Diagnostics Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Protocol

Title of project
High sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction (AMI) in people with acute chest pain

Name of External Assessment Group (EAG) and project lead
Kleijnen Systematic Reviews Ltd. Assessment Group

Project lead: Marie Westwood
Second Contact: Penny Whiting
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York YO19 6FD
Tel: 01904 727983
Email: marie@systematic-reviews.com; penny@systematic-reviews.com

Health economics lead: Thea van Asselt
Second contact: Bram Ramaekers
Department of Clinical Epidemiology and Medical Technology Assessment
Maastricht University Medical Centre
P.O. Box 5800
6200 AZ Maastricht
The Netherlands
Tel: +31-43-3875587
Email: thea.van.asselt@mumc.nl; bram.ramaekers@mumc.nl
1 Plain English Summary
Heart disease is a leading cause of death in the UK, with myocardial infarction (MI) (heart attack) accounting for approximately 5% of all deaths recorded in 2011. Many people attend hospital with chest pain and suspected MI; chest pain has been reported as the most common cause of hospital admissions in the UK and 2011-2012 statistics showed that it accounted for approximately 5% of all emergency admissions. It is important to diagnose people who are suspected of having an MI as early as possible in order to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will actually have an MI and there are many other possible causes of chest pain (e.g. gastrooesophageal disorders, muscle pain, anxiety, or stable ischaemic heart disease). Tests which can quickly tell which patients do not have MI could therefore avoid unnecessary hospital admissions and anxiety for many people.

Some types of MI can be easily and quickly diagnosed using an electrocardiogram (ECG). Others are currently diagnosed based on levels of certain proteins in the blood (cardiac biomarkers) such as troponins, which go up when heart muscle is damaged. However, because it takes time for levels to increase to amounts which can be measured, diagnosis can be delayed for up to 12 hours after the first chest pain. New methods have recently been developed which can detect lower levels of troponins in the blood (high sensitivity troponin tests). The use of these methods may help to achieve earlier diagnosis or rule-out of MI.

This diagnostics assessment report will assess the clinical- and cost-effectiveness of high sensitivity troponin tests, used as single tests or repeated over a short time, for the diagnosis of people who present to hospital with chest pain and suspected MI.
2  Decision problem

2.1  Population

The primary indication for this assessment is the early rule-out of acute myocardial infarction (AMI) and consequent early discharge in people presenting with acute chest pain and suspected, but not confirmed, non-ST segment elevation myocardial infarction (NSTEMI). The assessment will also consider the potential effects of early diagnosis of AMI and of reduced specificity of testing.

Acute coronary syndrome (ACS) is the term used to describe a spectrum of conditions caused by coronary artery disease (CAD). ACS arises when atheromatous plaque ruptures or erodes leading to vasospasm, thrombus formation and distal embolisation, obstructing blood flow through the coronary arteries. It incorporates three distinct conditions: unstable angina, ST segment elevation myocardial infarction (STEMI) and NSTEMI. Coronary artery disease and myocardial infarction are a significant health burden in the UK, with Office of National Statistics (ONS) mortality data for 2011 showing 23,705 deaths from AMI and 64,435 deaths from ischaemic heart disease; AMI accounted for approximately 5% of all deaths recorded in 2011 and ischaemic heart disease accounted for approximately 13%.1

Acute coronary syndrome usually presents as chest pain and chest pain has been reported as the most common cause of hospital admissions in the UK;2 Hospital Episode Statistics (HES) for 2011-2012 show 243,197 emergency admissions for chest pain, accounting for approximately 5% of all emergency admissions.3 However, many people presenting with acute chest pain will have non-cardiac underlying causes, such as gastro-oesophageal disorders, muscle pain, anxiety, or stable ischaemic heart disease. A 2003 study on the impact of cardiology guidelines on the diagnostic classification of people with ACS in the UK reported that the majority people admitted to hospital with chest pain have either no ischaemic heart disease or stable ischaemic heart disease.4 Hospital Episode Statistics (HES) for 2011-2012 are consistent with this observation, showing diagnoses of AMI in 47,783 emergency admissions and unstable angina in 32,369 admissions; this represents approximately 20% and 13% of emergency admissions with chest pain, respectively.3 Accurate and prompt differentiation of ACS (in particular AMI), stable CAD and other causes of chest pain is therefore vital to ensure appropriate and timely intervention where required and to avoid unnecessary hospital admissions.

