

# High sensitivity troponin for the diagnosis of acute myocardial infarction in A&E – modelling impact and implementation in the South West

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## EXECUTIVE SUMMARY

This project was originally commissioned by the SW Academic Health Science Network (SW AHSN) in July 2014. It focussed on an investigation of the use of high sensitivity cardiac troponin (hs-ctn) in the diagnostic pathway for patients presenting with chest pain at Emergency Departments (ED) across the seven acute trusts in the south-west region. Specifically, given recent NICE guidance which recommends the use of hs-ctn for early rule out of myocardial infarction (MI), we modelled the patient pathway and simulated the likely impact of service delivery changes for individual trusts. We also examined the barriers and facilitators to establishing early rule out strategies as well as modelling the likely impacts of changes (eg. reduced patient waits and admissions).

A key part of this research was an extensive literature review into the use of hs-ctn in the diagnostic pathway for chest pain. This was conducted using established systematic review methodology and led to a publication in the BMJ.

Early project work established working relationships with the seven acute trusts engage with key stakeholders in each of these organisations and obtain the necessary data and permissions to drive our analysis and modelling. This proved a lengthy process since we needed to obtain data from two separate sources (A&E admissions data and Biochemistry data) and map between these datasets. In addition we needed to obtain ethical approval from each trust to obtain the data.

Having obtained the primary data for analysis of the pathway, the decision was made to focus primarily on four of the seven trusts in the area (Plymouth, Yeovil, Exeter and Taunton). Extensive statistical analysis was conducted on the primary data collected. Pathway mapping workshops then formed the basis for the construction of a discrete-event simulation of the patient pathways at each of these trusts which was used to gauge the impact of potential changes.

A significant number of structured meetings with stakeholders at each trust were conducted to determine key aspects of interest and understand the major issues with delivery of the diagnostic pathway. In addition, an instructive visit to Southmead hospital in Bristol, where successful adoption of three hour rule out has been attained, was undertaken to assess the key issues essential for implementation.

Another component of the project was a small Public-Patient Involvement (PPI) workshop conducted to gauge how patients experience the diagnostic pathway.

Key findings indicate that although all seven acute trusts in the SW region use hs-ctn in the diagnostic pathway for chest pain, few are using it to its full potential. In addition, the NHS 4 hour ED target necessitates patients are admitted to short stay wards even when 3 hour rule out strategies are implemented. The benefits of reduced admissions due to implementation of the 3 hour rule out are therefore hard to assess directly although clear reductions in length of stay for patients as well as greater use of short-stay wards in ED rather than full admission of patients to MAU or specialist wards can be avoided.

Given the considerable interest in this work it would seem there is a strong basis for continued development of the project to look at ways in which recommendations can be implemented. The current interest in extending the use of hs-ctn to facilitate single test rule out, for instance, is a key area of interest. In general there are a range of areas where we feel there is scope for extending this work. These include: the use of the simulation pathway model to investigate other potential innovations in management of acute chest pain (e.g. use of CT coronary angiography), use of the model as a tool for implementation of change and/or engagement with patients, standardising methods for presenting algorithms and protocols across trusts (to facilitate sharing of best practice), investigation of most suitable troponin threshold levels in older patients, and the extension of the health economic component to incorporate constraints imposed by current ED processes in hospitals and investigate if changes in these processes are required to realise the potential of new diagnostic technology.

## INTRODUCTION

This report presents a structured outline of the key components of the project. The clinical and regional context for the work is described followed by a summary of the research objectives and a more detailed account of component elements giving methods and summary outputs. We conclude with a discussion which lists barriers, facilitators, recommendations and looks at the potential for further work in this area. Many of the detailed outputs from our work are contained in the extensive appendices which focus on the modelling and analysis outputs for individual trusts.

## CLINICAL CONTEXT

Coronary artery disease (CAD) is the leading cause of death in developed countries and is expected in coming decades to become the leading cause of death worldwide(1). CAD is the most common cause of death in the UK accounting for 94 000 deaths each year, with approximately one in five men and one in seven women dying from the disease. It is also the most common cause of premature death, causing almost 31 000 premature deaths each year(2).

The most dramatic manifestation of CAD is the development of acute coronary syndrome (ACS). The usual presentation of ACS includes typical angina - substernal chest pain or constricting discomfort in the chest - which may radiate to the arms, jaws and back and may be accompanied by other symptoms such as nausea, vomiting, shortness of breath, sweating, light-headedness and particularly a combination of those(3-5). Atypical presentation without angina may occur in up to 40% of the cases subsequently diagnosed with ACS and significantly increases the probability of misdiagnosis and suboptimal treatment (6).

Patients presenting to the emergency department (ED) with symptoms suggestive of ACS are risk stratified by combining information from the patient's history and demographics, clinical examination, resting ECG and the results from a cardiac troponin (ctn) assay. Based on the initial ECG, patients are assigned one of the following working diagnoses:

- ST-segment elevation myocardial infarction (STEMI);
- Non-ST-segment elevation acute coronary syndrome (NSTEMI ACS); and
- Non-ACS diagnosis.

Patients with persistent ST-segment elevation have total or nearly total occlusion of a coronary artery and benefit from early invasive treatment. They are immediately admitted to hospital and the results from the troponin test play no role in this decision. Patients assigned to the NSTEMI ACS group undergo further testing and clinical observation and, eventually, receive one of the following diagnoses:

- NSTEMI if ctn is abnormally elevated and the pattern of change (rise or fall in concentration) suggests AMI;
- UA if the troponin levels are normal but there is sufficient evidence of myocardial ischemia which explains the current symptoms; or,

- Non-ACS diagnosis; significant proportion of patients, however, are discharged without a clear diagnosis which may leave patients feeling anxious and out of control.

Since the diagnostic utility of the clinical examination, patient's history and the ECG results is limited cardiac biomarkers and, more specifically, troponin assays play pivotal role in the risk stratification of patients suspected of ACS and in the diagnosis of AMI. Standard troponin assays, however, lack the sensitivity to rule out AMI in the early hours of symptoms onset and, therefore, second measurement 6 – 9 hours after the first one is necessary (5). This diagnostic algorithm, though allowing for a reliable exclusion of AMI results in a large number of emergency admissions as even low risk patients with normal ECG and first negative troponin have to be admitted for a confirmatory test before AMI is definitely ruled out. Chest pain is one of the most common reasons for ED visits and accounts for approximately 5% of all emergency admissions, even though less than 40% of the admitted patients are ultimately diagnosed with ACS(7).

A wide range of biomarkers have been investigated as a potential solution to the early rule out problem. So far, however, the most promising candidate is the new generation of cardiac troponin assays, the so called 'high sensitivity' assays, which, when combined with all diagnostic information available at the early stage of the diagnostic pathway, have relatively high sensitivity and might be able to help clinicians identify those patients that have very low risk of AMI.

