Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Optimal Use Report

November 2012
Volume 2, Issue 1

High-Sensitivity Cardiac Troponin for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department: A Clinical and Cost-Effectiveness Evaluation

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

Production of this report is made possible through a financial contribution from Health Canada.

ISSN: 1927-0127

TABLE OF CONTENTS

1 CONTEXT AND POLICY ISSUES

When patients with chest pain (or other symptoms suggestive of acute coronary syndrome [ACS]) present at an emergency department (ED), investigations are rapidly conducted to rule out ACS. ACS represents a spectrum of clinical presentations of myocardial ischemia ranging from ST segment elevation myocardial infarction (STEMI) to non-STEMI (NSTEMI) and unstable angina (UA).[1-3] STEMI is diagnosed by specific electrocardiogram (ECG) findings and portends a high risk of cardiac death. NSTEMI and UA are typically caused by myocardial ischemia but of differing severity depending on the presence of myocardial necrosis and are often clinically indistinguishable because of the similarity in symptoms and transient or non-specific ECG findings of ischemia at presentation. In 2000, the European Society of Cardiology and the American College of Cardiology (ESC/ACC) jointly redefined myocardial necrosis to incorporate troponin (cTn) assays as a diagnostic determinant. In 2007, the ESC/ACC/American Heart Association (AHA) updated the definition of MI and advocated a **"**rise and/or fall**"** of cTn during a six to nine-hour time period using the 99th percentile in a reference population as the cut-off for classifying an acute and evolving MI.[3] Therefore, in patients with suspected MI, but without ECG STEMI criteria, the cTn level is the discriminating criterion between NSTEMI and UA.

In Canada, there are two cTn tests available: cardiac troponin T (cTnT) and cardiac troponin I (cTnI). As of 2012, the manufacturer of the cTnT reagent will start to replace the conventional reagent with a high-sensitivity cTnT (hs-cTnT) reagent. High-sensitivity cTnI (hs-cTnI) is not yet available, but its introduction to the market is expected within the next year. In the emergency medicine community, this move to high-sensitivity assays is generating concern. A higher-sensitivity assay will potentially result in earlier identification of patients experiencing an MI (or those who are not and can be safely discharged from the ED with no further investigations). However, the use of high-sensitivity assays may also be associated with lower clinical specificity. Lower specificity could result in higher false-positive rates; that is situations where patients are incorrectly identified as having NSTEMI. Therefore, the use of hs-cTnT could lead to additional investigations and more vascular interventions (e.g., angiogram). This in turn could increase the pressure on EDs, cardiology referrals, and cardiac catheterization suites, potentially resulting in additional costs to the health care system and increased anxiety to patients.

Because of the changing landscape of cTn tests there is a need to independently compare the performance of the various assays (hs-cTnT with cTnT, cTnI, and hs-cTnI) and to determine the comparative clinical and economic impact of using these tests. A recent Rapid Response review of hs-cTnT by CADTH revealed that there is a lack of information on the economic impact of cTn tests. Given the gap in economic information and the need for good quality guidance on the use of cTn tests, a full health technology assessment (HTA) along with optimal use recommendations will inform the purchasing and clinical use of the most appropriate cTn assay, depending on the individual institutional context and provide guidance for clinicians in institutions electing to use hs-cTnT or hs-cTnI to reduce the impact of the lower specificity of these new assays. To gain efficiencies, the clinical evaluation component of the HTA will be built on the recent CADTH rapid review.

This HTA project will evaluate the clinical and cost-effectiveness of hs-cTnT and hs-cTnI for the early diagnosis of ACS in the ED.

2 RESEARCH QUESTIONS

1. What is the diagnostic test performance of hs-cTnT and hs-cTnI assays compared with each other as well as with conventional cTnT and sensitive cTnI assays in patients with suspected ACS symptoms in the ED?
2. What is the clinical effectiveness of hs-cTnT and hs-cTnI assays compared with each other as well as with conventional cTnT and sensitive cTnI assays in patients with suspected ACS symptoms in the ED?
3. What is the cost-effectiveness of hs-cTnT and hs-cTnI assays compared with each other as well as with conventional cTnT and sensitive cTnI assays in patients with suspected ACS symptoms in the ED?
4. What is the budget impact associated with the adoption of hs-cTnT and hs-cTnI assays compared with each other as well as with conventional cTnT and cTnI assays in patients with suspected ACS symptoms in the ED?