STEMI can usually be diagnosed on presentation by electrocardiogram, hence the main diagnostic challenge in the investigation of suspected ACS is the detection or rule-out of NSTEMI. Investigation of ACS can also involve identification of people with unstable angina (CAD with worsening symptoms, but no evidence of myocardial necrosis). However, cardiac biomarkers are becoming increasingly sensitive and recent European Society of Cardiology
(ESC) and American College of Cardiology (ACC) guidelines enable AMI to be diagnosed with any rise and/or fall of troponin to above the laboratory reference range.\textsuperscript{5,6} This has resulted in fewer people being classified as having unstable angina with no myocardial damage and more people being classified as having NSTEMI.\textsuperscript{7}

Since the development of protein biomarkers of myocardial damage in the 1980s, the number of biomarker assays available has proliferated, cardiac specificity has increased, and the role of biomarkers in the diagnostic work-up of acute chest pain has expanded. The most recent two years of Hospital Episode Statistics show the number of Emergency Department attendances, where the first recorded investigation was a cardiac biomarker, rising from 13,743 in 2010-2011 to 28,379 in 2011-2012.\textsuperscript{3} Cardiac troponins I and T (cTnI and cTnT), together with cardiac troponin C, form the troponin-tropomyosin complex which is responsible for regulating cardiac muscle contraction. cTnI and cTnT are used clinically as markers of cardiomyocyte necrosis, indicative of AMI. Troponin assays are intended for use in conjunction with clinical history taking and electrocardiography (ECG) monitoring as, although specificity is high, troponins may also be elevated in many other conditions including myocarditis, congestive heart failure, severe infections, renal disease and chronic inflammatory conditions of the muscle or skin. Standard biochemical diagnosis of NSTEMI is based on elevation of the cardiac biomarker troponin above the 99\textsuperscript{th} percentile of the reference range for the normal population.\textsuperscript{8} Elevated troponin levels have been shown to be associated with an increased risk of adverse cardiac outcomes.\textsuperscript{9} However, the optimal sensitivity of standard troponin assays for MI occurs several hours after the onset of symptoms;\textsuperscript{10} this is reflected in current clinical guidelines, which recommend cTnI or cTnT testing at initial hospital assessment and again 10-12 hours after the onset of symptoms.\textsuperscript{11,12} Since the majority of people presenting with chest pain do not have NSTEMI, where presentation is within a few hours of symptom onset, delayed biomarker measurement may result in unnecessary periods of extended observation or hospitalisation and associated costs. The development of cardiac biomarkers which can be used at an earlier stage without reduction in sensitivity is, therefore, desirable.

### 2.2 Intervention technologies

High-sensitivity cTn (hs-cTn) assays are now available, which are able to detect lower levels of troponin in the blood. Current generations of commercially available assays have analytical sensitivities up to 100 times greater than was the case for early troponin assays (1 ng/L versus 100 ng/L).\textsuperscript{13} Use of these high-sensitivity assays enable the detection of small changes in cTn levels, and may enable AMI to be ruled out at an earlier time after the onset of acute chest pain. Use of the hs-cTn assays has the potential to facilitate earlier discharge for people with normal cTn levels and earlier intervention for those with elevated levels of cTn. The recommended definition of an hs-cTn assay uses two criteria:\textsuperscript{13,14}
The total imprecision, co-efficient of variation (CV), of the assay should be ≤10% at the 99th percentile value for the healthy reference population.

The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally >95%) of healthy individuals.

A number of high-sensitivity cTnI and cTnT (hs-cTnI and hs-cTnT) assays are currently available for use in the NHS in England and Wales; all are designed for use in clinical laboratory settings.

**ARCHITECT high-sensitivity troponin I assay (Abbott Diagnostics)**

The ARCHITECT hs-cTnI STAT assay can be used with the Abbott ARCHITECT i2000SR and i1000SR analysers. The assay is a quantitative, chemiluminescent micro particle immunoassay (CMIA) for serum or plasma samples. Results are available within 16 minutes. The ARCHITECT hs-cTnI STAT assay can detect cTnI in 96% of the reference population, and has a recommended 99th percentile cut-off of 26.2ng/L with a CV of 4%. The assay is CE marked and available to the NHS.