Cardiac troponin assays were first developed in the late 1980s. Since then a significant number of different research and commercial assays have been introduced, each new generation demonstrating better diagnostic and analytical performance (8). All assays are of the capture type where an immobilised antibody specifically binds either cTnI or cTnT present in a specimen, which could be either serum or heparin plasma. Cardiac troponin I assays are marketed by different companies and, as they are not standardised, different results may be obtained for the same patient sample depending on the specific assay and platform used. Therefore, their results are not interchangeable and reference values and decision limits need to be determined separately for each one of them (9). In contrast, the patent for the cTnT assay is held jointly by its developer Hugo Katus and Roche Diagnostics, the latter one being the sole manufacturer of this assay.

High sensitivity assays were developed in order to overcome two major limitations of earlier generation tests: the low analytical sensitivity that does not allow small increases in cTn concentrations to be detected early after the onset of symptoms; and the low analytical precision exceeding the recommended  $\leq 10\%$  coefficient of variation (CV) at the diagnostic threshold defined as the 99<sup>th</sup> percentile of a healthy reference population. A range of different assays are marketed as sensitive and high sensitive despite the significant differences in their analytical and diagnostic performance. To avoid confusion, it has been suggested that a troponin assay should be classified as highly sensitive if the following two criteria are met: firstly, its total imprecision (coefficient of variation) at the 99<sup>th</sup> centile of the healthy reference population is 10% or less; secondly, measureable concentrations above the limit of detection and below the 99<sup>th</sup> centile are attainable for at least 50% of the reference population (10). Over the past few years in the United Kingdom, standard troponin assays have gradually been replaced with high sensitivity ones. Although authoritative data on how and to what extent they are used in different National Health Service trusts are unavailable, anecdotal evidence strongly suggests both that standard troponin assay use

remains common and that where used high sensitivity assays are being used in the same manner as standard troponin assays, not capitalising on their greater sensitivity.

To rectify the situation, the National Institute for Health and Care Excellence (NICE) has recently published guidance on the clinical application of high sensitivity troponin assays in the early rule-out of AMI. The guidance recommends the Elecsys Troponin T high-sensitive assay (Roche Diagnostics) and the ARCHITECTSTAT high sensitive troponin I (Abbott Laboratories) for use with early rule-out protocols that include blood samples taken at the patient's presentation to the ED and a second sample three hours later. A third assay, the AccuTnI+3 (Beckman Coulter) has also been evaluated, but owing to insufficient evidence it is recommended only for use in clinical research. The guidance also recommends the use of the 99th centile as a cut-off value when deciding whether to rule out AMI or to refer the patient for further investigations(11). Similar recommendations have recently been published by the European Society of Cardiology (12).

Since most of the NHS trusts in the South West of England use the Elecsys Troponin T high-sensitive assay (herein after referred to as hs-cTnT) the review focused on this particular assay which, as already mentioned above, is one of the two cardiac troponin assays recommended for clinical use by NICE. The assay is a modification of Roche's fourth generation standard troponin T assay. The specifications provided by the manufacturer are as follows. The assay's limit of blank (the highest apparent analyte concentration expected to be found when replicates of a blank sample containing no analyte are tested) is 3 ng/L, the limit of detection (the lowest analyte concentration likely to be reliably distinguished from the limit of blank and at which detection is feasible) is 5 ng/L, and the limit of quantification (the lowest analyte concentration that can be reproducibly measured with coefficient of variation of 10% or less) is 13 ng/L. The 99th centile of a healthy reference population recommended as a positivity threshold for the diagnosis of AMI is 14 ng/L, and the estimated turnaround time is 18 minutes. The assay is also available as a short turnaround time version with an estimated turnaround time of nine minutes (13). It is commercially available and in clinical use worldwide with the exception of the United States, where it is used for research but has not yet obtained clearance from the US Food and Drug Administration (10).

## **REGIONAL CONTEXT**

The area of interest for this study is defined by the NIHR SW CLAHRC (and SW AHSN) boundary which includes Isles of Scilly, Cornwall, Devon, and most of Somerset (see Figure 1: Map Figure 1 below). Within this area, seven acute trusts serve approximately 2,000,000 people (2011 census). The approximate catchment populations for trusts range from 160,000 to 450,000, with ED attendances each year ranging from 45,000 to over 100,000. The predicted number of admissions for chest pain is estimated based on a figure of 5% of all attendances (see Table 1).

All seven trusts have protocols for the management of acute chest pain within ED. Patients with acute MI are transferred immediately to a cardiac catheterisation laboratory. Since Yeovil District Hospital and the North Devon District Hospital do not have this facility, patients are transferred by ambulance to Musgrove Park Hospital or the Royal Devon and Exeter Hospital respectively. Ambulance crews serving any of these hospitals may direct patients who are diagnosed with MI in the community if the nearest hospital does not provide cardiac catheterisation.



The EDs in each trust have an explicit ACS protocol which follow broadly the same principles although important differences are present which are discussed below. High Sensitivity troponin testing is used in all seven acute trusts with Yeovil and Taunton using Troponin I and the rest using Troponin T.



Figure 1: Map showing the seven regional acute trusts

Trust Name	Location of acute hospital	Approx. ED Chest pain Attendances per year *	Cardiac Catheterisation available?	Type of HS troponin test used
Royal Devon and Exeter NHS Foundation Trust	Exeter	8000	YES	Troponin T
Plymouth Hospitals NHS Trust	Plymouth	9000	YES	Troponin T
Yeovil Hospital NHS Foundation Trust	Yeovil	4400	NO	Troponin I
Taunton and Somerset NHS Foundation Trust	Taunton	6800	YES	Troponin I
Royal Cornwall Hospitals NHS Trust	Truro	8700	YES	Troponin T
South Devon Healthcare NHS Foundation Trust	Torquay	7500	YES	Troponin T
North Devon Healthcare NHS Trust	Barnstaple	3200	NO	Troponin T

Table 1 : Seven Acute Trusts Outline (\*estimate based on population catchment)

## PROJECT OBJECTIVES

The project objectives as defined at the outset are listed below:

- **Systematically review research on hs troponin T:** obtain summary estimates of the sensitivity and specificity of hs-cTnT (Roche® Diagnostics) for the diagnosis of AMI in patients presenting to the ED with symptoms suggestive of ACS.
- **Survey existing practice in SW:** identify the current variation in the use of cardiac troponin tests and admissions for observation of acute chest pain suspected of being MI across the SW Peninsula.
- **Model the impact of service changes:** predict the impact of using the high sensitivity troponin measurement on current patterns of health service use.
- **Identify the barriers and facilitators :** outline the factors necessary for the development of consistent and efficient use of high sensitivity troponin across hospitals within the SW Peninsula
- **PPI meeting:** To gain an initial insight into patients' experience of the chest pain pathway and to obtain feedback on NICE diagnostic guidance DG15 regarding early rule out of myocardial infarction using high-sensitivity troponin tests (Information for the public, <https://www.nice.org.uk/guidance/dg15/informationforpublic>).

## RESEARCH COMPONENTS

The major research components required to address the project objectives above are listed here:

- Systematic Review of Evidence
- Patient-Public Involvement workshop
- Pathway and process mapping
- Data sourcing
- Data analysis
- Pathway modelling and simulation

These are described in sequence below. In each case, we first outline the approach and methods adopted and then summarise outputs.

