	0.715	0.696	0.734
TIMI score	Complete case analysis	Any troponin positive	0.680	0.657	0.701
		First troponin positive	0.668	0.645	0.689
	Imputed analysis	Any troponin positive	0.693	0.674	0.712
		First troponin positive	0.675	0.655	0.694

ROC, receiver-operator characteristic.





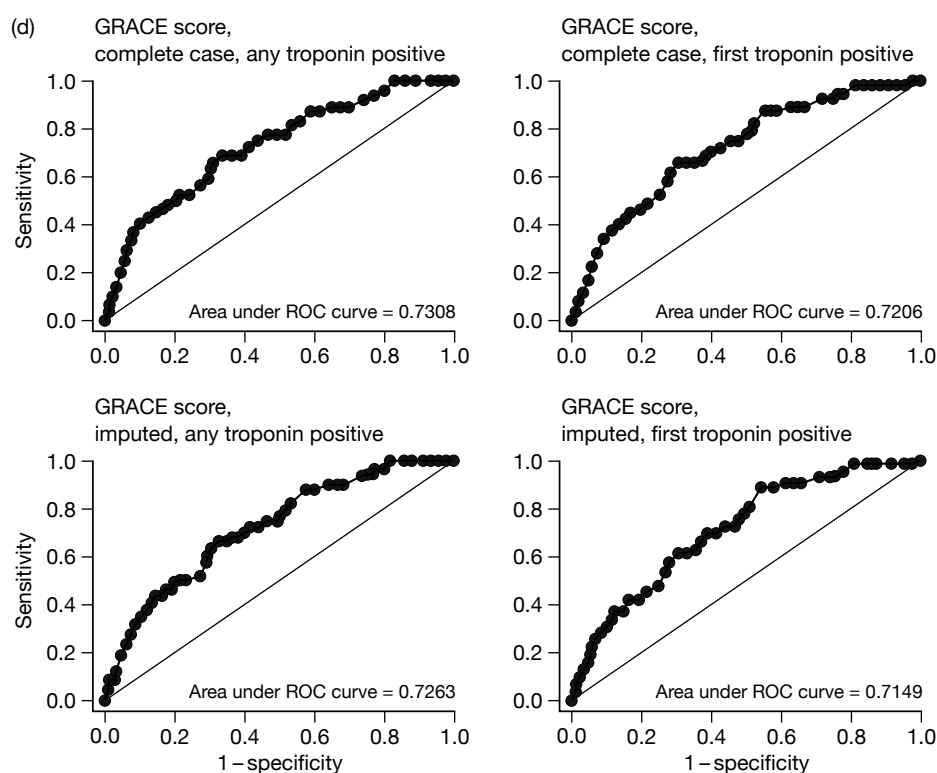


FIGURE 8 Receiver-operator characteristic curves for GRACE and TIMI scores. (a) TIMI score and 30-day major adverse events (MAEs). (b) GRACE score and 30-day MAEs. (c) TIMI score and 90-day MAEs. (d) GRACE score and 90-day MAEs.

Chapter 4

Discussion

Effectiveness of point-of-care panel assessment

Point-of-care panel assessment with CK-MB (mass), myoglobin and troponin at baseline and 90 minutes increased the proportion of patients with acute undifferentiated chest pain successfully discharged home after ED assessment (defined as having left the hospital or with a decision to discharge by 4 hours after attendance and no major adverse event over the following 3 months). The difference in the proportion of patients in hospital persisted until 24 hours after attendance and resulted in a shorter median length of initial hospital stay for patients in the point-of-care group and a greater proportion of the point-of-care group having no inpatient days over the 3 months of the trial. However, it did not lead to any difference in the mean length of initial hospital stay or any difference in the mean number of inpatient days over the 3-month follow-up. This appeared to be due to a small number of patients with very long hospital stays and/or large number of inpatient-days that increased the variance for these variables and which were over-represented in the point-of-care group.

These findings suggest that the benefit of point-of-care panel assessment may depend upon one's perspective. The proportion successfully discharged and the median length of stay describe the experience of the typical patient. Patients and clinicians may perceive benefit from point-of-care panel assessment, reducing the proportion of patients admitted and the duration of hospital stay for a typical patient. Hospital bed use is best estimated from the mean length of stay and mean number of inpatient days. When these are multiplied by the number of patients they produce an estimate of the total bed-days used by the patient cohort. Point-of-care panel assessment may reduce patient turnover (i.e. the number of patients being admitted and using hospital beds), but our data suggest that it will not significantly reduce hospital bed use.

Point-of-care panel assessment was associated with increased use of coronary care and administration of clopidogrel, but reduced use of aspirin. The last two findings appear to match each other, with 5% more patients in the point-of-care group receiving clopidogrel and 5% fewer receiving aspirin. These findings suggest a potential benefit from point-of-care panel assessment but one that is difficult to extrapolate into measures that are meaningful to the patient, such as improved survival or quality of life. They do, however, incur additional costs and are considered in the economic analysis.

Point-of-care panel assessment was not associated with any significant differences in investigations, cardiac interventions, ED attendances and subsequent hospital admissions over the following 3 months, although the non-significant differences in these areas of resource use contributed to the economic analysis. Point-of-care panel assessment was associated with a borderline significant increase in chest pain-related outpatient attendances, but this was one of many hypothesis tests and could be a chance finding.

From the patient's perspective, point-of-care panel assessment was associated with no significant differences in health utility at 1 or 3 months, or time taken off work. It was associated with higher overall satisfaction with care, with more patients in the point-of-care group assessing their care as being excellent or very good, and fewer assessing it as good, fair or poor. Point-of-care

panel assessment received a more favourable rating on 2 of the 10 dimensions of satisfaction measured: the urgency of assessment and the personal interest shown in the patient and his or her medical problems. There were no significant differences between the study groups on the other dimensions.

These findings suggest a modest patient preference for point-of-care panel assessment. However, patients were not blinded and would have been aware of whether they were receiving the experimental intervention or standard care. Their preference for point-of-care panel assessment may therefore reflect a positive response to receiving the 'new' intervention in a trial rather than a specific preference for the intervention.

Major adverse event rates were low, with only 62 out of 2243 patients (3%) having any major adverse event over 3 months, including only eight deaths and 10 non-fatal MIs. There were no significant differences in overall major adverse event rates or the rates of any individual event. CIs for adverse event rates were wide and the study was only originally powered to detect a relatively high 2% absolute increase in major adverse event rates.

We looked in detail at the major adverse events occurring in patients who were discharged after ED assessment, as these are the patients in whom a causal link between initial diagnostic assessment and major adverse event might be strongest. For example, if a patient was discharged after ED assessment had failed to identify MI then this could increase the risk of adverse outcome. Four patients in the point-of-care arm and one in the standard-care arm suffered adverse events after ED discharge. In all but one case the adverse event occurred more than 1 month after initial assessment. This relatively long time between intervention and outcome makes it difficult to assert a causal link. Furthermore, all five patients presented relatively late after their pain and received biomarker testing after a relatively long delay from worst symptoms. It is therefore very unlikely that any of these patients had a missed diagnosis of MI at their initial presentation.

Cost-effectiveness of point-of-care panel assessment

Overall, the economic analysis showed that point-of-care panel assessment was unlikely to be cost-effective compared with standard care. The main analysis produced a 0.888 probability that standard care dominated point-of-care panel assessment (i.e. was cheaper and more effective). The cost-effectiveness analysis was planned as an analysis of the incremental cost per QALY of point-of-care panel assessment. However, the main difference between the strategies and the main driver of cost-effectiveness was cost. The difference in QALYs between the two groups was small (0.003 QALYs) and non-significant ($p = 0.250$). The difference in costs between the two groups was £211 and bordered on being significant ($p = 0.056$). Hence, it appears that point-of-care panel assessment may increase costs despite reducing hospital admissions and inpatient days.

There appear to be a number of reasons for this. First, point-of-care panel assessment is associated with an additional £53 per patient for initial ED assessment. Most of this (£38) is related to the point-of-care machine, but additional staff time to undertake the tests also adds to the costs. It is possible that using the machine for other ED patients (thus reducing the amount charged for equipment) or using a simple protocol (such as a single troponin measurement) could reduce the additional costs associated with point-of-care panel assessment. We undertook a sensitivity analysis assuming that the machine costs were only £6.17 per patient instead of £38.13, but this did not markedly change the overall result, with there still being a 0.869 probability that standard care was dominant.

Point-of-care panel assessment was also associated with markedly higher mean costs for cardiac interventions, coronary care and intensive care. These failed to compensate for a £31 per patient saving from reduced inpatient days. The cost differences were not statistically significant but still added to the overall cost difference between point-of-care panel assessment and standard care. It could be argued that intensive care admissions are unlikely to be related to the initial diagnostic process. Indeed, one patient who suffered serious complications after CABG accounted for most of the intensive care days. We therefore undertook a sensitivity analysis with intensive care costs excluded. Although the difference in costs was reduced from £211 to £154, the probability of standard care being dominant remained high at 0.876.

The finding that there is a very low probability of point-of-care panel assessment being cost-effective is perhaps surprising given that the trial showed it was associated with a statistically significant improvement in its primary outcome measure, the proportion of patients successfully discharged home. However, it appears that earlier diagnosis may have an impact on other clinical decisions in addition to discharge home from the ED. In particular, admissions to coronary care and cardiac interventions were more frequent in the point-of-care group. One possible explanation for the increase in coronary care costs, for example, is that early recognition of troponin elevation may prompt admission to the coronary care unit, whereas an elevated 12-hour troponin after admission to a general ward is unlikely to prompt transfer to coronary care.

Variation between the participating sites

The analysis of the primary outcome and cost-effectiveness analysis showed marked differences between the participating sites. As described in the primary efficacy results section (see *Chapter 3*), these differences are probably due to differences in the facilities available for managing patients with chest pain and the standard care processes normally undertaken at the hospital. All hospitals, except Leicester, showed an effect from point-of-care panel assessment upon the primary outcome. The most marked effect occurred at hospitals in which chest pain patients were subject to a target of spending no more than 4 hours in the ED and standard care involved a 12-hour troponin. In these hospitals there was a significant difference in the primary outcome, which persisted until about 24 hours after attendance. At Leeds, where all patients with chest pain were cared for on a clinical decision unit that was not subject to a 4-hour target, the effect of point-of-care panel assessment was delayed until around 6 hours after attendance. At Derriford, where the standard care guidelines recommended a 6-hour troponin, the effect of point-of-care panel assessment was short-lived and not noticeable after 8 hours from attendance. The exception of Leicester is probably explained by trial factors. The Leicester Research Office stipulated that only doctors who had received full training in GCP could undertake trial recruitment. This meant that the research nurses were overwhelmingly responsible for recruiting patients and producing point-of-care test results. This probably meant that the clinical decision-makers (doctors) were not engaged in the trial and did not act on the test results.

The differences between the sites in the primary outcome are not reflected in differences in mean costs per patient. This is perhaps unsurprising as the overall analysis showed that the increase in the proportion successfully discharged with point-of-care panel assessment did not translate into cost savings. Mean costs were higher in the point-of-care arm at five hospitals and lower at one. It is possible that the overall conclusion that point-of-care panel assessment is unlikely to be cost-effective does not apply at some of the sites, such as Leeds and Derriford. However, we should be careful about drawing conclusions from individual site cost data because cost variances are large and most of the cost differences at individual sites were not statistically significant. The apparently dramatically higher costs associated with point-of-care panel assessment at

Edinburgh, in particular, can be at least in part accounted for by two patients in the point-of-care arm with very high costs due to prolonged hospital stays.

However, in general terms it is possible that inpatient treatment patterns differ between hospitals and that in some settings point-of-care panel assessment in the ED does not lead to higher costs of inpatient care. If this were the case then point-of-care would have the potential to be cost-effective, as is suggested with the confidence ellipses in *Figure 7*. Previous work on chest pain units has tried to identify the combination of costs and admission rates that would make such initiatives cost-effective.⁵³ Similar studies could be worthwhile here.