**AccuTnI+3 troponin I assay (Beckman-Coulter)**

The AccuTnI+3 hs-cTnI assay is currently being approved for use on both the Beckman Coulter Access 2 and DxI analysers. The assay is a quantitative, two-site paramagnetic particle chemiluminescent sandwich immunoassay for serum or plasma samples. The AccuTnI+3 assay has a recommended 99th percentile cut-off of 40ng/L with a CV of 10%. The assay has been submitted for CE mark approval, and has an anticipated NHS launch date of September 2013.

**The Elecsys troponin T high-sensitive assay (Roche)**

The Elecsys cTnT-hs and Elecsys cTnT-hs STAT assays can be used on the Roche Elecsys 2010 analyser and the cobas Modular Analytics e series immunoassay analysers. The assay is a quantitative, sandwich electrochemiluminescence immunoassay (ECLIA) for serum and plasma samples. Results are available within 18 minutes with the standard assay and within 9 minutes if the STAT assay is used. Both versions of the assay can detect cTnT in 61% of the reference population and have a recommended 99th percentile cut off of 14ng/L with a CV of <10%. Both versions of the assay are CE marked and available to the NHS.

A summary of the product properties of hs-cTnI and hs-cTnT assays available as single tests or cardiac biomarker panels in the NHS in England and Wales is provided in Table 1.

hs-cTn assays can be used as single diagnostic tests, or in combination with other cardiac biomarkers, e.g. heart fatty acid binding protein (H-FABP) and copeptin. The use of combinations of cardiac biomarkers may increase sensitivity, where a positive result on
either test is considered to be indicative of AMI, though this increase may be achieved at the expense of decreased specificity. Conversely, if a positive result on both tests is required before AMI is diagnosed, increased specificity and reduced sensitivity are likely. It is currently unclear which, if any, of the available cardiac biomarkers could add clinical benefit if used in combination with hs-cTnl and hs-cTnT, compared to hs-cTnl and hs-cTnT alone. A recent systematic review reported some data for combination testing, but none of the identified studies of troponins combined with other biomarkers used high sensitivity methods.\textsuperscript{7} Retrospective analysis of data from one arm of a randomised controlled trial by the same authors provided some indication that the use of H-FABP in combination with hs-cTn, on admission, may increase sensitivity for AMI without decreasing specificity.\textsuperscript{15} However, this increase was equivalent to the sensitivity achieved by serial hs-cTn testing on admission and at 90 minutes.\textsuperscript{15} However, these tests are not readily available for analytical platforms in routine use in the NHS and discussions at the scoping stage of this assessment concluded that practical applications of H-FABP and copeptin assays and evidence for their effectiveness are not yet sufficiently developed to justify their inclusion.

This assessment will consider hs-cTn assays used singly or in series, up to four hours after the onset of chest pain or up to four hours after presentation (as reported); for serial troponin measurements, both data on change in troponin levels and peak troponin will be considered (as reported).
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>System</th>
<th>Assay</th>
<th>LoD (ng/L)</th>
<th>LoB (ng/L)</th>
<th>99&lt;sup&gt;th&lt;/sup&gt; percentile (ng/L)</th>
<th>CV at 99&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>Turnaround time (mins)</th>
<th>CE marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Diagnostics</td>
<td>ARCHITECT STAT hs-cTnI</td>
<td>1.1 to 1.9</td>
<td>0.7 to 1.3</td>
<td>26.2</td>
<td>4%</td>
<td>16</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Beckman Coulter (not CE marked)</td>
<td>Access and UniCel Dxl AccuTnI+3</td>
<td>10</td>
<td>&lt;10</td>
<td>40.0</td>
<td>10%</td>
<td>13</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td>Elecsys cTnT-hs</td>
<td>5</td>
<td>3</td>
<td>14</td>
<td>&lt;10%</td>
<td>18</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td>Elecsys cTnT-hs STAT</td>
<td>5</td>
<td>3</td>
<td>14</td>
<td>&lt;10%</td>
<td>9</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

* Information supplied to NICE by the manufacturer
LoD: limit of detection
LoB: limit of blank
2.3 Care pathway