## SYSTEMATIC REVIEW

### Methods

We used the methods recommended by the Cochrane Collaboration's Diagnostic Test Accuracy Group (14). Bespoke search strategy was developed and adapted for each database searched (see paper published in the BMJ for more details) (15). The following electronic databases were searched: Ovid Medline and Medline in-process, Ovid Embase, Science Citation Index, Medion database, Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), Research Portfolio Online Reporting Tools (RePORT, formally CRISP), and International Network of Agencies for Health Technology Assessment (INAHTA). The initial validation study of the high sensitivity troponin T assay was published in 2010 (16). To capture earlier studies using the pre-commercial version of the assay, we extended the search period back to January 2006 and hand

searched the reference lists of all relevant publications including systematic reviews and relevant opinion papers.

One reviewer did the initial selection on the basis of titles and abstracts. Full text copies of potentially relevant publications were obtained and screened independently by two reviewers, with all discrepancies resolved through discussion or arbitration by a third reviewer. We selected studies for inclusion in the review if they met the following pre-specified criteria: diagnostic cohort studies, evaluating the diagnostic accuracy of the Roche hs-ctn assay for the diagnosis of AMI, in patients presenting to the ED with suspected ACS, against a reference standard based on the contemporary universal definition of acute myocardial infarction (17) and published in peer reviewed journals. Two reviewers independently abstracted all relevant data from the included publications and assessed their methodological quality and applicability using a tailored version of the QUADAS-2 tool (18).

We constructed two-by-two tables, calculated sensitivity and specificity with 95% confidence intervals, and created coupled forest plots for each subset of data. If appropriate, we pooled the results from individual studies to obtain summary estimates for sensitivity and specificity. We explored heterogeneity in the first instance through visual examination of the forest plot and the receiver operating characteristics plot for each set of raw data. We considered the following sources of heterogeneity and, if appropriate, added them to a bivariate regression model: target condition, reference test, patients' characteristics, and QUADAS-2 items. We did sensitivity analysis to check the robustness of the results. As standard funnel plots and tests for publication bias are not recommended in meta-analysis of diagnostic accuracy studies, we did not investigate publication bias (19).

## Outputs

The electronic searches identified 3071 records, of which 141 full text articles were assessed for eligibility. Thirty nine of them met the criteria for inclusion in the review, and one additional paper was included from the hand search. We conducted three separate meta-analyses. Twenty studies (23 papers) reporting the diagnostic accuracy of the test at the patient's presentation to the ED and using 14 ng/L as a diagnostic threshold were included in the first one. The second one included six studies (7 papers) reporting the accuracy of hs-cTnT at either 3 ng/L or 5 ng/L. And in the third meta-analysis we pooled results from 5 studies (six papers) reporting the accuracy of the test in patients  $\geq 70$  years of age.

At 14 ng/L the summary sensitivity was 89.5% (95% confidence interval 86.3% to 92.1%) and the summary specificity was 77.1% (68.7% to 83.7%). This means that if the pre-test probability is 21% (the median prevalence of the target condition across the studies), then 21 of 100 tested patients will have a final diagnosis of AMI; of them, between 18 and 19 will test positive (true positives) and two or three will test negative (false negatives). Of the 79 without the target condition, between 54 and 66 will test negative (true negatives) and between 13 and 25 will test positive (false positives).

At 3-5 ng/L the summary sensitivity was 97.4% (94.9% to 98.7%) and the summary specificity was 42.4% (31.2% to 54.5%). This means that of 21 patients with AMI, between 20 and 21 will test positive (true positives) and between none and one will be missed (false negatives). Of the 79

without the target condition, between 25 and 43 will test negative (true negatives) and between 36 and 54 will test positive (false positives).

Of the five studies reporting the diagnostic accuracy of the assay in patients  $\geq 70$  years old four provided data for the 14 ng/L cut-off and were included in a meta-analysis. When random effects bivariate model was used to pool the results the following summary estimates were obtained: sensitivity 97.6% (95%CI: 94.3% - 99.0%) and specificity 32.0% (95%CI: 14.2% - 57.2%). Given the small number of studies and the fact that we were mainly interested in the sensitivity of the test (the ability of a single presentation sample to rule out AMI), we conducted a secondary analysis by simplifying the model and pooling sensitivity separately. The summary estimate for sensitivity was similar to that obtained from the bivariate random effects model: 98% (95% - 100%). Also, one study reported the accuracy of a 99<sup>th</sup> percentile derived from a reference group of presumably healthy  $\geq 75$  years old subjects, 70.6 ng/L, which gave sensitivity of 94% (95%CI: 87% - 98%) and specificity of 77% (95%CI: 71% - 82%). Two studies reported the performance of delta troponin (change in concentration between two measurements) and confirmed that better overall accuracy could be achieved by using absolute rather than relative changes. A diagnostic algorithm using a combination of baseline troponin and 0-3 hour absolute change showed 100% sensitivity and negative predictive value but only about 54% specificity.

More detailed presentation of the results from the systematic review could be found in the paper we published in the BMJ (15).

## PATIENT-PUBLIC INVOLVEMENT (PPI)

### Methods

Patients associated with PenCLAHRC's user involvement group who had direct or indirect (as relatives) experience with myocardial infarction or chest pain of suspected cardiac origin were invited to participate in a group discussion and to answer pre-specified questions related to their experience. Also, they were asked to comment on the accessibility of the recently published NICE diagnostic guidance DG15 (11) regarding early rule out of myocardial infarction using high-sensitivity troponin tests. Link to the guidance was emailed to them prior to the event with a list of provisional questions.

### Outputs

**Participants:** Four patients took part in the event; all of them were  $\geq 50$  years old, two female and two male; all patients had direct experience with ACS; one of them had suffered three episodes of ACS-related chest pain; one of the patients had experience as a researcher. The following topics were covered:

**Onset of chest pain: circumstances, timing and decision to seek help:** Patients' stories differed significantly in terms of when and where the symptoms started, their reactions to the symptoms and the events that followed up to the point of arrival at the A&E.

- Male 1's first episode of chest pain (2003) started early in the morning while he was asleep. The pain felt as if "someone was sitting on my chest" and, after phoning the ambulance, he

was taken to hospital. His second episode happened while he was at the GP surgery. The third time the chest pain was quite different, “like very bad indigestion”.

- Female 1 was in a car park when the pain started (2012). The pain felt as if she was running fast and hit a lamp post. She managed to get into her car and, since the pain eased up a bit, she decided to drive home. However, the pain did not go away and she phoned her GP surgery and got an appointment. The results from the ECG and the blood tests suggested unstable angina rather than MI but also showed that she might have had an MI in her 20s when she had experienced a similar episode of chest pain.
- Female 2’s husband came from work on Friday (2001) not feeling very well. On Monday, he went to see his GP who told him that he was “having a heart attack and send him home”. Her husband did not take it too seriously, “probably because the doctor did not take it seriously” and it took another two-three weeks before he was referred to a cardiologist. Her own cardiac problems were first diagnosed when she went to see her GP with a gynaecological complaint.
- Male 2 had a phone call with a bad news and, as a reaction, got a chest pain (2003). He suspected heart attack and phoned the ambulance straight away.

In general, patients had positive experience from the ambulance; it had arrived soon after they had phoned and they commented that “all staff was efficient, reassuring and helpful”.