Variation over time

The effect of point-of-care panel assessment could change over time as a result of clinicians becoming familiar with the technology and changing their decision-making in response to the point-of-care results. In particular, the change in the recommended decision-making threshold for point-of-care troponin could have changed the proportion of patients successfully discharged after point-of-care assessment. Conversely, standard care could change over time and start to mimic point-of-care panel assessment, thus leading to contamination of the control group and a bias towards no effect.

We analysed the primary outcome and deviations from the recommended point-of-care protocol at quarterly intervals to explore whether the effect of point-of-care panel assessment changed over time. Only two patients in the control group received the combination of tests used in the point-of-care machine (CK-MB, myoglobin and troponin) either from the machine itself or from the hospital laboratory, so we did not examine deviations from standard care over time. Deviations from the recommended point-of-care protocol remained relatively constant over time, so there was no evidence that developing experience with the technology eliminated these problems. However, the proportion successfully discharged in the point-of-care arm decreased during the middle third of the trial and increased in the last third, while the proportion successfully discharged in the standard-care arm steadily fell over the trial. The first finding may be explained by the amendment to the troponin threshold in the recommended point-of-care protocol that advised discharge instead of admission for patients with a non-rising troponin in the range 0.03–0.07 µg/l. The second finding may be due to clinical staff becoming progressively more cautious during the trial. However, we must be careful not to overinterpret these findings as they are based on relatively small numbers.

Other studies of point-of-care cardiac markers

The RATPAC trial is the first randomised trial to evaluate whether a panel of point-of-care cardiac markers designed to rule out MI in ED patients with acute chest pain can change clinical decision-making and lead to changes in patient care. Previous studies^{22,23} have evaluated the point-of-care panel and laboratory testing in the same cohort to compare the times taken to receive a test result and have shown that turnaround times are shorter with point-of-care testing, but few studies have compared practice in cohorts with or without point-of-care testing. Ng *et al.*²⁴ compared management with the point-of-care panel with previous practice without the test and found a 40% reduction in coronary care unit admissions. This contrasts with RATPAC, in which we found that point-of-care panel assessment was associated with increased coronary care use. There are two potential explanations for this discrepancy. First, the study by Ng *et al.*²⁴ may have been confounded by changes in practice occurring over time that would have been controlled for in RATPAC by the randomised design. Second, the study by Ng *et al.*²⁴ was

undertaken in a health-care system and patient cohort with much higher coronary care use, so there was much greater potential to reduce admissions. This illustrates the difficulties in extrapolating findings relating to health service use between diverse settings.

Other studies, including randomised trials, have evaluated point-of-care testing by directly comparing use of a point-of-care troponin assay with use of a laboratory assay, rather than evaluating a point-of-care protocol as we did in RATPAC. As outlined in *Chapter 1*, such studies have produced mixed results, with Collinson *et al.*¹² finding reduced length of coronary care unit stay and overall hospital stay, Renaud *et al.*¹³ reporting reduced time to anti-ischaemic therapy and physician notification of results, but no change in ED length of stay or patient outcomes, and Ryan *et al.*¹⁴ finding that the effect of point-of-care testing varied between settings, with length of stay in the ED being increased in one hospital and decreased in another. These studies are not directly comparable with RATPAC because they compare only the process of using a point-of-care versus a laboratory assay, whereas RATPAC evaluated a point-of-care protocol involving a specific panel of tests designed to rule out MI in patients with acute chest pain. However, the inconsistencies noted between the findings of these studies and the variability between the sites involved in RATPAC suggest that the effects of point-of-care testing are inconsistent, whether one is simply examining the effect of point-of-care testing itself or point-of-care testing is being used to deliver a specific protocol.

Strengths and weaknesses of the study

As a randomised trial, RATPAC has the strength of providing an unbiased comparison between the point-of-care protocol and standard care. Allocation of treatment group was concealed until the patient was irreversibly entered into the trial and the low rate of withdrawals before the primary outcome, coupled with analysis being as randomised, meant that the benefits of randomisation were preserved. The trial was pragmatic, in that the only difference between study groups was the availability of point-of-care panel assessment, and involved six diverse hospitals, so findings from the study can be generalised across the NHS. We measured a range of important outcomes and undertook cost-effectiveness analysis using data from real patients, thus avoiding having to make assumptions about how patients would be managed. The economic analysis used standard methods recommended by NICE⁴¹ to allow comparison of the cost-effectiveness of point-of-care panel assessment with other competing demands for NHS resources.

The study also had a number of limitations that should be taken into account when interpreting the findings. We obviously could not blind patients or carers to whether they had been randomised to intervention or control. In some respects this does not matter for a pragmatic trial where we are simply interested in whether an intervention works rather than how or why it works, but it may be important in interpreting patient-reported outcomes. Patients who are randomised to the standard-care group may feel that they have had a potentially valuable intervention withheld and may respond negatively when asked for their opinion. Response rates for the patient questionnaire were, as anticipated, around 70%, so there is the potential for responder bias. It is notable in this respect that response rates were lower in the standard-care group, perhaps reflecting a reduced level of engagement in those who did not receive the study intervention.

Point-of-care testing, and troponin assays in particular, is a rapidly developing area of technology. This created inevitable difficulties in selecting the appropriate machine and assay to use, and in providing guidance for the interpretation of results. We believe that our decision to change from the Biosite troponin assay to the more sensitive Stratus CS Analyser has been vindicated by recent publications^{7,8} that show the value of high-sensitivity troponin assays and suggest that

these will become standard. However, working with a relatively new assay created problems with interpreting low positive results and led to our having to change the recommended protocol during the trial. These issues are not limited to the RATPAC trial and the introduction of highly sensitive troponin assays into practice is likely to be complicated by difficulties deciding how to manage patients with levels close to, or just below, the diagnostic threshold. Thus, it can be argued that the difficulties encountered in the trial in terms of machine malfunction and assay interpretation merely reflect the difficulties encountered in normal practice. However, an inevitable side effect of undertaking evaluation of a developing technology may be a degree of bias against the new technology, in that clinicians may take time to develop familiarity and the technology may ultimately perform better when it is in widespread use.

The trial was terminated before the target of 3130 patients was reached so it did not have the originally planned power. For the primary outcome this was compensated by the actual control admission rate being higher than the original estimate of the baseline admission rate. The trial was originally powered to detect a doubling of the major adverse event rate from 2% to 4%. In the event, at the time it was terminated it only had conditional power of < 10% to detect such a difference. It is therefore possible that point-of-care panel assessment may achieve increased successful discharges at the expense of an increase in major adverse events that the trial was not powered to detect. However, detailed examination of the adverse events suggests that there is unlikely to be a strong association between point-of-care panel assessment and adverse events. Most of the events occurred in patients who had been admitted after ED assessment. Of the five cases that occurred after discharge, only one occurred within the time span of a typical hospital admission. In general, the low adverse event rate in this study, especially deaths and non-fatal MI, should provide some reassurance that in this selected low-risk population the risk of adverse outcome shortly after attendance is very low.

The trial was deliberately designed as a pragmatic evaluation of a specific point-of-care protocol. The intervention was therefore a composite of the point-of-care technology and the cardiac marker panel. This type of pragmatic evaluation carries the disadvantage that we cannot clearly isolate which element of the intervention is effective (or ineffective). It is thus possible that the effects recorded in this study were due to the biomarker panel, rather than point-of-care technology, and could have been achieved using laboratory assays if turnaround times were sufficiently rapid.

The trial was undertaken at six diverse NHS hospitals and all participating centres contributed substantially to recruitment. The variation in the participating hospitals is likely to reflect variation in practice across the NHS.¹¹ This variation means that although we may conclude that our findings apply in general across the NHS it is possible that point-of-care panel assessment may be more or less effective or cost-effective in specific hospitals. The methods used for cost-effectiveness in particular are appropriate for NHS-wide decision-making but may not reflect the costs, effects and priorities of specific individual hospitals.

Imputation methods were used to estimate missing values on the basis of observed values. Recent methods favour the approach of generating multiple imputed data sets (multiple imputation). The main potential limitation of multiple imputation arises from the implicit assumption that the observed data are representative of those that are missing. In other words, these data must be missing at random. With regard to the imputation of staff costs using the microcosting study data, it is likely that this assumption holds, as the sample on which this study was conducted was chosen at random. In the case of the imputation of community health service costs, it may be that the assumption is more tenuous. For example, it may be that patients who are well are less likely to respond to the follow-up survey. Imputation may overestimate costs in these cases. On the other hand, severely ill patients may also have higher rates of non-response. In this case,

imputation would probably underestimate costs. However, given the follow-up procedures of the RATPAC study, it is less likely that data from such patients were not recorded.

Other limitations of imputation methods include small numbers and a proportion of missing values higher than some percentage, typically set at 30%. In the case of the staff costs imputed from the microcosting data, this assumption is violated, as the missing data rate is about 90%. However, the method of imputation used in this case was one of choosing the value from the patient with complete data which matches closest that of the incomplete case, which is less prone to result in a biased estimate, although it may result in underestimation of the variability.

Implications for practice

The RATPAC trial has shown that point-of-care panel assessment with CK-MB (mass), myoglobin and troponin leads to increased successful discharge after ED assessment, but probably costs more than standard care, and is unlikely to be considered a cost-effective use of NHS resources. This means that from an NHS perspective it would not be appropriate to recommend widespread adoption of the point-of-care panel unless specific reasons can be identified as to why it might be worth paying more to reduce the proportion of patients requiring hospital admission. From the perspective of an individual hospital, the decision of whether or not to use the point-of-care panel will depend upon the specific needs of the ED and acute specialties, and whether it may be considered worthwhile to pay the potential additional costs of point-of-care panel assessment to achieve a specific service outcome, such as discharging more patients from the ED within the 4-hour time frame.

It is important to recognise that RATPAC evaluated a specific point-of-care combination for a specific purpose and that care should be taken not to extrapolate findings beyond this specific role. The RATPAC trial results suggest that a rule-out diagnostic testing protocol, which would be expected to lead to a substantial reduction in admissions, may, in practice, have only a modest effect and that a reduction in hospital admissions may not lead to health service cost savings. Although these findings may provide some useful insights when considering the wider role of point-of-care testing, they should not be extrapolated to all point-of-care tests in all settings.

Other findings from the RATPAC trial may have implications for practice and future developments in chest pain care. In particular, the very low rate of adverse events and the observation that most occur after the typical time span of hospital admission suggest that the value of hospital admission for these selected low-risk patients should be brought into question. Most of the investigations and interventions that may benefit patients can be delivered without hospital admission. If the purpose of hospital admission is simply to monitor patients thought to be at risk of adverse outcome then the data from this study suggest that admission for this purpose is unlikely to be worthwhile.

Implications for future research

The very low adverse event rates suggest that further research is required to evaluate the benefit of hospital admission and explore ways of managing acute chest pain that do not require hospital admission. RATPAC has shown that rapid diagnostic testing can make a modest impact upon hospital admissions. It may be that a substantial reduction in admissions can be achieved only through a fundamental restructuring of the way in which acute chest pain is assessed. This would involve moving from a 'rule-out' approach, where the aim is to identify low-risk patients who can be discharged home (with the rest being admitted), to a 'rule-in' approach, where the

aim is to identify high-risk patients for hospital admission and treatment (with the rest being discharged home).

The RATPAC proposal recognised that this is a rapidly developing field and made provisions for future studies accordingly. We have stored blood samples from all participants in the point-of-care group and will be using these samples to test new and emerging assays. This should be coupled with economic evaluation and modelling to explore the potential impact of new early biomarkers with different levels of sensitivity and specificity. Development of biomarkers has tended to accept loss of specificity in the attempt to optimise sensitivity. However, poor specificity has potentially important economic consequences that need to be explored and better understood.

Analysis of the individual sites involved in the RATPAC trial showed marked variation in standard practice and in the effect of the intervention upon the primary outcome. This suggests that point-of-care panel assessment could be more effective or cost-effective in specific settings. Further research should be undertaken to assess in what circumstances point-of-care panel assessment could be effective and cost-effective.