Diagnostic assessment

The assessment of patients with suspected ACS is described in NICE clinical guideline 95 (CG95) “Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin.”\(^{11}\) The guideline specifies that initial assessment should include a resting 12-lead ECG along with a clinical history, a physical examination and biochemical marker analysis. For people in whom a regional ST-segment elevation or presumed new left branch bundle block is seen on ECG, management should follow NICE clinical guideline 167 (CG167) “The acute management of myocardial infarction with ST-segment elevation.”\(^{16}\) People without persistent ST-elevation changes on ECG, i.e. with suspected non-ST-segment-elevation ACS (NSTE-ACS), should receive further investigation using cardiac biomarkers with the aim of distinguishing NSTEMI from unstable angina. NICE CG95 makes the following recommendations on the use of cardiac biomarkers:\(^{11}\)

- Take a blood sample for cTnI or cTnT on initial assessment in hospital. These are the preferred biochemical markers to diagnose acute MI.

- Take a second blood sample for cTnI or cTnT measurement 10-12 hours after the onset of symptoms.

- Do not use biomarkers such as natriuretic peptides and high sensitivity C-reactive protein to diagnose an ACS.

- Do not use biomarkers of myocardial ischaemia (such as ischaemia modified albumin) as opposed to markers of necrosis when assessing people with acute chest pain.

- Take into account the clinical presentation, from the time of onset of symptoms and the resting 12-lead ECG findings, when interpreting troponin measurements.

CG95 recommends that a diagnosis of NSTEMI should be made using the universal definition of myocardial infarction.\(^8\) However, the third universal definition of myocardial infarction has been up-dated since the publication of CG95.\(^{17}\) The most recent version states that AMI is defined as “The detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischaemia, new or presumed new significant ST-segment-T wave changes or new left branch bundle block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy.”
The Scottish Intercollegiate Guidelines Network guideline 93 (SIGN 93) provides similar recommendations on the diagnostic work-up of people with suspected ACS, stating that:

- Immediate assessment with a 12-lead ECG
- Repeat 12-lead ECG if there is diagnostic uncertainty or change in clinical status, and at discharge
- Serum troponin measurement on arrival at hospital
- Repeat serum troponin measurement 12 hours after the onset of symptoms
- Troponin concentrations should not be interpreted in isolation, but with regard to clinical presentation

Guidelines from the European Society of Cardiology on the diagnostic assessment of people with a suspected NSTE-ACS are consistent with those of NICE and SIGN, but additionally acknowledge the use of high-sensitivity troponin assays and make recommendations on a fast track rule out protocol. The guidelines state that hs-cTn assays have a negative predictive value (NPV) of greater 95% for acute myocardial infarction on admission; including a second sample of hs-cTn at 3 hours can increase this to 100%.

**Management/treatment**

NICE clinical guideline 94 (CG94) provides recommendations on the management of people with suspected NSTE-ACS “Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction.” The guideline states that initial treatment should include a combination of antiplatelet (aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors) and antithrombin therapy, and should take into account contraindications, risk factors and the likelihood of percutaneous coronary intervention. SIGN 93 makes similar recommendations. It is recommended that people with a diagnosis of NSTEMI, who are assessed as being at low risk of future complications, receive conservative treatment with aspirin and/or clopidogrel, or aspirin in combination with ticagrelor. People at a higher risk of future complications should be offered coronary angiography (within 96 hours of admission) with subsequent coronary revascularisation by percutaneous coronary intervention or coronary artery bypass grafting where indicated. Additional testing to quantify inducible ischaemia may also be used, before discharge, to identify those who may need further intervention and SIGN 93 also recommends functional testing to identify people at higher risk. SIGN 93 states that people in whom an elevated troponin level is not observed may be discharged for further follow up according to clinical judgement and, in some cases, the results of ischaemia testing.
Longer term follow-up of people who have had an acute myocardial infarction is described in full in NICE Clinical Guideline 48 (CG48) “Secondary prevention in primary and secondary care for patients following a myocardial infarction”. This includes recommendations on lifestyle changes, cardiac rehabilitation programmes, drug therapy (including a combination of ACE inhibitors, aspirin, beta-blockers and statins), and further cardiological assessment to determine whether coronary revascularisation is required.20

3 Objectives
The overall objective of this project is to summarise the evidence on the clinical- and cost-effectiveness of new, high sensitivity troponin assays for the management of adults presenting with acute chest pain, in particular for the early (within four hours of presentation) rule-out of AMI. The following research questions have been defined to address the review objectives:

- What is the clinical effectiveness of new, high sensitivity troponin (hs-cTn) assays (used singly or in series) compared with conventional diagnostic assessment, for achieving early discharge within four hours of presentation, where AMI is excluded without increase in adverse outcomes?