Patients commented that calling or going to see the GP when experiencing a chest pain might be more common than expected, especially if the patient feels “rubbish” (no clear symptoms indicating heart attack). They had mixed feelings about their experience with the GPs that ranged from “empathic response from a normally brusque GP!” to the GP reacting as if the condition was not serious. In the latter case the doctor’s reaction had an impact on the patient’s willingness to seek further help and lead to delayed treatment. However, patients believed that, in general, the GPs will phone the ambulance if they suspect a heart attack: “if you see the ambulance in front of the GP surgery, it means somebody is having a heart attack”.

Another point made was that the decision to phone ambulance or go to the GPs might also be determined by location; thus, in rural areas it might be quicker to call or go to the surgery than to call and wait for an ambulance.

***Time of blood tests and information about the tests the patient is about to undergo:*** Patients had different experiences in terms of explanations offered about the diagnostic procedures they had to undergo. During his first episode Male 1 was feeling very poorly and could not remember much of what had happened before his admission to the ward. However, the doctors had given all the necessary information to his wife and she was able to tell him afterwards.

While Female 1 received a very clear explanation about the tests the doctors were about to perform and what they meant, Male 2 received very little information which, in his view, was highly insufficient.

For Male 1 and Male 2 the blood tests were done within 30 min of their arrival to the A&E and the doctor came to see them soon after that. Female 1 commented that she “had to wait from event

(4.30 pm) to about 2 pm the following day for diagnosis. Might have been better to have troponin tests at the GP's. Rural distance adds to problem. I was advised not to travel home and wait for the results - a 50-mile round trip - so was compelled to stay when I did not want to".

**Explanations of results and discharge from hospital and follow up:** During Male 1's first episode, the doctors initially explained the test results to his wife. He spent three weeks in hospital and had a visit from a cardiac nurse who told him what had happened and what he needed to do.

Female 2 said that her husband was not interested in the results, only wanted to know if he was alright and could go back to work. However, his reaction was different to different explanations. The first time the fact that the doctors "did not take it seriously" made him believe that it was not serious and he was reluctant to go to another appointment. The second time the doctor was able to explain the diagnosis (heart attack) in terms of clogged pipes etc. and her husband was more cooperative and engaged.

Before being discharged, Female 1 had a chat with the doctor who explained all the procedures and results: "Tests done were what I wanted and expected. All explained as to why they were being done, what they meant. Full explanation of results with consultant afterwards". However, for her it was still a strange experience: "This dreadful thing happened to me and now I can go home just like that!" which was compounded by the fact that: "No information when sent home after being told 'not a heart attack', but very scary thing".

Male 2, on the other hand, did not receive much explanation of the test results. He pointed out that "paperwork doesn't follow you" when the patient is moved from A&E to MAU to the ward and it sometimes feels as if there is no continuity and the doctors are not aware of previous results. He was discharged by a junior doctor who just did the paperwork and did not give him much explanation. He compared his experience here with that in the USA where he had received private care. In the USA, prior to being discharged the doctor sat with him and explained everything they had done, the results and the implications, which he found very reassuring and helpful.

For both Male 2 and Female 1 there was no follow up. Both visited their GPs a few weeks after the episode for different reasons but the GPs had not received any information about the chest pain: "Discharged with no further support emotionally and physically from RD&E or GP". Female 2 said that in their case, the communication between the GP and the hospital was much better. Patients recommended that "being informed more and followed properly" could improve their experience.

**Other comments:** Patients discussed the fact that, in their experience, the quality of care was very different in different hospitals. Female 2 and her husband had "horrible experience" in one hospital while the experience in another in the region was much better.

**Feedback on NICE diagnostic guidance DG15 (Information for the public):** Female 1 stated: "I found this very clear and easy to understand, and had no problem with the more 'technical' language, as I am already familiar with them from my own research and treatment." The other patients commented that the text "... is not written in plain English and does not feel written 'for the patient'":

- Lots of technical terms such as “assay”, “troponin” etc. makes it difficult to read, especially when they appear early in the text before accessible explanations have been provided
- This may discourage patients to read any further
- To make the text more accessible, It would be helpful if specialist terms are hyperlinked to definitions written in plain English that patients could access immediately just by clicking on the link.

## **PATHWAY AND PROCESS MAPPING**

### **Methods**

In order to determine the diagnostic pathway for patients presenting at ED with chest pain, we initially obtained the standard diagnostic/treatment protocol for chest pain suspicious of a cardiac cause from each of the participating trusts (these are shown in the respective appendices). We then re-drew these protocols using Standard Business Mapping Notation in Microsoft Visio© so that we had a standardised format which we could use to compare across trusts (the standardised diagrams are also shown in the appendices).

Having standardised and studied the protocols, we held a number of detailed meetings with key practitioners (ED consultants, ED nurses, cardiologists, bio-chemists, administrators etc.) at each of the participating trusts to determine more about the processes adopted at their hospital and also the extent to which their protocol represents actual practice. We then subsequently organised process mapping sessions with staff at each trust to build up a more detailed picture of their pathway. These interactive mapping sessions were generally conducted using a whiteboard and coloured pens and were also sound recorded (with consent) for reference. Examples of the raw outputs from these mapping sessions are given in the appendices as well as schematic representations in Visio.

### **Outputs**

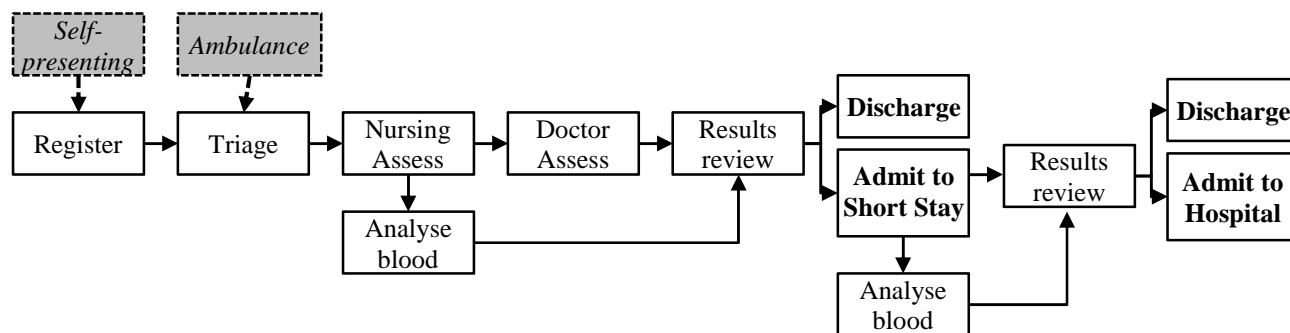
The pathway analysis for each individual trust involved in this study is contained within each respective appendix. Although there are significant differences in the pathways for patients at the different trusts in our study there is also a strong level of commonality which we have summarise here and highlighted some of the key significant aspects.

### ***Common current practice***

A generic pathway map for patients presenting to ED with chest pain is shown (suspected of non-STEMI ACS) in Figure 2 below.