Analysis of GRACE and TIMI scores

We undertook this analysis as a secondary objective of the study unrelated to the primary objectives of evaluating point-of-care panel assessment. The GRACE and TIMI scores have been developed and validated on patients with diagnosed ACS to predict adverse events, usually up to 1 month. Our analysis suggests that they have limited prognostic value in low-risk patients with undifferentiated chest pain, with TIMI performing no better than patient age as a predictor and GRACE performing only slightly better (and also being more complex to calculate). This is perhaps not surprising since both were developed in populations with diagnosed ACS and a high risk of major adverse events. Developing a new clinical risk score in the low-risk population with undifferentiated chest pain may produce an instrument with greater prognostic value. Alternatively, it could be argued that the risk of adverse outcome in this population is so low that attempts to discriminate between those at very low risk and those at moderately low risk are unlikely to be successful.

Chapter 5

Conclusions

Point-of-care panel assessment with CK-MB (mass), myoglobin and troponin increases the proportion of patients with acute undifferentiated chest pain who are successfully discharged home after ED assessment. This leads to a reduced proportion of patients being in hospital at any time over the next 3 months and a reduced median length of initial hospital stay, but no change in mean hospital stay or inpatient days. Point-of-care panel assessment is also associated with increased use of coronary care and may be associated with increased use of other interventions. It is unlikely to be considered cost-effective in the NHS, with a 0.888 probability that standard care is dominant. Cost-effectiveness is mainly driven by differences in mean cost, with point estimates suggesting that point-of-care panel assessment is £211 per patient more expensive than standard care.

Acknowledgements

We would like to thank Margaret Jane for her invaluable clerical assistance; David Gaze at St George's Hospital, London, for his helpful advice and assistance with all things blood tube related; staff involved at the NHS sites for all their hard work; Francis Morris for advice on ED data; and Siemens for providing the Stratus CS Analyser machines and technical support and assistance.

Contributions of authors

Steve Goodacre (Professor of Emergency Medicine, Health Services Research, University of Sheffield) Chief Investigator, conception and design of the study, analysis and interpretation of the data, writing the report and final approval of the version to be published.

Liz Cross (Research Associate, Health Services Research, University of Sheffield) Project management, analysis and interpretation of the data, drafting and revising the report and final approval of the version to be published.

Mike Bradburn (Senior Medical Statistician, Clinical Trials Research Unit, University of Sheffield) Trial statistician, analysis and interpretation of the data, writing the report and final approval of the version to be published.

Patrick Fitzgerald (Research Fellow, Health Economics and Decision Science, University of Sheffield) Health economics, analysis and interpretation of the data, writing the report and final approval of the version to be published.

Alasdair Gray (Consultant in Emergency Medicine, Royal Infirmary of Edinburgh) Conception and design of the study, analysis and interpretation of the data, revising the report and final approval of the version to be published.

Alistair Hall (Professor of Clinical Cardiology, University of Leeds) Conception and design of the study, analysis and interpretation of the data, revising the report and final approval of the version to be published.

Paul Collinson (Consultant in Chemical Pathology, St George's Hospital, London) Conception and design of the study, analysis and interpretation of the data, drafting and revising the report and final approval of the version to be published.

List of contributors

Project Management Group

Charlotte Arrowsmith (RATPAC Research Nurse, Derriford Hospital, Plymouth); Julian Barth (Consultant in Chemical Pathology, Leeds General Infirmary/Co-applicant); Jonathan Benger (Professor of Emergency Care, University of the West of England/Co-applicant); Mike Bradburn (Senior Medical Statistician, Clinical Trials Research Unit, University of Sheffield); Simon Capewell (Professor of Epidemiology, University of Liverpool/Co-applicant); Tim Chater (Database Manager, Clinical Trials Research Unit, University of Sheffield); Tim Coats (Professor of Emergency Medicine/Co-applicant); Paul Collinson (Consultant in Chemical Pathology, St George's Hospital, London/Co-applicant); Cindy Cooper (Director, Clinical Trials

Research Unit, University of Sheffield); Mandy Cooper (RATPAC Research Nurse, Leicester Royal Infirmary); Judy Coyle (RATPAC Research Nurse, Edinburgh Royal Infirmary); Liz Cross (Trial Manager, Health Services Research, University of Sheffield); Simon Dixon (Professor of Health Economics, Health Economics & Decision Science/Co-applicant); Patrick Fitzgerald (Research Fellow, Health Economics & Decision Science, University of Sheffield); Emma Gendall (RATPAC Research Nurse, Frenchay Hospital, Bristol); Steve Goodacre (Professor of Emergency Medicine, Health Services Research, University of Sheffield/Chief Investigator); Emma Goodwin (RATPAC Research Nurse, Barnsley Hospital); Alasdair Gray (Consultant in Emergency Medicine, Royal Infirmary of Edinburgh/Co-applicant); Alistair Hall (Professor of Clinical Cardiology, University of Leeds/Co-applicant); Kevin Hall (RATPAC Research Nurse, Barnsley Hospital); Taj Hassan (Consultant in Emergency Medicine, Leeds General Infirmary/Co-applicant); Julian Humphrey (Consultant in Emergency Medicine, Barnsley Hospital); Steven Julious (Senior Lecturer in Medical Statistics, Medical Statistics Group, Health Services Research, University of Sheffield/Co-applicant); Jason Kendall (Consultant in Emergency Medicine, Frenchay Hospital, Bristol); Vanessa Lawlor (RATPAC Research Nurse, Frenchay Hospital, Bristol); Sue Mackness (RATPAC Research Nurse, Leicester Royal Infirmary); Yvonne Meades (RATPAC Research Nurse, Leeds General Infirmary); David Newby (Professor of Cardiology, University of Edinburgh/Co-applicant); Dawn Newell (RATPAC Research Nurse, Leicester Royal Infirmary); Doris Quartey (RATPAC Research Nurse, Leeds General Infirmary); Karen Robinson (RATPAC Research Nurse, Leicester Royal Infirmary); Glen Sibbick (RATPAC Research Nurse, Leicester Royal Infirmary); Jason Smith (Consultant in Emergency Medicine, Derriford Hospital, Plymouth); and Roz Squire (RATPAC Research Nurse, Derriford Hospital, Plymouth).

Trial Steering Committee

Simon Carley, Consultant in Emergency Medicine, Manchester Royal Infirmary (Independent Member); Paul Collinson, Consultant in Chemical Pathology, St George's Hospital, London (Co-applicant); Liz Cross, Research Associate, Health Services Research, University of Sheffield (Trial Manager); Sue Dodd, CHD Emergency & Acute Care Manager (Vascular Programme), Department of Health (Independent Member); Marcus Flather, Director Clinical Trials & Evaluation Unit, Royal Brompton Hospital, London (Chair); Steve Goodacre, Professor of Emergency Medicine, Health Services Research, University of Sheffield (Chief Investigator); Sara Hilditch, Statistician, Director of Statistical Services Unit, Sheffield University (Independent Member); Enid Hirst (Lay Representative); Richard Hudson, Quality Assurance Manager, Research Office, Academic Division, University of Sheffield (Sponsor Representative); Jason Kendall, Consultant in Emergency Medicine, Frenchay Hospital, Bristol (Investigator Representative); and Rebecca Whitlock-Moss, Programme Manager, NIHR HTA (Funder Representative).

Data Monitoring Committee

Mike Bradburn, Senior Medical Statistician, Clinical Trials Research Unit, University of Sheffield (Trial Statistician); Liz Cross, Research Associate, Health Services Research, University of Sheffield (Trial Manager); Steve Goodacre, Professor of Emergency Medicine, Health Services Research, University of Sheffield (Chief Investigator); John Greenwood, Senior Lecturer/Consultant Cardiologist, Academic Unit of Cardiovascular Medicine, Leeds General Infirmary (Independent Clinician); Jon Nicholl, Professor of Health Services Research, University of Sheffield (Acting Chair); Helen Thorpe, Principal Statistician, Clinical Trials Research Unit, University of Leeds (Chair and Independent Statistician); and William Townend, Consultant in Emergency Medicine, Hull Royal Infirmary (Independent Clinician).

Publications

1. Goodacre SW, Bradburn M, Cross E, Collinson PO, Gray A, Hall AS on behalf of the RATPAC research team. The RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers): a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Heart* 2011;**97**:190–6.
2. Bradburn M, Goodacre S, Fitzgerald P, Coats TJ, Gray AJ, Hassan TB, *et al.* Inter-hospital variation in the RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers). *Emerg Med J* 2011. In press.
3. Fitzgerald P, Goodacre SW, Cross E, Dixon S. Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers). *Acad Emerg Med* 2011;**18**:488–95.
4. Goodacre SW, Bradburn M, Mohamed A, Gray A. Evaluation of Global Registry of Acute Cardiac Events and Thrombolysis in Myocardial Infarction scores in patients with suspected acute coronary syndrome. *Am J Emerg Med* 2011. In press. doi: 10.1016/j.ajem.2010.09.013.

References

1. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. *Heart* 2005;**91**:229–30.
2. Department of Health (DoH). *The National Service Framework for Coronary Heart Disease*. London: DoH; 2000.
3. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;**50**:2173–95.
4. Ebell MH, White LL, Weismantel D. A systematic review of troponin T and I values as a prognostic tool for patients with chest pain. *J Fam Pract* 2000;**49**:746–53.
5. Bertrand ME, Simoons ML, Fox KAA, Wallentin LC, Hamm CW, McFadden E, *et al.* 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.
6. Goodacre S, Calvert N. Cost effectiveness of diagnostic strategies for patients with acute, undifferentiated chest pain. *Emerg Med J* 2003;**20**:429–33.
7. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, *et al.* Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;**361**:858–67.
8. Keller T, Zeller T, Peetz D, Tziwas S, Roth A, Czyz E, *et al.* Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;**361**:868–72.
9. 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.
10. Goodacre S, Nicholl J, Dixon S, Cross E, Angelini K, Arnold J, *et al.* Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004;**328**:254–7.
11. Goodacre S, Nicholl J, Beahan J, Quinney D, Capewell S. National survey of emergency department management of patients with acute, undifferentiated chest pain. *Br J Cardiol* 2003;**10**:50–4.
12. Collinson PO, John C, Lynch S, Rao A, Canepa-Anson R, Carson E, *et al.* A prospective randomised controlled trial of point-of-care testing on the coronary care unit. *Ann Clin Biochem* 2004;**41**:397–404.
13. Renaud B, Maison P, Ngako A, Cunin P, Santin A, Hervé J, *et al.* Impact of point-of-care testing in the emergency department evaluation and treatment of patients with suspected acute coronary syndromes. *Acad Emerg Med* 2008;**15**:216–24.
14. Ryan RJ, Lindsell CJ, Hollander JE, O'Neil B, Jackson R, Schreiber D, *et al.* A multicenter randomized controlled trial comparing central laboratory and point-of-care cardiac marker testing strategies: the Disposition Impacted by Serial Point of Care Markers in Acute Coronary Syndromes (DISPO-ACS) trial. *Ann Emerg Med* 2009;**53**:321–8.
15. Kendall J, Reeves B, Clancy M. Point of care testing: randomised controlled trial of clinical outcomes. *BMJ* 1998;**316**:1052–7.

16. Ebell MH, Flewelling D, Flynn CA. A systematic review of troponin T and I for diagnosing acute myocardial infarction. *J Fam Pract* 2000;**49**:550–6.
17. 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**:478–94.
18. 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 +1.6 ng/ml. *Am Heart J* 1998;**136**:237–44.
19. Fesmire FM, Christensen RH, Focys 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.
20. McCord J, Nowak RM, McCullough PA, Foreback C, Borzak S, Tokarski G, *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.
21. Apple FS, Christensen RH, Valdes R, Andriak Aj, Berg A, Duh SH, *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.
22. Newby LK, Storrow AB, Gibler WB, Garvey JL, Tucker JF, Kaplan AL, *et al.* Bedside multimarker testing for risk stratification in chest pain units: the CHECKMATE study. *Circulation* 2001;**103**:1832–7.
23. 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.
24. Ng SM, Krishnaswamy P, Morissey R, Clopton P, Fitzgerald R, Maisel AS, *et al.* Ninety-minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol* 2001;**88**:611–17.
25. Hamilton AJ, Swales LA, Neill J, Murphy JC, Darragh KM, Rocke LG, *et al.* Risk stratification of chest pain patients in the emergency department by a nurse utilizing a point of care protocol. *Eur J Emerg Med* 2008;**15**:9–15.
26. Rathore S, Knowles P, Mann APS, Dodds PA. Is it safe to discharge patients from accident and emergency using a rapid point of care triple cardiac marker test to rule out acute coronary syndrome in low to intermediate risk patients presenting with chest pain? *Eur J Int Med* 2008;**19**:537–40.
27. Straface AL, Myers JH, Kirchick HJ, Blick KE. A rapid point-of-care cardiac marker testing strategy facilitates the rapid diagnosis and management of chest pain patients in the emergency department. *Am J Clin Pathol* 2008;**129**:788–95.
28. Eggers KM, Oldgren J, Nordenskjold A, Lindahl B. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *Am Heart J* 2004;**148**:574–81.
29. Antman EM, Cohen M, Berninck PJ, Horacek T, Papuchis G, Mautner B, *et al.* The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–42.
30. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, *et al.* A validated prediction model for all forms of acute coronary syndrome. *JAMA* 2004;**291**:2727–33.