- What is the accuracy of new, hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the diagnosis of AMI in adults with acute chest pain?

- What is the accuracy of new, hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation), for the prediction of major adverse cardiac events (MACE) (cardiac death, non-fatal MI, revascularisation, or hospitalisation for myocardial ischaemia) during 30 day follow-up in adults with acute chest pain?

- What is the cost-effectiveness of using new, hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation), compared with the current standard of serial troponin T and/or I testing on admission and at 10-12 hours post-admission?

4 Methods for assessing clinical effectiveness
Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care21 and NICE Diagnostics Assessment Programme manual.22
4.1 Inclusion and exclusion criteria
Separate inclusion criteria were developed for each of the clinical effectiveness questions. These are summarised in Table 2.
### Table 2: Inclusion criteria

<table>
<thead>
<tr>
<th>Question</th>
<th>What is the accuracy of hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the diagnosis of AMI in adults with acute chest pain?</th>
<th>What is the effectiveness of hs-cTn assays (used singly or in series) compared with conventional diagnostic assessment, for achieving successful early discharge of adults with acute chest pain within 4 hours of presentation?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants:</strong></td>
<td>Adults (≥18 yrs) presenting with acute ‘pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source’ due to a suspected, but not proven, AMI</td>
<td></td>
</tr>
<tr>
<td><strong>Setting:</strong></td>
<td>Secondary or tertiary care</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions (index test):</strong></td>
<td>Any hs-cTnT or hs-cTnI test*, listed in Table 1, hs-cTn assays (used singly or in series**, such that results are available within 3 hours of presentation)</td>
<td></td>
</tr>
<tr>
<td><strong>Comparators:</strong></td>
<td>Any other hs-cTn test, as specified above, or no comparator</td>
<td>Troponin T or I measurement on presentation and 10-12 hours after the onset of symptoms</td>
</tr>
<tr>
<td><strong>Reference standard:</strong></td>
<td>Universal definition of AMI, including measurement of troponin T or I (using any method not defined as a hs-cTn test) on presentation and 10-12 hours after the onset of symptoms in ≥80% of the population or occurrence of MACE (any definition used in identified studies) during 30 day follow-up</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Outcomes$:</strong></td>
<td>Test accuracy (the numbers of true positive, false negative, false positive and true negative test results)</td>
<td>Early discharge (≤4 hrs after initial presentation) without MACE during follow-up, incidence of MACE during follow-up, re-admission to hospital during follow-up, time to discharge, patient satisfaction or health-related quality of life (HRQoL) measures</td>
</tr>
<tr>
<td><strong>Study design:</strong></td>
<td>Diagnostic cohort studies</td>
<td>RCTs (CCTs will be considered if no RCTs are identified)</td>
</tr>
</tbody>
</table>

* A high sensitivity assay is defined as one which has a CV ≤10% at the 99th percentile value for the healthy reference population, and where the LoD allows measurable concentrations to be attained for at least 50% of healthy individuals  
** For serial troponin assays, both data on change in troponin levels and peak troponin values will be considered  
$^5$ studies that used only new diagnostic ECG changes or outcome-based MACE (cardiac death, non-fatal MI, revascularisation, or hospitalisation for myocardial ischaemia) alongside a troponin-based reference standard will be included  
$^{55}$ Any estimates of the relative accuracy/effectiveness of different hs-cTnT or hs-cTnI tests, or will be derived from direct, within study comparisons
4.2 Search strategy
Search strategies will be based on intervention (high-sensitivity troponin assays) and target condition, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care\textsuperscript{21} and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.\textsuperscript{24} Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will be developed separately.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords associated with high sensitivity troponin T/I will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies from 2005 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) \url{http://regional.bvsalud.org/php/index.php?lang=en}
- International Network of Agencies for Health Technology Assessment (INAHTA) Publication (Internet) \url{http://www.inahta.org/}
- Biosis Previews (Web of Science)
- Conference Proceedings Citation Index – Science (Web of Knowledge)
- NIHR Health Technology Assessment Programme (Internet)
- Aggressive Research Intelligence Facility (ARIF) database (Internet) \url{http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx}
- MEDION database (Internet) \url{http://www.mediondatabase.nl/}
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet)
Completed and ongoing trials will be identified by searches of the following resources (2005-present):

- NIH ClinicalTrials.gov [http://www.clinicaltrials.gov/]
- Current Controlled Trials [http://www.controlled-trials.com/]
- WHO International Clinical Trials Registry Platform (ICTRP) [http://www.who.int/ictrp/en/]

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. References in retrieved articles and relevant systematic reviews will be checked.