Typically the pathway begins with an assessment of whether the pain is likely to be cardiac in origin and has either lasted for ~10-15 minutes and/or is still ongoing. In this case there is an initial standard set of procedures, including the administration of medications, recording of the time of onset of pain, performing an ECG, inserting an intravenous cannula and sending a sample for blood tests including troponin. Upon completion of triage, patients wait for a variable length of time to see a doctor, based upon the urgency of their condition and the number of patients of similar and greater urgency who are already waiting. If the patient continues to report pain, repeat ECG recordings and/or continuous monitoring may be instituted.





**Figure 2: Typical pathway in ED for patients presenting with Chest Pain**

A doctor's assessment typically consists of a period of clinical history taking and examination, plus appraisal of any investigations already undertaken, including any recorded ECGs. The doctor will usually reach a working diagnosis based on combination of the symptoms, their character and severity, the previous medical history of the patient, and the results of any other observations and tests, such as pulse rate, blood pressure and ECG records. By relating their clinical impression to the protocol, the doctor may decide either that the patient is able to go home, that the patient definitely requires admission, that further investigations are required, or that a discussion with a more senior doctor is warranted. In the latter case, s/he will usually conduct a more targeted and shorter review of the patient depending on the experience of the first doctor. In the event that the patient is able to be discharged, a formal GP referral may or may not be made. In the event that the patient is to be admitted, a formal handover is made to another medical team. Alternatively the ED doctors may decide to do further investigations before making a final decision. This will usually include troponin tests if they have not already been sent.

### **Blood sampling**

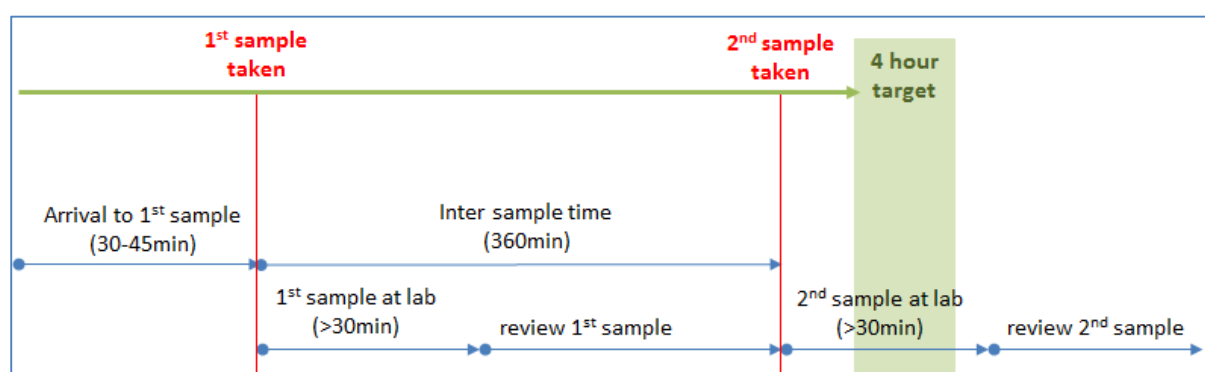
Blood samples for troponin are generally sent before the doctor assessment. Depending on the trust, samples are either taken by hand to the laboratory and deposited at the reception, or sent by an automated transit system. Upon arrival at the laboratory, samples may be left at a collection point for an unknown period before being retrieved and booked in by laboratory staff. They are then sent for analysis. A small percentage of samples may be unsuitable for analysis, usually due to haemolysis (damage to the blood cells during sampling).

Once the result is available there may be a further delay until the result is reviewed by the requesting doctor. Usually, these results are reviewed whenever either the doctor or the nurse responsible for the patient has time between other tasks. In the case of a patient approaching the four hour target, it is likely that additional measures to chase up the result will be taken in an attempt to avoid a breach. If the result is not available and a patient must be moved, responsibility for reviewing the result passes to the admitting destination. This may either take place as results become available, or on formal ward rounds. Therefore the patient may be admitted for a variable length of time depending on the relation between time of admission and ward round times.



### The four hour target

It is a Department of Health requirement that 95% of patients seen in ED must be seen and treated within four hours. Consequently, ED staff responsible for monitoring the target (usually a senior nurse) will follow the progress of the patient. A 'breach' is most likely to occur whenever the diagnosis is unclear and further investigations are needed. In that case, they will assess the likelihood of a breach occurring whilst the results of these investigations are awaited. If a breach is considered likely, a short term admission will be arranged. Some trusts have designated areas within the ED, sometimes known as clinical decision units (CDU), which serve as a waiting area for patients who are simply awaiting the results of investigations. This avoids the need to admit these patients to a full scale medical ward although technically such patients are admitted which overcomes the issue of breaching the 4 hour target. If this facility is not available, then the patient will be referred to another medical team and typically admitted to a short stay ward such as a Medical Admissions Unit (MAU)



**Figure 3: Timeline showing how the Four Hour target for ED necessitates admissions for 3 hour rule-out to avoid breaches**

The implications of the 4 hour target for current protocols is that unless patients present very late with their symptoms (thus obviating the need for a second troponin test), those deemed to be at lower risk of ACS will require a short stay admission simply to complete troponin testing, even if their symptoms do not otherwise warrant admission. We discovered that some trusts (e.g. Plymouth) require a short stay admission even when the wait time to the definitive sample is within the scope of the 4 hour target.

## DATA SOURCING

### Methods

We contacted the data managers of the seven acute trusts within the SW region for relevant data. To build the model required two sets of data, one relating to ED patient presentations and the other to the results of troponin samples performed on those patients.

In terms of troponin tests, we required the date, time, location, overall turnaround time and result of any troponin tests carried out in ED or subsequently as part of the same clinical episode. After

submitting our initial requests we became aware of some other important parameters, for example the time taken between a result being reported and its being reviewed by a doctor.

Altogether we were able to get data relating to troponin results from all seven trusts but data relating to ED episodes from only five (RD and E, Plymouth, Taunton, Truro, Yeovil).

### *Data problems and limitations*

#### *Identification of patients suitability*

We aimed to identify from ED data all those patients presenting who complained of symptoms suggestive of ACS. Some trusts provided a filtered search based on “CHEST PAIN” in the presenting complaint fields (Yeovil, Truro). Others provided either a set of all patients who had troponin tests or a random sample of these. The proportion of modellable patients then depended on the appropriateness of troponin requesting locally. For these datasets, we carried out a search of presenting complaint fields and diagnostic codes, and assigned each patient a numeric code for each. Presenting complaint codes were then used to decide which patients to allocate to the model. For the Derriford data, an additional complexity was that there was no presenting complaint information recorded as part of the ED data, and therefore this had to be extracted from data recorded on the troponin request. However, no details were provided on samples originating from ‘ED. Since patients who only received a single troponin test from ED comprised the majority of the patients, it was unclear how suitable these were for inclusion.

#### *Modelling the troponin values*

We were unable to demonstrate a clear relationship between patients’ troponin levels and elapsed time, in the case of any patients for whom levels might be expected to rise. This was due to a combination of large patient level variability, uncertainty over the time of onset of symptoms, and also possible misclassification of patients by ED in terms of diagnosis. The latter probably occurred in situations where troponin results were not available to the ED doctors therefore the patient diagnosis was updated after admission. Therefore we used a published time series profile<sup>1</sup> based on 18 patients with STEMI who presented to ED within 6 hours of onset, in order to model the troponin rise associated with MI. We assumed that patients without a real diagnosis of MI simply undergo random variation about their baseline value.