31. Burtonwood C, Halloran S. *Report 06020: three point of care devices for troponin measurement*. London: NHS Purchasing and Supply Agency, Centre for Evidence-based Purchasing; 2006.
32. 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.
33. Heeschen C, Goldmann BU, Moeller RH, Hamm CW. Analytical performance and clinical application of a new rapid bedside assay for the detection of serum cardiac troponin I. *Clin Chem* 1998;**44**:1925–30.
34. Heeschen C, Goldmann BU, Langenbrink L, Matschuck G, Hamm CW. Evaluation of a rapid whole blood ELISA for quantification of troponin I in patients with acute chest pain. *Clin Chem* 1999;**45**:1789–96.
35. Altinier S, Mion M, Cappelletti A, Zaninotto M, Plebani M. Rapid measurement of cardiac markers on Stratus CS. *Clin Chem* 2000;**46**:991–3.
36. Goodacre S, Cross E, Lewis C, Nicholl J, Capewell S, on behalf of the ESCAPE Research Team. The ESCAPE cluster randomised trial: effectiveness and safety of chest pain assessment to prevent emergency admissions. *BMJ* 2007;**335**:659–62.
37. 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**:369–76.
38. Conway Morris A, Caesar D, Gray S, Gray A. The TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. *Heart* 2006;**92**:1333–4.
39. Keating L, Benger J, Beetham R, Bateman S, Veysey S, Kendall J, Pullinger R. The PRIMA study: presentation IMA in the emergency department. *Emerg Med J* 2006;**23**:764–8.
40. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, *et al*. Good research practices for cost-effectiveness analysis alongside clinical trials: The ISPOR RCT-CEA Task Force Report. *Value Health* 2001;**8**:521–33.
41. National Institute for Clinical Excellence (NICE). *Guide to the methods of technology appraisal*. London: NICE; 2004.
42. Netten A, Curtis L. *Unit costs of health and social care 2004*. Canterbury: University of Kent, Personal Social Services Research Unit; 2004.
43. Department of Health (DoH). *NHS reference costs 2005*. URL: www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en
44. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost effectiveness acceptability curves. *Health Econ Lett* 2001;**10**:779–87.
45. Schafer J. *Analysis of incomplete multivariate data*. London: Chapman & Hall/CRC; 2000.
46. Rubin D. *Multiple imputation for nonresponse in surveys*. New York, NY: J Wiley & Sons; 1987.
47. Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. *Value Health* 2005;**8**:1–2.
48. Oluboyede Y, Goodacre S, Wailoo AJ on behalf of the ESCAPE Research Team. Cost-effectiveness of chest pain unit care in the NHS. *BMC Health Serv Res* 2008;**8**:174.

49. Medical Research Council. *Guidelines for Good Clinical Practice in Clinical Trials*. 1998. URL: www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416
50. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary*. No. 58, March 2008. London: BMA and RPS; 2008.
51. Goodacre S, Morris F, Arnold J, Angelini K. Is a chest pain observation unit likely to be cost saving in a British hospital? *Emerg Med J* 2001;**18**:11–14.
52. Curtis L. *PSSRU unit costs of health and social care*. Canterbury: PSSU; 2008.
53. Goodacre S, Dixon S. Is a chest pain observation unit likely to be cost effective at my hospital? Extrapolation of data from a randomised controlled trial. *Emerg Med J* 2005;**22**:418–22.
54. Department of Health. *NHS reference costs 2007–8*. URL: www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_098949.xls

Appendix 1

Point-of-care protocol



Step 1

- Collect an Investigation Pack from near RATPAC machine (Stratus CS Analyser).
- Contains two green top tubes, two yellow top tubes, four small clear top tubes, two rotors, two cannulae, one Lab Form.

Note: the small tubes are for the labs, please do not remove from bag.

Step 2 – sample 1

- Take point-of-care (PoC) blood samples (one yellow top and one green top) and routine bloods (normal tubes).
- Label the yellow top sample with bar code and attach corresponding bar code label to Lab Form in pack.
- Label green top sample with same bar code.
- Scan bar coded green top tube in Stratus.
- Enter patient study number (given by randomisation system) into Stratus and also add to Lab Form.
- Please process green top sample in Stratus within 20 minutes.
- Return yellow top sample and Lab Form to pack and store in fridge.

Step 3

- Collect three reagent strips from fridge: troponin I (green), myoglobin (red), creatine kinase MB (CK-MB) (blue).
- Invert green top tube gently several times (*do not shake*).
- Process green top tube in Stratus as per instructions.
- Results produced in 20 minutes.
- After processing remove cannula unit and tube from the Stratus and discard appropriately.

Step 4 – interpretation of sample 1 results

- Fix results slip in patient notes (*important*):
 - Troponin I ≥ 0.03 $\mu\text{g/l}$ = positive result. *Admit* to hospital.
 - If *no* detectable troponin or < 0.03 $\mu\text{g/l}$ = negative result. Finish assessing patient for 90 minutes then take sample 2.

Step 5 – sample 2

- At least 90 minutes from first sample, take second blood samples (one yellow top and one green top).
- Label as before with corresponding bar codes on tubes and Lab Form.
- Return yellow top to pack and store in fridge.
- Process green top as before in Stratus.
- Results produced in 20 minutes – keep printout with notes again.

Step 6

- Remove cannula unit and tube from the Stratus and discard appropriately.
- Add corresponding small labels (without bar code) to two small tubes for each yellow top sample.
- Send tubes in pack with Lab Form to Clinical Biochemistry Lab (within 12 hours).

Note: Ignore remaining labels.

Step 7 – interpretation of sample results

- Calculate CK-MB (mass) gradient = second CK-MB (mass) – first CK-MB (mass), for example $4.52 - 3.11 = 1.41$ (negative).
- Calculate percentage increase in myoglobin (m) = $100 \times [(second\ m - first\ m) / first\ m]$, for example $100 \times [(40 - 25) / 25] = 60\%$ (positive).
 - If any of the following, admit to hospital (positive cardiac markers):*
 - troponin I $\geq 0.03\ \mu\text{g/l}$
 - CK-MB (mass) $> 5\ \mu\text{g/l}$ on both samples
 - CK-MB (mass) gradient on second sample $1.6\ \mu\text{g/l}$ higher than first sample
 - myoglobin on second sample 25% higher than first sample.
 - If cardiac markers negative, consider for discharge home.*

Appendix 2

Futility analysis

1. Following the problems surrounding the inadvertent release of some RATPAC data to the HTA, Professor Tom Walley, Director of the HTA programme, asked me to act as an interim chair of RATPAC's Data Monitoring and Ethics Committee (DMEC) in order to advise on whether the data supported the extension request.
2. I have met the RATPAC statisticians and reviewed the method that they used to calculate the conditional power of RATPAC. They used a method favoured by HTA, by calculating the power of achieving a statistically significant result given the current data and accruing new data up to the proposed sample size in accordance with the effect size specified in the alternative hypothesis in the protocol.
3. The current conditional power for the primary outcome (discharge home from the ED) recalculated using data to May 2009 is > 99.9%. The conditional power against the one secondary outcome that was originally powered in the protocol, major cardiac events, is < 10%. The current conditional power cannot be calculated for other secondary outcomes as no effect sizes were specified in alternative hypotheses in the protocol.
4. The conditional power calculation suggests that there could be a case for stopping for efficacy. There are no specific efficacy stopping criteria approved by the RATPAC DMEC in their charter, and this was appropriate because the primary outcome is not related to any direct clinical end point. Nevertheless, the absence of such criteria cannot be taken to mean that the trial should continue irrespective of any possible outcome, and the charter makes it clear that the DMEC can recommend stopping if the results are 'convincing' or futile.
5. In effect, the futility analysis suggests that the data must already be highly significant and that *there is no chance that future data could change the result*. This is not a situation that I had ever envisaged, but is, in fact, simply another type of futility.*
6. There are some other important considerations. First, the trial is being operated in several centres and the statisticians tell me that the results are not uniform across the centres, so that there may be important information on the variation in effect. Second, there are the other secondary outcomes, such as EQ-5D scores, satisfaction with care, re-attendance and readmission, which we know nothing about. Most importantly, the question of the cost-effectiveness of the intervention may not have been resolved, and this is the critical outcome for the NHS.
7. In summary, there are grounds for stopping the trial for futility. There is no chance that future data can change the result for the primary end point. However, as with all trials, RATPAC is also providing a great deal of other information on variability between centres, subgroups, and important secondary end points, whose current status we do not know about. The value of this information has to be weighed against the cost of the extension request.

Jon Nicholl
Acting as the interim chair of the RATPAC DMEC
12 May 2009

*Futility is usually understood to mean that there is little or no chance that future data could lead to a significant result. However, what we should mean by futility is that there is little or no chance future data could change the result. Thus, continuing a trial with a significant result that cannot be changed is as futile as continuing a trial with a non-significant result that cannot be changed. This is not the same as stopping for efficacy. Stopping for efficacy is based on a test of

the results under H_0 , not on the conditional power of achieving a significant result under H_1 . It is possible to stop for efficacy, even though it would not be technically futile to continue (i.e. the result could change). It is also possible to set the stopping rules for efficacy so tight that the reverse could happen, i.e. it is technically futile to continue though the efficacy stopping rule has not been reached.

Appendix 3

Primary outcome details at each hospital

Supplemental tables

TABLE 47 Primary outcome at Barnsley

	PoC [<i>n</i> (%)]	SC [<i>n</i> (%)]	Total [<i>n</i> (%)]
Successfully discharged	110 (68)	43 (26)	153 (47)
Not successfully discharged	52 (32)	121 (74)	173 (53)
Reason for no successful discharge			
In hospital 4 hours after arrival and no decision has been made to discharge	50 (31)	121 (74)	171 (52)
Initially discharged but re-attended with major adverse event	2 (1)	0	2 (1)
Discharge success by initial status			
Initially discharged	112 (69)	43 (26)	155 (48)
Not in hospital at 4 hours	105 (65)	43 (26)	148 (45)
In hospital at 4 hours, decision made to discharge	7 (4)	0	7 (2)

PoC, point of care; SC, standard care.
OR=5.95 (95% CI 3.69 to 9.61), $p<0.001$.

TABLE 48 Primary outcome at Derriford

	PoC [<i>n</i> (%)]	SC [<i>n</i> (%)]	Total [<i>n</i> (%)]
Successfully discharged	43 (26)	21 (13)	64 (20)
No successfully discharged	121 (74)	143 (87)	264 (80)
Reason for no successful discharge			
In hospital 4 hours after arrival and no decision has been made to discharge	121 (74)	142 (87)	263 (80)
Initially discharged but re-attended with major adverse event	0	1 (1)	1 (<1)
Discharge success by initial status			
Initially discharged	43 (26)	22 (13)	65 (20)
Not in hospital at 4 hours	29 (18)	18 (11)	47 (14)
In hospital at 4 hours, decision made to discharge	14 (9)	4 (2)	18 (5)

PoC, point of care; SC, standard care.
OR=2.42 (95% CI 1.36 to 4.30), $p=0.003$.