No restrictions on language or publication status will be applied. Date restrictions will be based on expert advise on the earliest appearance of literature of high sensitivity troponin assays. Searches will take into account generic and other product names for the intervention. An example search strategy is presented in Appendix 1; these will be adapted as necessary following consultation with clinical experts. The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist. Identified references will be downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles will be checked for additional studies. The final list of included papers will also checked on PubMed for retractions, errata and related citations.

4.3 Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participant characteristics (e.g. demographic characteristics and cardiac risk factors, etc.), details of the hs-cTnT or hs-cTnI test (manufacturer, timing, baseline (onset of symptoms or presentation), definition of diagnostic threshold, etc.), details of comparator cardiac biomarker tests (manufacturer, timing, definition of diagnostic threshold, etc.), details of reference standard (manufacturer, timing and diagnostic threshold for conventional troponin T or I testing), clinical outcomes (number of participants discharged early (up to 4 hrs after initial presentation), incidence of MACE during follow-up, re-attendance at or readmission to hospital during follow-up, time to discharge, any patient satisfaction or HRQoL
measures), and test performance outcome measures. Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4 Quality assessment strategy
The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool. Diagnostic accuracy studies will be assessed using QUADAS-2. The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Where sufficient data are available the results of quality assessment may be used to inform stratified meta-analyses in order to explore the impact if individual components of study quality upon the findings of the review. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Methods of analysis/synthesis
If available data allow, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions of hs-cTnT and hs-cTnl, used singly or in series, up to four hours from the onset of chest pain/presentation will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve. If more than one RCT evaluates the same clinical outcome in patients assessed with the same intervention (hs-cTnT or hs-cTnl assay method) and comparator (standard diagnostic assessment), then data will be pooled on treatment effect (e.g. hazard ratio, odds ratio, relative risk, weighted mean difference). The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs. Any estimates of the relative accuracy/effectiveness of different hs-cTnT or hs-cTnl tests, used singly or in series, will be derived from direct, within study comparisons. Where sufficient data are available, clinically relevant subgroup analysis will be considered (e.g. gender, ethnicity, time from symptom onset, NSTEMI population versus mixed population, previous MI, renal function, risk stratification/pre-test probability).

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research
question addressed and by hs-cTnT or hs-cTnI assay, and mode of application (single or serial testing). A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

5  Methods for synthesising evidence of cost-effectiveness

5.1  Identifying and reviewing published cost-effectiveness studies

Search strategy
Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed. A review of published economic evaluations will be undertaken on the following databases, utilising a methodological study design filter where appropriate:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (Wiley)
- Health Economic Evaluation Database (HEED (Wiley)
- EconLit (EBSCO)
- Research Papers in Economics (REPEC) (Internet)
http://repec.org/

Supplementary searches may be undertaken to focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses that study hs-cTn assays or cardiac biomarker panels that include hs-cTn assays. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

5.2  Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to determine the cost-effectiveness of new, hs-cTn assays (used singly or in series, up to four hours from the onset of chest pain/presentation), compared with the current standard of serial troponin T and/or I testing on admission and at 10-12 hours post-admission for the early rule out of acute myocardial infarction in people with acute chest pain.
**Diagnosis and treatment strategies**

The analysis will consider the long term consequences of clinical validity and prognostic value (i.e. prediction of major cardiac adverse events in patients admitted as compared to those discharged) of the different tests. For tests for which clinical validity and/or prognostic value is unclear, when feasible, assumptions will be made to provide some indication of the (range) of cost-effectiveness outcomes.

A sensitivity analysis will be used to investigate the effect of varying the prevalence (i.e. the pretest-probability) of MI (0% to a clinically relevant upper limit, e.g. 20%); the main analysis will use a prevalence of 7-8%, which is derived from the RATPAC trial.\(^{35}\) In addition, a no testing strategy will be included in this sensitivity analysis, since a troponin test may not be indicated when clinical judgment assesses that the probability that a patient is experiencing an MI as low.