#### *1.2.2.3 Other limitations*

We were unable to obtain any data either from the local ambulance trust (SWASFT) or the NHS trusts to indicate how long patients wait before seeking help. There is evidence that this may vary not only according to diagnosis but also to factors such as patient gender age, initial symptoms and previous experience with chest pain (see Patient-Public Involvement above). A review of the recent literature revealed only one UK based publication with summary data, for patients found to have acute MI<sup>2</sup>. It is possible that patients with less serious chest pain may have a longer waiting time.

Although we were able to obtain some estimates of ambulance handling times from the SWASFT, these only related to patients with MIs diagnosed by ambulance crew ECGs. Furthermore, because such patients are often routed to an alternative hospital with cardiac catheterisation facilities, it resulted in a shortage of data for trusts without such facilities. Also, we were unable to relate the

data provided into the arrival times of patients at the respective EDs and so we would not be able to model the correct daily variation in arrivals. We therefore decided to model the patients' pain to hospital delay from the literature and assume that this delay is independent of time of day. Our Evidence Synthesis Team (EST) therefore conducted a systematic search of recent papers related to delay from onset of pain, published since 2011, and returned a set of related references from which only one relevant UK based publication could be identified<sup>2</sup>. Since this paper also only related to patients with diagnosed ACS, we assume that patients without such an eventual diagnosis have a similar time delay before seeking help.

The patient level data provided by the trusts consisted primarily of a series of time stamps indicating when relevant processes were initiated but without any clue as to how long they took to complete. The logic of Simul8 is that patients wait for a variable length of time in queues before undergoing procedures of variable length. In order to set up the model, we calculated the times between the onset of processes and then configured the model so that these times were allocated to the queue, with no (or token amount of) time allocated to the processes themselves. The modelled variability in the process times would therefore be the same as in the real system. In the case of Taunton, we were not able to get any internal time stamps, and only the first series of troponin tests.

We were not able to get any data relating to ECG records, their interpretation, or other risk scores such as GRACE scores commonly in use. We were therefore unable to fully model any decision making that might involve these parameters

We were not able to get any data relating to the time delay between a sample result being reported and the time that the doctor reviews it. We therefore assumed that if the result were not available when the doctor review occurred, that the patient would be admitted and the result subsequently checked.

### *Distributions of processing times*

Typically we were supplied with the following relating to each patient:

- Arrival time
- Triage time
- Time seen by doctor
- Discharge time.

We calculated a series of process times (e.g. arrival-to-triage) as the intervals between these time stamps. We then investigated their distributional shape using statistical software (R, STATFIT, STATA) to find suitable parameter values in order to fit approximate distributions. These are detailed in Appendix C

## **DATA ANALYSIS**

### **Methods**

Having obtained the source data from participating trusts, we conducted a range of descriptive statistical analyses to determine the key characteristics of the system of care for each of the trusts.

These detailed analyses and graphs are shown in the appendices and include:

- **Volume data**
  - **Number of episodes**
  - **Age**
  - **Destinations**
  - **Time-dependent variation in attendance**
  - **Mode of arrival**
- **Process times**
  - Arrival to triage interval
  - Arrival to first sample
  - Patient wait times
  - Time to consultation
  - **Time of day effects**
  - **Arrival to departure**
- **Troponin samples**
  - **No of tests**
  - **Admissions/discharges by test number**
  - **Breakdown by age group**
  - **Breakdown by ED diagnosis**

These analyses also provide the basis for calculation of the key input parameters needed to population the simulation pathway model and for the validation tests of the model.

## **Outputs**

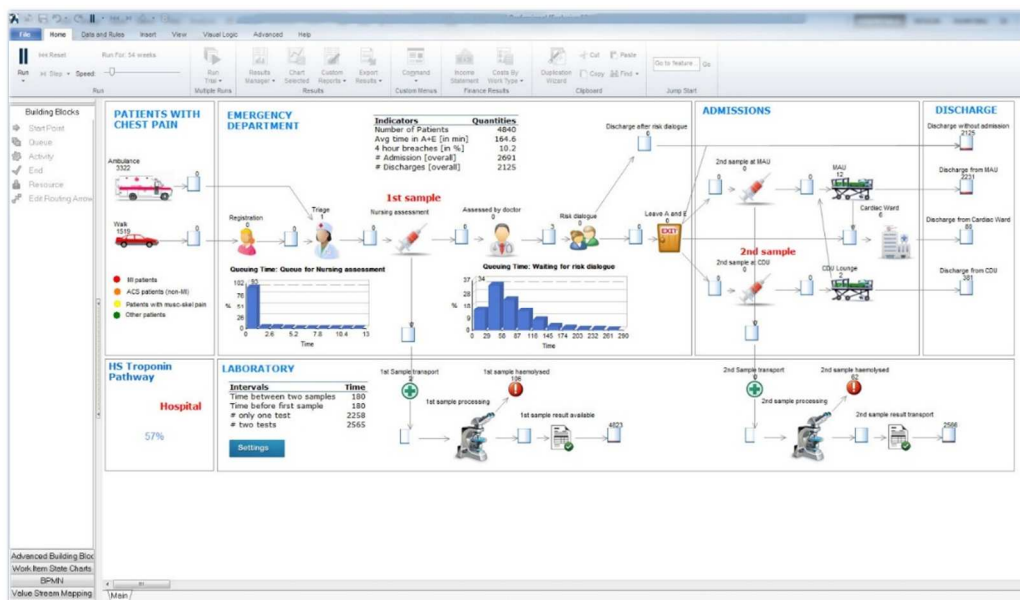
Full presentation of the data analysis outputs are given for each of the participating trusts in the respective appendices.

## **PATHWAY MODELLING AND SIMULATION**

### **Methods**

We chose a discrete event simulation (DES) to model the patient pathway in this project, using the Simul8 software (Simul8 Corp. Boston MA USA). DES in essence represents dynamic processes as a series of queues and activities through which entities (eg patients) pass in real time. It is well suited to modelling time based systems such as diagnostic pathways (where patients in a hospital ED department undergoing assessments by medical and nursing staff and await the outcomes of further investigations). In order to tailor the model to each trust, we first built a generic simulation based on the chest pain protocols received. We then undertook individual discussions with representatives from each trust in order to incorporate individual trust level variations in policy (for example, the presence or otherwise of a short stay admission unit within the ED department). We parameterised the simulated process and queueing times based on real data, generated from either standard or custom-built probability distributions. A more detailed outline of the simulation model for each trust is included within the respective appendices.

Our model is a simplification of the real system in which we attempt to capture those parts that would be likely to change under the introduction of ‘what if’ scenarios. In the model, we represent therefore the arrival of patients, as well as booking in, triage, nurse and doctor assessments, blood sampling, patient review and discharge from ED to selected destinations. We choose not to model aspects of the system that have little perceived relevance to the modelling problem, or for which we could not obtain sufficient data. A screenshot of the simulation is shown in Figure 4 below.