TABLE 49 Primary outcome at Edinburgh

	PoC [n (%)]	SC [n (%)]	Total [n (%)]
Successfully discharged	104 (46)	16 (7)	120 (27)
Not successfully discharged	124 (54)	208 (93)	332 (73)
Reason for no successful discharge			
In hospital 4 hours after arrival and no decision has been made to discharge	123 (54)	208 (93)	331 (73)
Initially discharged but re-attended with major adverse event	1 (<1)	0	1 (<1)
Discharge success by initial status			
Initially discharged	105 (46)	16 (7)	121 (27)
Not in hospital at 4 hours	90 (39)	16 (7)	106 (23)
In hospital at 4 hours, decision made to discharge	15 (7)	0	15 (3)

PoC, point of care; SC, standard care.
 OR=10.90 (95% CI 6.16 to 19.31), $p<0.001$.

TABLE 50 Primary outcome at Frenchay

	PoC [n (%)]	SC [n (%)]	Total [n (%)]
Successfully discharged	50 (21)	9 (4)	59 (13)
Not successfully discharged	183 (79)	222 (96)	405 (87)
Reason for no successful discharge			
In hospital 4 hours after arrival and no decision has been made to discharge	182 (78)	222 (96)	404 (87)
Initially discharged but re-attended with major adverse event	1 (<1)	0	1 (<1)
Discharge success by initial status			
Initially discharged	51 (22)	9 (4)	60 (13)
Not in hospital at 4 hours	44 (19)	5 (2)	49 (11)
In hospital at 4 hours, decision made to discharge	7 (3)	4 (2)	11 (2)

PoC, point of care; SC, standard care.
 OR=6.74 (95% CI 3.23 to 14.07), $p<0.001$.

TABLE 51 Primary outcome at Leeds

	PoC [n (%)]	SC [n (%)]	Total [n (%)]
Successfully discharged	1 (1)	8 (5)	9 (3)
Not successfully discharged	172 (99)	163 (95)	335 (97)
Reason for no successful discharge			
In hospital 4 hours after arrival and no decision has been made to discharge	172 (99)	163 (95)	335 (97)
Initially discharged but re-attended with major adverse event	0	0	0
Discharge success by initial status			
Initially discharged	1 (1)	8 (5)	9 (3)
Not in hospital at 4 hours	1 (1)	8 (5)	9 (3)
In hospital at 4 hours, decision made to discharge	0	0	0

PoC, point of care; SC, standard care.
 OR=0.12 (95% CI 0.01 to 0.96), $p=0.046$.

TABLE 52 Primary outcome at Leicester

	PoC [<i>n</i> (%)]	SC [<i>n</i> (%)]	Total [<i>n</i> (%)]
Successfully discharged	50 (30)	49 (30)	99 (30)
Not successfully discharged	115 (70)	115 (70)	230 (70)
<i>Reason for no successful discharge</i>			
In hospital 4 hours after arrival and no decision has been made to discharge	115 (70)	115 (70)	230 (70)
Initially discharged but re-attended with major adverse event	0	0	0
<i>Discharge success by initial status</i>			
Initially discharged	50 (30)	49 (30)	99 (30)
Not in hospital at 4 hours	50 (30)	44 (27)	94 (29)
In hospital at 4 hours, decision made to discharge	0	5 (3)	5 (2)

PoC, point of care; SC, standard care.

OR=1.02 (95% CI 0.64 to 1.63), *p*=0.933.

Appendix 4

Health economic parameter values used directly in model

Item	Deterministic value	Distributions for probabilistic sensitivity analysis					No. In RATPAC data
		Initial type	Parameter 1	Parameter 2	Transformed (if required)	Parameter 1	Parameter 2
Overall prevalence of ACS	11.8%	Beta	Alpha 264	Beta 1979			2243
Probabilities							
<i>Point-of-care arm</i>							
Frequency of PoC two-panel test	12.3%	Beta	138	987			1125
Test outcome positive given ACS (sensitivity)	78.8%	Beta	886	239			1125
Test outcome negative given no ACS (specificity)	74.6%	Beta	103	35			138
Admission positive test	98.7%	Beta	974	13			987
Admission negative test	100.0%	Fixed					116
Intervention (given admission)	0.0%	Fixed					1009
Alphas							
Thrombolysis	0.9%	Dirichlet	1				116
PCI	16.4%		19				116
CABG	8.6%		10				116
2×PCI	2.6%		3				116
PCI + CABG	0.9%		1				116
Thrombolysis + PCI + CABG	0.9%		1				116
No intervention	69.8%		81				116
Death after admission (assumes no intervention)	0.9%	Beta	1	115			116
Discharge	99.1%	Complement					116
Subsequent diagnosis given negative test	3.5%	Beta	35	974			1009
Subsequent intervention (admitted) after discharge							
PCI	31.4%	Dirichlet	11				35
PCI + CABG	2.9%		1				35
No intervention	65.7%		23				35
<i>Standard care arm</i>							
Prevalence of ACS	11.3%	Beta	126	992			1118
Test outcome positive given ACS (sensitivity)	82.5%	Beta	104	22			126
Test outcome negative given no ACS (specificity)	99.6%	Beta	988	4			992

Distributions for probabilistic sensitivity analysis							
Item	Deterministic value	Initial type	Transformed (if required)		No. In RATPAC data		
			Parameter 1	Parameter 2	Parameter 1	Parameter 2	
Admission given positive test	100%	Fixed					108
Admission given negative test	0.0%	Fixed					1010
Intervention (given admission)							
Thrombolysis	0.9%	Dirichlet	1				108
PCI	22.2%		24				108
CABG	3.7%		4				108
2×PCI	0.9%		1				108
PCI + CABG	0.9%		1				108
No intervention	71.3%		77				108
Death after admission (assumes no intervention)	0.9%	Beta	1	107			108
Discharge	99.1%	Complement					108
Subsequent diagnosis given negative test	2.2%	Beta	22	987			1009
Subsequent intervention (admitted) after discharge							
PCI	22.7%	Dirichlet	5	17			22
CABG	4.5%		1	21			22
No intervention	72.7%		16	6			22
Costs							
<i>Point-of-care arm^a</i>							
PoC test per panel cost ^b							
ED costs ^c	£21.33	Fixed					
			Mean	SD	Mean	Variance	
Staff ^d	£60.76	Log normal	60.76	34.15	3.970	0.275	122
Overheads	£19.32	Log normal	19.32	6.06	2.914	0.094	1125
Cardiac marker tests	£28.58	Log normal	28.58	16.35	3.211	0.283	1125
Medications	£5.56	Log normal	5.56	22.70	0.280	2.872	1125
Angiograms	£1.85	Log normal	1.85	15.39	-1.513	4.254	1125
ECGs	£33.44	Log normal	33.44	11.61	3.453	0.114	1125
Stay (if not admitted)	£21.62	Log normal	21.62	21.81	2.723	0.702	1125
Hospital stay (admitted from first ED presentation)							
PCI	£3058.46	Log normal	3058.46	2216.03	7.815	0.422	19

Distributions for probabilistic sensitivity analysis								
Item	Deterministic value	Initial type	Transformed (if required)		No. In RATPAC data			
			Parameter 1	Parameter 2				
CABG	£7155.76	Log normal	7155.76	4003.15	Normal	8.740	0.272	10
2×PCI	£2960.83	Log normal	2960.83	1587.27	Normal	7.867	0.253	3
PCI + CABG	£5247.99	Fixed	5247.99					1
Thrombolysis + PCI + CABG	£4452.18	Fixed	4452.18					1
No intervention	£2036.35	Log normal	2036.35	3013.93	Normal	7.039	1.160	81
Hospital stay (after discharge from ED)								
Thrombolysis	£0.00	Fixed						
PCI	£1386.02	Log normal	1386.02	1831.44	Normal	6.729	1.010	11
PCI + CABG	£2762.10	Fixed	2762.10					1
No intervention	£1648.11	Log normal	1648.11	1595.36	Normal	7.077	0.661	23
Hospital stay if no ACS diagnosed	£201.76	Log normal	201.76	728.86	Normal	3.986	2.643	974
Standard care arm								
ED costs								
Staff	£49.21	Log normal	49.21	22.54	Normal	3.801	0.190	124
Overhead costs	£17.09	Log normal	17.09	6.82	Normal	2.764	0.148	1118
Cardiac marker tests	£38.00	Log normal	38.00	14.98	Normal	3.565	0.144	1118
Medications	£5.21	Log normal	5.21	20.91	Normal	0.230	2.840	1118
Angiograms	£0.93	Log normal	0.93	10.96	Normal	−2.543	4.941	1118
ECGs	£35.39	Log normal	35.39	12.52	Normal	3.507	0.118	1118
Stay (if not admitted)	£13.86	Log normal	13.86	18.58	Normal	2.115	1.028	1118
Hospital stay (admitted from first ED presentation)								
Thrombolysis	£1381.05	Fixed	1381.05					1
PCI	£2320.10	Log normal	2320.10	1973.05	Normal	7.477	0.544	24
CABG	£6449.23	Log normal	6449.23	2233.36	Normal	8.715	0.113	4
2×PCI	£8573.45	Fixed	8573.45					1
Thrombolysis + PCI	£4728.39	Fixed	4728.39					1
No intervention	£1875.44	Log normal	1875.44	2311.45	Normal	7.075	0.924	77
Hospital stay (after discharge from ED)								
PCI	£939.11	Log normal	939.11	693.28	Normal	6.627	0.435	5
CABG	£6683.74	Fixed	6683.74					1
No intervention	£1398.31	Log normal	1398.31	1373.55	Normal	6.905	0.675	16

Distributions for probabilistic sensitivity analysis									
Item	Deterministic value	Transformed (if required)				No. in RATPAC data		Mean	SD
		Initial type	Parameter 1	Parameter 2	Parameter 2	Parameter 1	Parameter 2		
Hospital stay if no ACS diagnosed	£229.95	Log normal	229.95	661.58	Normal	4.324	2.228	988	
<i>Either arm</i>									
Hospital diagnostic test costs	£50.35	Log normal	50.35	89.34	Normal	3.208	1.423	2243	
Further ED attendances with no admission	£14.06	Log normal	14.06	54.19	Normal	1.261	2.764	2243	
Outpatient clinic visits	£31.44	Log normal	31.44	88.76	Normal	2.351	2.194	2243	
Planned follow-up care									
GP surgery visits	£152.66	Log normal	152.66	137.14	Normal	4.732	0.592	1292	
GP home visits	£11.03	Log normal	11.03	48.61	Normal	0.893	3.016	1088	
Nurse home visits	£7.80	Log normal	7.80	47.18	Normal	0.240	3.627	1083	
Social worker home visits	£5.52	Log normal	5.52	62.97	Normal	-0.731	4.877	1078	
Intervention									
CABG ⁵⁴	£6806.86	Fixed							
PCI ⁵⁴	£2012.97	Fixed							
Thrombolysis (medication only) ⁵⁰	£780.00	Fixed							
Long-term care cost of treatment ⁶	£10,748 (inflated to 2007–8 values) ⁵²	2005–6 cost	£10,079	£2200	Normal	£10,748	£2346		
Health-related quality of life									
<i>Point-of-care arm</i>									
QALYs (from admission after first ED presentation)									
Thrombolysis	0.107	Fixed	0.107					1	
PCI	0.154	Normal	0.154	0.038				19	
CABG	0.157	Normal	0.157	0.047				10	
2×PCI	0.169	Normal	0.169	0.034				3	
PCI+ CABG	0.096	Fixed	0.096					1	
Thrombolysis + PCI+ CABG	0.208	Fixed	0.208					1	
No intervention	0.154	Normal	0.154	0.044				81	

Distributions for probabilistic sensitivity analysis						
Item	Deterministic value	Initial type	Parameter 1	Parameter 2	Transformed (if required)	No. In RATPAC data
QALYs (after discharge from ED)						
PCI	0.153	Normal	0.153	0.014		11
PCI + CABG	0.169	Fixed	0.169			1
No intervention (if admitted)	0.139	Normal	0.139	0.053		23
If no ACS diagnosed	0.156	Normal	0.156	0.047		974
<i>Standard-care arm</i>						
QALYs (from admission after first ED presentation)						
Thrombolysis						
PCI	0.208	Fixed	0.208			1
CABG	0.160	Normal	0.160	0.040		24
2 × PCI	0.139	Normal	0.139	0.029		4
Thrombolysis + PCI	0.073	Fixed	0.073			1
No intervention	0.208	Fixed	0.208			1
QALYs (after discharge from ED)	0.155	Normal	0.155	0.039		77
QALYs (after discharge from ED)						
PCI	0.160	Normal	0.160	0.026		5
PCI + CABG	0.158	Fixed	0.158			1
No intervention (if admitted)	0.148	Normal	0.148	0.044		16
If no ACS diagnosed	0.158	Normal	0.158	0.042		988
<i>Other</i>						
Utility – death	0					
QALYs for long-term care with CHD ^a	6.829	Normal	6.829	0.340		
Lifetime accumulated QALYs for a UK person 55 years old in 2008 (30.3 years for males, 33.3 years for females) ^e	20	Normal	20	5		

^a RATPAC microcosting study.