**Model structure**

Published studies that report on the value of hs-cTn assays from initial diagnosis through to intermediate (e.g. admissions/discharges) and final (reinfarction, survival) health outcomes may not be available for all tests listed in the scope. In order to be able to report on tests listed in the scope for which no data on these health outcomes is available, an alternative scenario analysis could be performed assuming equal prognostic value of the tests. Necessary choices and definitions regarding the final structure of the model will depend on the findings from the literature review and consultation with clinical experts.

In order to be consistent with earlier related assessments, the economic model used in an earlier Health Technology Assessment\(^{7}\) will be used as a starting point. This diagnostic model compares various testing strategies (i.e. a troponin test on arrival, a 10-hour troponin test, and a biomarker + troponin strategy) and calculates long-term costs and QALYs for each of these strategies. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of diagnosis and treatment pathways for these patients, and are representative of current care within the NHS, will be determined for useful information and/or methods.

**Issues relevant to analyses:**

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.
A simple draft model structure is presented (Appendix 3); this may be developed/expanded as indicated and as available data allow.

**Health outcomes**
Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

**Costs**
Resource utilisation will be estimated for the diagnostic tests and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

6 **Handling of information from the companies**
All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 19/12/2013. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any ‘commercial in confidence’ data provided by manufacturers, and specified as such, will be highlighted in **blue and underlined** in the assessment report (followed by company name in parentheses). Any ‘academic in confidence’ data provided by manufacturers, and specified as such, will be highlighted in **yellow and underlined** in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 **Competing interests of authors**
None

8 **Timetable/milestones**

<table>
<thead>
<tr>
<th>Milestones</th>
<th>Completion data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft protocol</td>
<td>02/09/2013</td>
</tr>
<tr>
<td>Final protocol</td>
<td>24/09/2013</td>
</tr>
<tr>
<td>Progress report</td>
<td>19/12/2013</td>
</tr>
<tr>
<td>Draft assessment report</td>
<td>18/02/2014</td>
</tr>
<tr>
<td>Final assessment report</td>
<td>18/03/2014</td>
</tr>
</tbody>
</table>
9 References


20


Appendix 1: Clinical effectiveness search

Embase (OvidSP): 1974-2013/08/27

Searched: 28.8.13

1  "high sensitivity cardiac troponin T"/ or high sensitivity troponin t assay/ (11)
2  "high sensitivity cardiac troponin I"/ or high sensitivity troponin i assay/ (3)
3  (Hstnt or hs-tnt or hsctnt or hsctnt or hsctnt or hsctnt or tnt-hs or tnt-hs or ctnhs or ctnhs or ctnhs or ctnhs or ctnhs or ctnhs).ti,ab,ot. (554)
4  (Hstni or hs-tni or hsctni or hsctni or tni-hs or tni-hs or ctnhs or ctnhs or ctnhs or ctns-ultra or accutni).ti,ab,ot. (178)
5  ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (1034)
6  ((troponin I or tni or ctni or tropl or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (583)
7  (troponin adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (1367)
8  or/1-7 (1970)
9  troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (18388)
10  (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (6235422)
11  9 and 10 (9001)
12  8 or 11 (9506)
13  thorax pain/ (43857)
14  ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot. (37469)
15  acute coronary syndrome/ (23835)
16  (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (26414)
17  exp heart infarction/ (263923)
18  exp Unstable-Angina-Pectoris/ (16429)
19  (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot. (374)
20  Unstable angina$.ti,ab,ot. (14517)
21  ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest or occlusion$)).ti,ab,ot. (232042)
22  (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP).ti,ab,ot. (83335)
23  or/13-22 (419725)
24  12 and 23 (5278)
25  limit 24 to yr="2005 -Current" (4125)
Appendix 2: Related NICE guidance


Appendix 3: Draft model structure
Decision tree modelling test phase and short term outcome (approximately 30 days)

Markov model long term outcome

Note: Event-free is truly event-free in the sense that patients in this health state have not experienced an MI (i.e. false positives and true negatives). Post-MI refers to patients who have already experienced an MI within the decision-tree period (either at presentation or in the subsequent three months) or who enter the Markov
model in the event-free state and experience an MI later on. Definitions of health states and other model details may differ in the final analysis depending on available data.