**Figure 4: Example Screenshot of Simul8 simulation used to model patient pathway**

Patients in the model arrive at the ED either by ambulance or by own transport, at variable intervals calculated from provided data. Own transport includes self or public transportation. Patients in the model have individual identifying labels, as well as others describing their age, gender, the time since the onset of their symptoms, and their true diagnosis. Modelled patients arriving by ambulance proceed directly to triage, whereas others queue at reception and then proceed to triage. All modelled patients then wait a variable length of time to see a doctor which is not dependent on mode of arrival. During this time their blood samples may be taken. Once patients see a doctor, they are then routed either towards discharge, or an admission area/ward according to the logic of the model. There is then a further variable delay before the patient is discharged.

The logic of handling blood samples in the model is similar to that of modelled patients. Each modelled sample is labelled to indicate the patient that it was taken from. They join a queue to be transported to the laboratory, are transported, arrive and join a queue for processing. A small percentage of samples are deemed to be haemolysed and a fresh sample is immediately requested and sent following the same routing as before. The result is then recorded and a result is checked for at the time of doctor assessment. If no result is available then the patient is admitted to a short stay unit and a further check is made. Patients with raised troponins are admitted to a Clinical Decision Unit, Medical Admissions Unit, or and coronary care unit depending on the perceived risk of cardiac event being present.

### Model validation

In order to test validity, the model was run for trial periods of 12 months, to ensure the outputs from the simulation matched those predicted by the data. Test validation statistics included the following outputs:

- The overall level of attendance
- The ratio of admissions to discharges
- The proportions and type of patients admitted by destination
- The proportion of patients breaching the 4 hour target

A close agreement between the simulated outputs and the actual historic data in these tests (see Figure 5 below) was obtained.

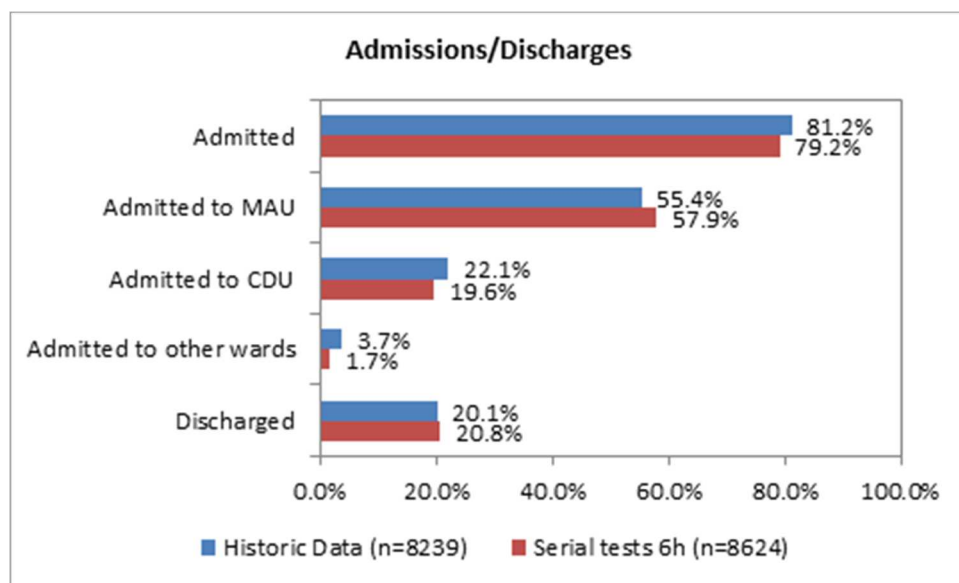


Figure 5: Comparison of actual and output data from pathway simulation model

### Alternative Scenarios

The principal scenario we wished to investigate concerned the implications of introducing a 3 hour rule out policy, i.e. discharging patients based on a clinically insignificant delta troponin based on an admission + 3 hour sample.

### Outputs

For each of the participating trusts the key outputs from the simulation model is included in the appendices.

### Cost analysis

One output from the modelling work in the project is to assess the cost saving implications if implementation of 3 hour rule out strategy (as recommended in the NICE guidance) is attained. Unfortunately analysis of this is highly problematic since as described patient 'admission' is seen to be a requirement even when this is 3 hour rule-out is implemented (see Figure 3 above). This is, in some sense, an artefact of the 4 hour ED treatment target and it is likely that the type of admission

may differ between different diagnostic protocols. Typically, for instance, patients awaiting their second blood test results will be 'admitted' into a short stay area located in the ED department itself. However it is not possible with current data to distinguish between the different types of admission within our model. Given the available data it is only possible currently to model marginal impact of a 3 hour strategy in terms of the reduction in length of stay time for patients in the hospital. This is not a very meaningful reflection of the actual benefits and therefore this analysis is not presented here.

## **DISCUSSION**

### **Barriers and Facilitators**

During the project's lifetime some of the trusts updated their chest pain protocols to reflect the recommendations made in the NICE diagnostic guidance DG15 (11). We have therefore concentrated our discussion on the more general factors which affect firstly the capacity of the trusts to measure the impact of the effected changes on various aspects of the trust's performance and to tailor the recommendations to the local context in order to achieve the best possible outcomes; and secondly, the barriers and facilitators to the implementation of early rule-out strategies that incorporate a single sample rule-out protocols which take advantage of the high negative predictive value of the highly sensitive troponin assays and may enable ED physicians to discharge higher proportion of patients directly from the ED without increased risk to the patients.

### **Routine data necessary to monitor performance of the pathway and enable further updates**

- Currently, most of the trusts do not collect and/or record all the data necessary to monitor the performance of the chest pain pathway and to enable regular revision of their protocols as new technology and practices become available and need to be implemented. Examples of such missing data include: time of chest pain onset, troponin values, time of blood draw.
- Routine data is not recorded consistently and with sufficient rigour. Processing and analysing such data is difficult and time consuming, the results are incomplete and lack the level of certainty required for making decisions.
- The system of data collection is not standardised across trusts which creates difficulties to compare performance and learn from each other's experience.
- Different trusts have different arrangements for making data available for research, especially when external research organisations are involved. In some cases, the arrangements are unclear or too cumbersome and discourage both internal and external use of the data; this makes the process of monitoring performance and updating current practice in accordance with new research evidence difficult.

### **Institutional arrangements for monitoring and updating the chest pain pathway**

- The current practice of updating the chest pain protocol relies on a single clinician reviewing newly published guidelines and related evidence and redrafting the protocol to reflect up-to-date recommendations. Such approach seems ineffective:
  - it rarely involves audit of routine data and analysis of barriers and facilitators specific to the local context;



- it does not take advantage of scientific methods to explore possible impact on performance;
- the update is sporadic and it takes long time for new technology and practice to be implemented;
- the new practice may not receive the immediate support of all stakeholders, especially if they are not involved in the review, and this may lead to partial and inconsistent implementation;
- the impact of the changes needs to be monitored and further adjustments to the pathway may need to be done to achieve best performance, which is not part of the current practice.