^b Siemens UK Ltd, personal communication.

^c RATPAC microcosting study.

^d ESCAPE Trial results.

^e Office for National Statistics cohort expectation of life, 2008 – principal projection (table 18; http://www.statistics.gov.uk/downloads/theme_population/Interim_Life/period_cohort_tables_index08.pdf). Source: RATPAC main study data, unless indicated.

Appendix 5

The RATPAC trial protocol

Project title: The RATPAC trial (HTA 06/302/19) (Randomised Assessment of Treatment using Panel Assay of Cardiac markers)

A randomised controlled trial (RCT) of point-of-care cardiac markers in the emergency department.

Planned investigation

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 (ED).

In patients presenting to the ED 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 ED 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 evaluate:

1. clinical prediction rules, such as the TIMI (thrombolysis in myocardial infarction) and GRACE (Global Registry of Acute Coronary Events) scores
2. 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 AMI.¹ 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.

Existing research

Chest pain due to suspected but not proven AMI is responsible for a substantial number of ED attendances and emergency hospital admissions in the UK NHS.² 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 resources.⁵

Evidence also suggests that these guidelines are often not followed in a busy emergency setting in which acute beds are limited. Collinson *et al.*⁷ showed that 7% of patients discharged after ED assessment for acute chest pain had elevated troponin levels at follow-up 2 days later. Goodacre *et al.*⁸ 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 2-day follow-up had been sent home from the ED. Our recent national survey of EDs⁹ asked the lead consultant what proportion of patients with undifferentiated chest pain would be admitted to hospital. Estimates varied from <20% to >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 practice.¹⁰ 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.^{11,12} A typical panel will use a combination of early markers, such as myoglobin or creatinine kinase (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 ED, they can potentially rule out AMI during ED 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,^{13,14} but there have been no systematic reviews of point-of-care cardiac panels.¹⁵ 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 presentation.^{16–20} This results in earlier identification of AMI than laboratory testing¹⁸ and expedited decision-making with turnaround times reduced by 55%.¹⁹ Meanwhile, comparison of patient management with the panel with previous practice showed a 40% reduction in coronary care unit admissions.²⁰

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 Ng *et al.*²⁰ may be confounded by changes in coronary care referrals over time and, originating from the USA, where coronary care usage is much higher than in the UK, may not be applicable to the UK NHS. Audit data from the UK suggest that point-of-care cardiac testing can reduce hospital admissions, but this finding is based on before/after audit that has yet to be published in a peer-reviewed journal.²¹

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 al.*,²² 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 al.*²³ showed that use of a variety of point-of-care tests for a heterogeneous group of patients in the ED 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 study.²⁴ This is a randomised trial being undertaken in the USA to compare point-of-care troponin I testing with 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.

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 EDs in the UK.

Emergency department staff will identify eligible patients, provide trial information and obtain written consent. Participants will then be randomly allocated to receive either (1) diagnostic assessment using the point-of-care biochemical marker panel or (2) 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. ED 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 ED only after the participant's details have been recorded, written consent has been confirmed and the participant irrevocably entered into the trial.

This is a pragmatic trial that is intended to determine whether point-of-care testing should be standard practice for patients presenting to the ED 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. First, as outlined above, while 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.

Second, 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,^{5,8} 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 model.²⁵

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 a 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 used only in recruited intervention group patients, and are recorded and accounted for at the end of the trial.

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 ED, 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 above, this combination has been widely evaluated in practice.^{16–20} Of the systems currently available, or soon to be available, the latest version of the Dade Behring Stratus CS Analyser has the most data as an instrument suitable both for the emergency laboratory and for use as a point-of-care testing (POCT) instrument.²⁶

Clinical staff will be trained to use the test and give guidance in interpretation of the results. We will provide a recommended protocol that will advise a first panel test immediately after initial ED 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 POCT 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 George's Hospital for analysis to address the secondary objectives of the study.

Planned inclusion/exclusion criteria

We will recruit people presenting to the ED 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 (> 1 mm ST deviation or > 3 mm 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 (CHD) 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 comorbidity 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 ED 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.

Proposed outcome measures

The primary outcome will be the proportion of patients successfully discharged home after ED assessment, defined as discharge with no adverse event (as defined below) during the following 3 months.

Secondary outcomes will include:

1. Health utility measured using the European Quality of Life-5 Dimensions (EQ-5D) self-complete questionnaire at 1 and 3 months after attendance.
2. Satisfaction with care measured at 1 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 as angiography, percutaneous intervention or bypass grafting).
4. Re-attendance at and/or re-admission to hospital over the following 3 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 criteria.¹

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 TIMI²⁷ and GRACE²⁸ scoring and admission/discharge decision from the ED. Research nurses will use ED 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 3 months.

Research nurses will check patient status (dead or alive) at 1 and 3 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 1 and 3 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 1 month only). Our previous study suggests a 70–80% response rate to this questionnaire.⁸ We will therefore contact the general practitioner of all participants who do not respond at 3 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.

Proposed sample size (N=3130)

We anticipate that 50% of subjects will be successfully discharged in the group managed without the marker panel.⁸ 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 two-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.^{8,29–31} 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,^{8,29} 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.

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 CHD). The results will be presented as adjusted odds ratios along with their corresponding 95% CIs. 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 data sets. ROC curves will be constructed using the derivation data set 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.

Economic evaluation

An economic evaluation will be undertaken alongside the trial using recommended practice.³² 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 Guidelines,³³ 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 ED, the use of diagnostic tests, admissions, re-admissions, 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 microcosting 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. ED cost per minute will be based on a study previously undertaken by the investigators,⁸ and amended using the microcosting data from this study. Panel costs will be based on purchase price, and the remaining costs will be valued using national unit costs.^{34,35} Total NHS cost up to 3 months after initial attendance will then be calculated. Quality-adjusted life-years (QALYs) will be calculated by the trapezium rule using the EQ-5D 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 QALY of using point-of-care cardiac marker testing compared with 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 frontier.³⁶ 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 imputation.³⁷ 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 uncertainty.³⁸ 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 uncertainties.³⁹

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 EDs. 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.

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 studies.^{16–20} Furthermore, our own previous studies^{7,8} 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 1 and 3 months, before questionnaires are mailed.

Submission to a Multicentre Research Ethics Committee is currently under way. We will complete Local Research Ethics Committee reviews during the first 6 months of the timetable.

Research governance

This trial will be conducted in accordance with MRC *Guidelines for GCP 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 (DMEC)
- 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 DMEC 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.

Project timetable and milestones

The project will start on 1 April 2007. Months 1–6 will involve staff recruitment and local ethics and research governance; months 7–18 will involve patient recruitment; and months 19–24 will involve completion of follow-up, data analysis, writing up and dissemination. The project will be completed by 31 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 ×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 6-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.

Expertise

The trial will be coordinated by a trial manager in the Sheffield CTRU, working with full statistical, clinical trials and health economic support. The applicants are a multidisciplinary 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^{8,40} (SG, SC, SD), randomised evaluation of point-of-care cardiac markers in coronary care²² (PC), evaluation of ischaemia-modified albumin in emergency care^{31,41} (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 Trial⁴² (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.^{43,44}

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 be user representative on the Trial Steering Group. She has also created a CHD user group consisting of five people with CHD 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.

References

1. Joint European Society of Cardiology/American College of Cardiology Committee. 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**:1502–13.
2. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. *Heart* 2005;**91**:229–30.
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. Department of Health (DoH). *The National Service Framework for Coronary Heart Disease*. London: DoH; 2000.
5. Goodacre S, Calvert N. Cost effectiveness of diagnostic strategies for patients with acute, undifferentiated chest pain. *Emerg Med J* 2003;**20**:429–33.
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, Cross E, Angelini K, Revill C, *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. *Br J Cardiol* 2003;**10**:50–4.
9. Price CP. Point of care testing. *BMJ* 2001;**322**:1285–8.
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 +1.6 ng/ml. *Am Heart J* 1998;**136**:237–44.
11. Fesmire FM, Christensen RH, Focys 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**:550–6.
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**:478–94.
14. Craig J, Bradbury I, Collinson P, Emslie C, Findlay I, Hunt K, *et al.* *Health Technology Assessment Report Number 4: the organisation of troponin testing services in acute coronary syndromes*. Glasgow: NHS Quality Improvement Scotland; 2003.
15. McCord J, Nowak RM, McCullough PA, Foreback C, Borzak S, Tokarski G, *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, Andriak Aj, Berg A, Duh SH, *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, Garvey JL, Tucker JF, Kaplan AL, *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 F, 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, Clopton P, Fitzgerald R, Maisel AS, *et al.* Ninety-minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol* 2001;**88**:611–17.
20. Rocke LGR, McNicholl BP, Hughes D, Dunn F. *Chest pain observation units: are they really necessary?* URL: <http://bmj.bmjjournals.com/cgi/eletters/328/7434/254#49899>
21. Collinson PO, John C, Lynch S, Rao A, Canepa-Anson R, Carson E, *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 cTnI testing on outcomes*. URL: <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, Horacek T, Papuchis G, Mautner B, *et al.* The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–42.
27. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, *et al.* A validated prediction model for all forms of acute coronary syndrome. *JAMA* 2004;**291**:2727–33.
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**:369–76.
29. Conway Morris A, Caesar D, Gray S, Gray A. The TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. *Heart* 2006;**92**:1333–4.
30. Keating L, Benger J, Beetham R, Bateman S, Veysey S, Kendall J, Pullinger R. The PRIMA study: presentation IMA in the emergency department. *Emerg Med J* 2006;**23**:764–8.
31. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, *et al.* Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force Report. *Value Health* 2005;**8**:521–33.
32. National Institute for Clinical Excellence (NICE). *Guide to the methods of technology appraisal*. London: NICE; 2004.
33. Netten A, Curtis L. *Unit costs of health and social care 2004*. University of Kent: Personal Social Services Research Unit; 2004.
34. Department of Health (DoH). *NHS reference costs 2005*. URL: 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 Econ Lett* 2001;**10**:779–87.
36. Schafer J. *Analysis of incomplete multivariate data*. London: 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 Health* 2005;**8**:1–2.
39. NHS Service Delivery and Organisation (NHSSDO). *The ESCAPE multicentre trial of the role of chest pain units in the NHS (NHS Service Delivery and Organisation Programme)*. URL: www.shef.ac.uk/~scharr/escape
40. Collinson PO, Gaze DC, Bainbridge K, Morris F, Morris B, Price A, *et al.* Utility of admission cardiac troponin and ischemia modified albumin (IMA) measurements for rapid evaluation and rule out of suspected acute myocardial infarction in the emergency department. *Emerg Med J* 2006;**23**:256–61.
41. Gray A, Goodacre S, Newby D, Masson M, Sampson F, Nicholl J, on behalf of the 3CPO trialists. Effectiveness of non-invasive ventilation in patients with acute severe cardiogenic pulmonary oedema. *New Engl J Med* 2008;**359**:142–51.

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**:138–42.

Health Technology Assessment programme

Director,
Professor Tom Walley, CBE,
 Director, NIHR HTA programme, Professor of Clinical Pharmacology,
 University of Liverpool

Deputy Director,
Professor Hywel Williams,
 Professor of Dermato-Epidemiology,
 Centre of Evidence-Based Dermatology,
 University of Nottingham

Prioritisation Group

Members

Chair, Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	Dr Nick Hicks, Consultant Adviser – Diagnostic Technologies and Screening Panel, Consultant Advisor–Psychological and Community Therapies Panel	Professor Ruairidh Milne, Director – External Relations	Professor Lindsay Turnbull, Professor of Radiology, Centre for the MR Investigations, University of Hull
Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham Chair – Pharmaceuticals Panel	Ms Susan Hird, Consultant Advisor, External Devices and Physical Therapies Panel	Dr John Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust	Chair – Diagnostic Technologies and Screening Panel
Dr Bob Coates, Consultant Advisor – Disease Prevention Panel	Professor Sallie Lamb, Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick Chair – HTA Clinical Evaluation and Trials Board	Chair – External Devices and Physical Therapies Panel	Professor Scott Weich, Professor of Psychiatry, Health Sciences Research Institute, University of Warwick Chair – Psychological and Community Therapies Panel
Dr Andrew Cook, Consultant Advisor – Intervention Procedures Panel	Professor Jonathan Michaels, Professor of Vascular Surgery, Sheffield Vascular Institute, University of Sheffield Chair – Interventional Procedures Panel	Dr Vaughan Thomas, Consultant Advisor – Pharmaceuticals Panel, Clinical Lead – Clinical Evaluation Trials Prioritisation Group	Professor Hywel Williams, Director of Nottingham Clinical Trials Unit, Centre of Evidence-Based Dermatology, University of Nottingham Chair – HTA Commissioning Board
Dr Peter Davidson, Director of NETSCC, Health Technology Assessment		Professor Margaret Thorogood, Professor of Epidemiology, Health Sciences Research Institute, University of Warwick Chair – Disease Prevention Panel	Deputy HTA Programme Director

HTA Commissioning Board

Chair, Professor Hywel Williams, Professor of Dermato-Epidemiology, Centre of Evidence-Based Dermatology, University of Nottingham	Deputy Chair, Professor Jon Deeks, Department of Public Health and Epidemiology, University of Birmingham	Professor Tom Walley, CBE, Professor of Clinical Pharmacology, Director, NIHR HTA programme, University of Liverpool
--	---	--

Members

Professor Ann Ashburn, Professor of Rehabilitation and Head of Research, Southampton General Hospital	Professor John W Gregory, Professor in Paediatric Endocrinology, Department of Child Health, Wales School of Medicine, Cardiff University	Dr Martin J Landray, Reader in Epidemiology, Honorary Consultant Physician, Clinical Trial Service Unit, University of Oxford	Professor E Andrea Nelson, Professor of Wound Healing and Director of Research, School of Healthcare, University of Leeds
Professor Peter Brocklehurst, Professor of Women's Health, Institute for Women's Health, University College London	Professor Steve Halligan, Professor of Gastrointestinal Radiology, University College Hospital, London	Professor Stephen Morris, Professor of Health Economics, University College London, Research Department of Epidemiology and Public Health, University College London	Professor John David Norrie, Chair in Clinical Trials and Biostatistics, Robertson Centre for Biostatistics, University of Glasgow
Professor Jenny Donovan, Professor of Social Medicine, University of Bristol	Professor Freddie Hamdy, Professor of Urology, Head of Nuffield Department of Surgery, University of Oxford	Professor Irwin Nazareth, Professor of Primary Care and Head of Department, Department of Primary Care and Population Sciences, University College London	Dr Rafael Perera, Lecturer in Medical Statistics, Department of Primary Health Care, University of Oxford
Professor Jonathan Green, Professor and Acting Head of Department, Child and Adolescent Psychiatry, University of Manchester Medical School	Professor Allan House, Professor of Liaison Psychiatry, University of Leeds		

HTA Commissioning Board *(continued)*

Professor Barney Reeves,
Professorial Research Fellow
in Health Services Research,
Department of Clinical Science,
University of Bristol

Professor Martin Underwood,
Professor of Primary Care
Research, Warwick Medical
School, University of Warwick

Professor Marion Walker,
Professor in Stroke Rehabilitation,
Associate Director UK Stroke
Research Network, University of
Nottingham

Dr Duncan Young,
Senior Clinical Lecturer and
Consultant, Nuffield Department
of Anaesthetics, University of
Oxford

Observers

Dr Tom Foulks,
Medical Research Council

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

HTA Clinical Evaluation and Trials Board

Chair,

Professor Sallie Lamb,
Director,
Warwick Clinical Trials Unit,
Warwick Medical School,
University of Warwick and Professor of
Rehabilitation,
Nuffield Department of Orthopaedic,
Rheumatology and Musculoskeletal Sciences,
University of Oxford

Deputy Chair,

Professor Jenny Hewison,
Professor of the Psychology of Health Care,
Leeds Institute of Health Sciences,
University of Leeds

Programme Director,

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of
Clinical Pharmacology, University of Liverpool

Members

Professor Keith Abrams,
Professor of Medical Statistics,
Department of Health Sciences,
University of Leicester

Dr Jennifer Burr,
Director, Centre for Healthcare
Randomised trials (CHART),
University of Aberdeen

Professor Paul Jones,
Professor of Respiratory Medicine,
Department of Cardiac and
Vascular Science, St George's
Hospital Medical School,
University of London

Professor Jonathan Sterne,
Professor of Medical Statistics
and Epidemiology, Department
of Social Medicine, University of
Bristol

Professor Martin Bland,
Professor of Health Statistics,
Department of Health Sciences,
University of York

Professor Linda Davies,
Professor of Health Economics,
Health Sciences Research Group,
University of Manchester

Professor Khalid Khan,
Professor of Women's Health and
Clinical Epidemiology, Barts and
the London School of Medicine,
Queen Mary, University of London

Mr Andy Vail,
Senior Lecturer, Health Sciences
Research Group, University of
Manchester

Professor Jane Blazeby,
Professor of Surgery and
Consultant Upper GI Surgeon,
Department of Social Medicine,
University of Bristol

Professor Simon Gilbody,
Prof of Psych Medicine and Health
Services Research, Department of
Health Sciences, University of York

Professor Richard J McManus,
Professor of Primary Care
Cardiovascular Research, Primary
Care Clinical Sciences Building,
University of Birmingham

Professor Clare Wilkinson,
Professor of General Practice and
Director of Research North Wales
Clinical School, Department of
Primary Care and Public Health,
Cardiff University

Professor Julia M Brown,
Director, Clinical Trials Research
Unit, University of Leeds

Professor Steven Goodacre,
Professor and Consultant in
Emergency Medicine, School of
Health and Related Research,
University of Sheffield

Professor Helen Rodgers,
Professor of Stroke Care, Institute
for Ageing and Health, Newcastle
University

Dr Ian B Wilkinson,
Senior Lecturer and Honorary
Consultant, Clinical Pharmacology
Unit, Department of Medicine,
University of Cambridge

Professor Alistair Burns,
Professor of Old Age Psychiatry,
Psychiatry Research Group, School
of Community-Based Medicine,
The University of Manchester &
National Clinical Director for
Dementia, Department of Health

Professor Dyfrig Hughes,
Professor of Pharmacoeconomics,
Centre for Economics and Policy
in Health, Institute of Medical
and Social Care Research, Bangor
University

Professor Ken Stein,
Professor of Public Health,
Peninsula Technology Assessment
Group, Peninsula College
of Medicine and Dentistry,
Universities of Exeter and
Plymouth

Observers

Ms Kate Law,
Director of Clinical Trials,
Cancer Research UK

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Diagnostic Technologies and Screening Panel

Members

Chair, Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, University of Manchester Mr Angus S Arunkalaivanan, Honorary Senior Lecturer, University of Birmingham and Consultant Urogynaecologist and Obstetrician, City Hospital, Birmingham Dr Diana Baralle, Consultant and Senior Lecturer in Clinical Genetics, University of Southampton	Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride Dr Diane Eccles, Professor of Cancer Genetics, Wessex Clinical Genetics Service, Princess Anne Hospital Dr Trevor Friedman, Consultant Liaison Psychiatrist, Brandon Unit, Leicester General Hospital Dr Ron Gray, Consultant, National Perinatal Epidemiology Unit, Institute of Health Sciences, University of Oxford Professor Paul D Griffiths, Professor of Radiology, Academic Unit of Radiology, University of Sheffield Mr Martin Hooper, Public contributor	Professor Anthony Robert Kendrick, Associate Dean for Clinical Research and Professor of Primary Medical Care, University of Southampton Dr Nicola Lennard, Senior Medical Officer, MHRA Dr Anne Mackie, Director of Programmes, UK National Screening Committee, London Mr David Mathew, Public contributor Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Department of Pathology & Microbiology, Barts and The London NHS Trust, Royal London Hospital Mrs Una Rennard, Public contributor	Dr Stuart Smellie, Consultant in Clinical Pathology, Bishop Auckland General Hospital Ms Jane Smith, Consultant Ultrasound Practitioner, Leeds Teaching Hospital NHS Trust, Leeds Dr Allison Streetly, Programme Director, NHS Sickle Cell and Thalassaemia Screening Programme, King's College School of Medicine Dr Matthew Thompson, Senior Clinical Scientist and GP, Department of Primary Health Care, University of Oxford Dr Alan J Williams, Consultant Physician, General and Respiratory Medicine, The Royal Bournemouth Hospital
--	--	---	---

Observers

Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health Dr Joanna Jenkinson, Board Secretary, Neurosciences and Mental Health Board (NMHB), Medical Research Council	Professor Julietta Patnick, Director, NHS Cancer Screening Programme, Sheffield Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health
--	--	---	---

Disease Prevention Panel

Members

Chair, Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick Medical School, Coventry Dr Robert Cook, Clinical Programmes Director, Bazian Ltd, London Dr Colin Greaves, Senior Research Fellow, Peninsula Medical School (Primary Care) Mr Michael Head, Public contributor	Professor Cathy Jackson, Professor of Primary Care Medicine, Bute Medical School, University of St Andrews Dr Russell Jago, Senior Lecturer in Exercise, Nutrition and Health, Centre for Sport, Exercise and Health, University of Bristol Dr Julie Mytton, Consultant in Child Public Health, NHS Bristol	Professor Irwin Nazareth, Professor of Primary Care and Director, Department of Primary Care and Population Sciences, University College London Dr Richard Richards, Assistant Director of Public Health, Derbyshire County Primary Care Trust Professor Ian Roberts, Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine	Dr Kenneth Robertson, Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow Dr Catherine Swann, Associate Director, Centre for Public Health Excellence, NICE Mrs Jean Thurston, Public contributor Professor David Weller, Head, School of Clinical Science and Community Health, University of Edinburgh
---	--	--	--

Observers

Ms Christine McGuire, Research & Development, Department of Health	Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool
---	---	---

External Devices and Physical Therapies Panel

Members

Chair,
Dr John Pounsford,
Consultant Physician North Bristol
NHS Trust

Deputy Chair,
Professor E Andrea Nelson,
Reader in Wound Healing and
Director of Research, University
of Leeds

Professor Bipin Bhakta,
Charterhouse Professor in
Rehabilitation Medicine,
University of Leeds

Mrs Penny Calder,
Public contributor

Dr Dawn Carnes,
Senior Research Fellow, Barts and
the London School of Medicine
and Dentistry

Dr Emma Clark,
Clinician Scientist Fellow & Cons.
Rheumatologist, University of
Bristol

Mrs Anthea De Barton-Watson,
Public contributor

Professor Nadine Foster,
Professor of Musculoskeletal
Health in Primary Care Arthritis
Research, Keele University

Dr Shaheen Hamdy,
Clinical Senior Lecturer and
Consultant Physician, University
of Manchester

Professor Christine Norton,
Professor of Clinical Nursing
Innovation, Bucks New University
and Imperial College Healthcare
NHS Trust

Dr Lorraine Pinnigton,
Associate Professor in
Rehabilitation, University of
Nottingham

Dr Kate Radford,
Senior Lecturer (Research),
University of Central Lancashire

Mr Jim Reece,
Public contributor

Professor Maria Stokes,
Professor of Neuromusculoskeletal
Rehabilitation, University of
Southampton

Dr Pippa Tyrrell,
Senior Lecturer/Consultant,
Salford Royal Foundation
Hospitals' Trust and University of
Manchester