### **Implementation of NICE guidance on high-sensitivity troponin assays as early rule-out tests**

- Based on simulation outputs, the 3 hour rule-out protocol recommended by NICE is unlikely to have a significant impact on the number of patients admitted to short-stay wards. This is because the result from the second troponin tests (completed at least 3 hours after the first blood sample has been taken) will generally not be available in time for the ED clinician to discharge the patient directly from the ED without breaching the four hour target. This includes not only the turn-around time of the second troponin tests but also the availability of an ED physician to review the results and make a decision. This means that the proportion of patients admitted to short stay wards to wait for the results from the second troponin is unlikely to decrease as a result of the new 3-hour protocol.
- However it may have impact on the total length of time that such patients spend in ED and the short-stay wards combined. Moreover, if the time from symptom onset to the first sample is reduced from 6 to 5 hours, in the case of single test rule-out, the number of admissions to the CDU may also be decreased.
- A range of additional factors other than the diagnostic accuracy and turn-around time of high-sensitivity troponin assays contribute to the total time for which patients move through the ED part of the chest pain pathway and are either admitted or discharged, the most important of them being:
  - Time between the first blood draw and the arrival of the sample in the laboratory (trusts have different arrangements and this may affect the overall turnaround time)
  - Time of the second blood sample (the first sample is usually taken within 30 min of patient's presentation; if the second sample is taken 3 hours later, this practically excludes the possibility of the result being available before the time of the clinician's review; as a result, most patients are admitted)
  - Time between the results from the second sample being available and the availability of a clinician to look at it.

### ***The North Bristol Example***

One instructive example of good practice in updating a clinical pathway and monitoring performance is given in by the North Bristol Trust. Here not only is there active interest in developing more efficient and effective pathways but also an established system and culture to support a process of continuous improvement of the pathway. This provides a framework for



evolutionary improvement over time rather than a 'one-shot' intervention in service delivery which may be essential given the constantly changing landscape and clinical guidance in this area. Key elements include the following:

- Strong clinical leadership – to drive and maintain change and improvements.
- Regular stakeholder meetings to review the diagnostic pathway – ensuring engagement and communication across relevant departments on a regular basis.
- Collaborative working between departments – to ensure joined up processes and planning of care
- Continuous feedback, review and evaluation of changes
- A framework for assessment of changes, regular on-going protocol development
- Active interest in current research in the area to inform service re-design
- Sharing of best practice with neighbouring acute trusts

In North Bristol Trust the importance and central role of key individuals in driving and promoting change was clearly evident a factor which may be essential in considering implementation of service changes.

### Single-test rule-out

- Identified evidence suggest that hs-ctn is sensitive enough to allow early rule-out of AMI in low risk patients who present >3 hrs after onset of symptoms and have undetectable troponin (<5ng/L) at presentation
- Most of the current evidence, however, relate to protocols that combine structured risk assessment (using risk assessment tools such as HEART or the Manchester ACS Decision) with the results from high-sensitivity troponin assays.
- None of the trusts use such risk assessment tools or have any experience with them.

### Further research potential

ED departments are currently experiencing considerable pressures of demand so advancements in practice which potentially reduce overheads and workload are of great interest to acute trusts. This was reflected in the strong engagement with this project from the participating trusts in the south-west. The work was carried out against a background of developing clinical guidance and changing service delivery. The continuing development of the diagnostic pathway for chest pain in ED such as the emerging interest in the use using hs-ctn for single test rule is a key area of interest and we believe our work has it has established a foundation for more extensive work in this field in terms of the network of collaborating organisations and the methods and models we have created.

Below are listed a number of areas where extensions of this work could be pursued:

- **Modelling further innovations** – the discrete event simulation pathway could be used to drive change in managing chest pain in the ED generally as well the more specific issue of implementing greater/more rational use of HS troponin. This includes the value of the tool in helping trusts deal with other potential innovations in management of acute chest pain and MI (e.g. the use of CT coronary angiography).

- **Tools for implementation** – the use of the model in this project to promote implementation of change. Such an extension could make use of service improvement personnel and methods and could engage directly with patients.
- **Standardising methods** – as part of this project we present a standardised means of presenting protocols and algorithms for chest pain across the trusts. This could be extended and include evaluation of different visual methods and design processes.
- **Exploring HS Troponin thresholds** - diagnostic threshold levels for particular patient groups (e.g. older patients) need to be explored to optimise patient pathways. Our project work and model could enhance this research.
- **Revisiting health economic modelling** of cost-effectiveness incorporating the insights achieved in this project. Research question – Do existing health economic analyses reflect constraints imposed by current ED processes in hospitals? Are changes in these processes required to realise the potential of new diagnostic technology?

## REFERENCES

1. Tyroler HA. Coronary heart disease epidemiology in the 21st century. *Epidemiol Rev.* 2000;22(1):7-13.
2. Office for National Statistics (ONS). Death registration summary tables - England and Wales, 2011 (Final) 2012 [updated 2014/01/03/18:18:21; cited 2014]. Available from: <http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-276695>.
3. Achar SA, Kundu S, Norcross WA. Diagnosis of acute coronary syndrome. *Am Fam Physician.* 2005;72(1):119-26.
4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol.* 2007;50(7):e1-e157.
5. NICE. CG95 Chest pain of recent onset: full guideline. NICE. 2010. Available at: <http://www.nice.org.uk/>. Accessed December 21, 2011.
6. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA.* 2000;283(24):3223-9.
7. Aldous S, Pemberton C, Richards AM, Troughton R, Than M. High-sensitivity troponin T for early rule-out of myocardial infarction in recent onset chest pain. *Emerg Med J.* 2012;29(10):805-10.
8. Schneider HG. Clinical Implications of Troponin Elevation. In: Jill Tate RJ, Allan Jaffe, Mauro Panteghini, editor. *Laboratory and Clinical Issues Affecting the Measurement and Reporting of Cardiac Troponin: A Guide for Clinical Laboratories The Clinical Biochemist Monograph.*: Australasian Association of Clinical Biochemists Inc.; 2012. p. 15-9.
9. M. P. Quality Requirements for Troponin Assays – an Overview. In: Jill Tate RJ, Allan Jaffe, Mauro Panteghini, editor. *Laboratory and Clinical Issues Affecting the Measurement and Reporting*

of Cardiac Troponin: A Guide for Clinical Laboratories. The Clinical Biochemist Monograph.: Australasian Association of Clinical Biochemists Inc.; 2012. p. 53-62.

10. Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clinical chemistry*. 2012;58(1):54-61.

11. Excellence. NifHaC. Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). NICE, 2014 (available at [www.nice.org.uk/guidance/dg15](http://www.nice.org.uk/guidance/dg15)). 2014.

12. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015.

13. Diagnostics. R. Elecsys® Troponin T high sensitive (TnT-hs). . 2014.

14. Collaboration. C. Diagnostic Test Accuracy Working Group: handbook for DTA reviews. . Available from: <http://srda.cochrane.org/handbook-dta-reviews>.

15. Zhelev Z, Hyde C, Youngman E, Rogers M, Fleming S, Slade T, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. *BMJ*. 2015;350.

16. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clinical Chemistry*. 2010;56(2):254-61.

17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third Universal Definition of Myocardial Infarction. *Circulation*. 2012;126(16):2020-35.

18. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine*. 2011;155(8):529-36.

19. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *Journal of clinical epidemiology*. 2005;58(9):882-93.