Dr Nefyn Williams,
Clinical Senior Lecturer, Cardiff
University

Observers

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Professor Tom Walley, CBE,
Director, NIHR HTA
programme, Professor of Clinical
Pharmacology, University of
Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy
Research Programme, Department
of Health

Interventional Procedures Panel

Members

Chair,
Professor Jonathan Michaels,
Professor of Vascular Surgery,
University of Sheffield

Deputy Chair,
Mr Michael Thomas,
Consultant Colorectal Surgeon,
Bristol Royal Infirmary

Mrs Isabel Boyer,
Public contributor

Mr Sankaran Chandra Sekharan,
Consultant Surgeon, Breast
Surgery, Colchester Hospital
University NHS Foundation Trust

Professor Nicholas Clarke,
Consultant Orthopaedic Surgeon,
Southampton University Hospitals
NHS Trust

Ms Leonie Cooke,
Public contributor

Mr Seumas Eckford,
Consultant in Obstetrics &
Gynaecology, North Devon
District Hospital

Professor Sam Eljamel,
Consultant Neurosurgeon,
Ninewells Hospital and Medical
School, Dundee

Dr Adele Fielding,
Senior Lecturer and Honorary
Consultant in Haematology,
University College London
Medical School

Dr Matthew Hatton,
Consultant in Clinical Oncology,
Sheffield Teaching Hospital
Foundation Trust

Dr John Holden,
General Practitioner, Garswood
Surgery, Wigan

Dr Fiona Lecky,
Senior Lecturer/Honorary
Consultant in Emergency
Medicine, University of
Manchester/Salford Royal
Hospitals NHS Foundation Trust

Dr Nadim Malik,
Consultant Cardiologist/Honorary
Lecturer, University of Manchester

Mr Hisham Mehanna,
Consultant & Honorary Associate
Professor, University Hospitals
Coventry & Warwickshire NHS
Trust

Dr Jane Montgomery,
Consultant in Anaesthetics and
Critical Care, South Devon
Healthcare NHS Foundation Trust

Professor Jon Moss,
Consultant Interventional
Radiologist, North Glasgow
Hospitals University NHS Trust

Dr Simon Padley,
Consultant Radiologist, Chelsea &
Westminster Hospital

Dr Ashish Paul,
Medical Director, Bedfordshire
PCT

Dr Sarah Purdy,
Consultant Senior Lecturer,
University of Bristol

Dr Matthew Wilson,
Consultant Anaesthetist,
Sheffield Teaching Hospitals NHS
Foundation Trust

Professor Yit Chiun Yang,
Consultant Ophthalmologist,
Royal Wolverhampton Hospitals
NHS Trust

Observers

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Professor Tom Walley, CBE,
Director, NIHR HTA
programme, Professor of Clinical
Pharmacology, University of
Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy
Research Programme, Department
of Health

Pharmaceuticals Panel

Members

Chair, Professor Imti Choonara, Professor in Child Health, University of Nottingham	Dr James Gray, Consultant Microbiologist, Department of Microbiology, Birmingham Children's Hospital NHS Foundation Trust	Dr Maria Kouimtzi, Pharmacy and Informatics Director, Global Clinical Solutions, Wiley-Blackwell	Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool
Deputy Chair, Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia	Dr Jurjees Hasan, Consultant in Medical Oncology, The Christie, Manchester	Professor Femi Oyeboode, Consultant Psychiatrist and Head of Department, University of Birmingham	Professor Donald Singer, Professor of Clinical Pharmacology and Therapeutics, Clinical Sciences Research Institute, CSB, University of Warwick Medical School
Dr Martin Ashton-Key, Medical Advisor, National Commissioning Group, NHS London	Dr Carl Heneghan, Deputy Director Centre for Evidence-Based Medicine and Clinical Lecturer, Department of Primary Health Care, University of Oxford	Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge	Mr David Symes, Public contributor
Dr Peter Elton, Director of Public Health, Bury Primary Care Trust	Dr Dyfrig Hughes, Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University	Ms Amanda Roberts, Public contributor	Dr Arnold Zermansky, General Practitioner, Senior Research Fellow, Pharmacy Practice and Medicines Management Group, Leeds University
Dr Ben Goldacre, Research Fellow, Epidemiology London School of Hygiene and Tropical Medicine		Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd	

Observers

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Dr Heike Weber, Programme Manager, Medical Research Council	Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health
Mr Simon Reeve, Head of Clinical and Cost- Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	

Psychological and Community Therapies Panel

Members

Chair, Professor Scott Weich, Professor of Psychiatry, University of Warwick, Coventry	Mrs Val Carlill, Public contributor	Dr Jeremy J Murphy, Consultant Physician and Cardiologist, County Durham and Darlington Foundation Trust	Dr Paul Ramchandani, Senior Research Fellow/Cons. Child Psychiatrist, University of Oxford
Deputy Chair, Dr Howard Ring, Consultant & University Lecturer in Psychiatry, University of Cambridge	Dr Steve Cunningham, Consultant Respiratory Paediatrician, Lothian Health Board	Dr Richard Neal, Clinical Senior Lecturer in General Practice, Cardiff University	Dr Karen Roberts, Nurse/Consultant, Dunston Hill Hospital, Tyne and Wear
Professor Jane Barlow, Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School	Dr Anne Hesketh, Senior Clinical Lecturer in Speech and Language Therapy, University of Manchester	Mr John Needham, Public contributor	Dr Karim Saad, Consultant in Old Age Psychiatry, Coventry and Warwickshire Partnership Trust
Dr Sabyasachi Bhaumik, Consultant Psychiatrist, Leicestershire Partnership NHS Trust	Dr Peter Langdon, Senior Clinical Lecturer, School of Medicine, Health Policy and Practice, University of East Anglia	Ms Mary Nettle, Mental Health User Consultant	Dr Lesley Stockton, Lecturer, School of Health Sciences, University of Liverpool
	Dr Yann Lefevre, GP Partner, Burrage Road Surgery, London	Professor John Potter, Professor of Ageing and Stroke Medicine, University of East Anglia	Dr Simon Wright, GP Partner, Walkden Medical Centre, Manchester
		Dr Greta Rait, Senior Clinical Lecturer and General Practitioner, University College London	

Observers

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Dr Morven Roberts, Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health
--	--	--	---

Expert Advisory Network

Members

Professor Douglas Altman,
Professor of Statistics in Medicine,
Centre for Statistics in Medicine,
University of Oxford

Professor John Bond,
Professor of Social Gerontology
& Health Services Research,
University of Newcastle upon Tyne

Professor Andrew Bradbury,
Professor of Vascular Surgery,
Solihull Hospital, Birmingham

Mr Shaun Brogan,
Chief Executive, Ridgeway
Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Regulation and
Improvement Authority, Belfast

Ms Tracy Bury,
Project Manager, World
Confederation of Physical Therapy,
London

Professor Iain T Cameron,
Professor of Obstetrics and
Gynaecology and Head of the
School of Medicine, University of
Southampton

Professor Bruce Campbell,
Consultant Vascular & General
Surgeon, Royal Devon & Exeter
Hospital, Wonford

Dr Christine Clark,
Medical Writer and Consultant
Pharmacist, Rossendale

Professor Collette Clifford,
Professor of Nursing and Head
of Research, The Medical School,
University of Birmingham

Professor Barry Cookson,
Director, Laboratory of Hospital
Infection, Public Health
Laboratory Service, London

Dr Carl Counsell,
Clinical Senior Lecturer in
Neurology, University of Aberdeen

Professor Howard Cuckle,
Professor of Reproductive
Epidemiology, Department
of Paediatrics, Obstetrics &
Gynaecology, University of Leeds

Professor Carol Dezateux,
Professor of Paediatric
Epidemiology, Institute of Child
Health, London

Mr John Dunning,
Consultant Cardiothoracic
Surgeon, Papworth Hospital NHS
Trust, Cambridge

Mr Jonathan Earnshaw,
Consultant Vascular Surgeon,
Gloucestershire Royal Hospital,
Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness,
Centre for Health Services
Research, University of Newcastle
upon Tyne

Professor Pam Enderby,
Dean of Faculty of Medicine,
Institute of General Practice
and Primary Care, University of
Sheffield

Professor Gene Feder,
Professor of Primary Care
Research & Development, Centre
for Health Sciences, Barts and The
London School of Medicine and
Dentistry

Mr Leonard R Fenwick,
Chief Executive, Freeman
Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher,
Antenatal Teacher and Tutor and
President, National Childbirth
Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, University
of Birmingham

Mr Tam Fry,
Honorary Chairman, Child
Growth Foundation, London

Professor Fiona Gilbert,
Consultant Radiologist and NCRN
Member, University of Aberdeen

Professor Paul Gregg,
Professor of Orthopaedic Surgical
Science, South Tees Hospital NHS
Trust

Bec Hanley,
Co-director, TwoCan Associates,
West Sussex

Dr Maryann L Hardy,
Senior Lecturer, University of
Bradford

Mrs Sharon Hart,
Healthcare Management
Consultant, Reading

Professor Robert E Hawkins,
CRC Professor and Director of
Medical Oncology, Christie CRC
Research Centre, Christie Hospital
NHS Trust, Manchester

Professor Richard Hobbs,
Head of Department of Primary
Care & General Practice,
University of Birmingham

Professor Alan Horwich,
Dean and Section Chairman,
The Institute of Cancer Research,
London

Professor Allen Hutchinson,
Director of Public Health and
Deputy Dean of ScHARR,
University of Sheffield

Professor Peter Jones,
Professor of Psychiatry, University
of Cambridge, Cambridge

Professor Stan Kaye,
Cancer Research UK Professor of
Medical Oncology, Royal Marsden
Hospital and Institute of Cancer
Research, Surrey

Dr Duncan Keeley,
General Practitioner (Dr Burch &
Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme
Director and Reader in
Psychology, Health Services
Research Unit, London School of
Hygiene and Tropical Medicine,
London

Professor James Lindesay,
Professor of Psychiatry for the
Elderly, University of Leicester

Professor Julian Little,
Professor of Human Genome
Epidemiology, University of
Ottawa

Professor Alistaire McGuire,
Professor of Health Economics,
London School of Economics

Professor Neill McIntosh,
Edward Clark Professor of Child
Life and Health, University of
Edinburgh

Professor Rajan Madhok,
Consultant in Public Health, South
Manchester Primary Care Trust

Professor Sir Alexander Markham,
Director, Molecular Medicine
Unit, St James's University
Hospital, Leeds

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Public Health Director,
Southampton City Primary Care
Trust

Dr Sue Moss,
Associate Director, Cancer
Screening Evaluation Unit,
Institute of Cancer Research,
Sutton

Professor Miranda Mugford,
Professor of Health Economics
and Group Co-ordinator,
University of East Anglia

Professor Jim Neilson,
Head of School of Reproductive
& Developmental Medicine
and Professor of Obstetrics
and Gynaecology, University of
Liverpool

Mrs Julietta Patnick,
Director, NHS Cancer Screening
Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe, Stoke
Poges

Professor William Rosenberg,
Professor of Hepatology and
Consultant Physician, University
of Southampton

Professor Peter Sandercock,
Professor of Medical Neurology,
Department of Clinical
Neurosciences, University of
Edinburgh

Dr Philip Shackley,
Senior Lecturer in Health
Economics, Sheffield Vascular
Institute, University of Sheffield

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St
James's University Hospital, Leeds

Dr Margaret Somerville,
Director of Public Health
Learning, Peninsula Medical
School, University of Plymouth

Professor Sarah Stewart-Brown,
Professor of Public Health,
Division of Health in the
Community, University of
Warwick, Coventry

Dr Nick Summerton,
GP Appraiser and Codirector,
Research Network, Yorkshire
Clinical Consultant, Primary Care
and Public Health, University of
Oxford

Professor Ala Szczepura,
Professor of Health Service
Research, Centre for Health
Services Studies, University of
Warwick, Coventry

Dr Ross Taylor,
Senior Lecturer, University of
Aberdeen

Dr Richard Tiner,
Medical Director, Medical
Department, Association of the
British Pharmaceutical Industry

Mrs Joan Webster,
Consumer Member, Southern
Derbyshire Community Health
Council

Professor Martin Whittle,
Clinical Co-director, National
Co-ordinating Centre for Women's
and Children's Health, Lymington

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.