3 METHODS

3.1 Literature Search Strategy

An information specialist using a peer-reviewed search strategy (Appendix 1) will perform the literature search. Searching the following bibliographic databases will identify published literature: MEDLINE (1946-present) with in-process records and daily updates through Ovid; Embase (1980 to 2012 current week); The Cochrane Library (2012, current issue), and HEED through Wiley; and PubMed (for non-MEDLINE records). The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts will be high-sensitivity cTn assay and medical emergency circumstances and acute myocardial infarction (AMI), cardiac ischemia, chest pain, or acute coronary syndrome.

Methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled clinical trials, comparative studies, and economic evaluations. Where possible, retrieval will be limited to the human population. The search will also be limited to English documents (with the exception of French Canadian technology assessments that are not translated). Regular alerts will be established to update the search until the end of the project.

We will identify grey literature (literature that is not commercially published) by searching relevant sections of the Grey Matters checklist (http://cadth.ca/resources/grey-matters). Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry representatives.

3.2 Selection Criteria and Method

Two reviewers (NA and GB) will independently screen the titles and abstracts for relevance using a predefined checklist (Appendix 2). Any discrepancies between reviewers will be discussed until consensus is reached. Full texts of any relevant titles or abstracts will be retrieved, and will be assessed by two independent reviewers (NA and GB) for inclusion, using

a checklist (Appendix 3), incorporating explicit predetermined criteria (Table 1). These will be checked for agreement, and any disagreement between reviewers will be discussed until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Table 1: Selection Criteria

Population	▪ Patients presenting to an ED with chest pain or other symptoms suggestive of ACS
Intervention	▪ hs-cTnT assay ▪ hs-cTnI assay
Comparator	▪ cTnT assay ▪ cTnI assay
Outcome	▪ Diagnostic Test Performance: • Sensitivity • Specificity • Positive likelihood ratio • Negative likelihood ratio • Area under the receiver operating characteristic curve (AUC) • Positive predictive value • Negative predictive value • Rates of false-positive tests • Rates of false-negative tests • Accuracy • ED time until diagnosis or detection of abnormal concentration ▪ Clinical: • Thromboembolic events (e.g., venous thromboembolism [VTE], deep vein thrombosis [DVT], or pulmonary embolism [PE]) • Acute cardiovascular events (e.g., ACS, AMI) • Chronic/non-acute cardiovascular events (e.g., coronary artery stenosis/narrowing seen on angiogram) • Revascularization procedures (e.g., angiograms, percutaneous coronary interventions [PCI], coronary artery bypass graft [CABG]) • Heart failure • Quality of life • Death • 30-day readmission rate* • 30-day recurrence rate* • 30-day mortality rate* • Any harm outcomes reported ▪ Economic: • Quality of life • Incremental cost-effectiveness ratio (ICER) • Cost per outcome unit • Cost per quality-adjusted life-year (QALY)
Study Design	HTAs, systematic reviews and meta-analyses, RCTs, non-randomized studies, economic evaluations.

3.3 Exclusion Criteria

Studies will be excluded if they do not meet the selection criteria, provide the results of a qualitative or a non-comparative quantitative study, or present preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials will also be excluded.

3.4 Data Extraction

One reviewer will perform data extraction for each article, using a predrafted data extraction form (Appendix 4). A second reviewer will check the abstracted data for accuracy. Two reviewers (NA and GB) will pilot data extraction forms a priori. A calibration exercise using a small number of studies will be undertaken to ensure consistency between the reviewers.

3.5 Critical Appraisal of Individual Studies

Two reviewers (NA and GB) will independently evaluate the quality of the included diagnostic studies using the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).[4] The QUADAS-2 is a tool that evaluates the risk of bias in the selection of patients, index test, reference standard, and flow and timing of the study. The tool also addresses concerns about the applicability of tests and signaling questions to help identify potential biases.

The methodological quality of the RCTs and comparative non-randomized studies will be assessed using a modified version of the Downs and Black instrument5 (Appendix 5). The assessment instrument, which has been modified to include the source of funding for studies, has a total score ranging from 0 to 28, with higher scores indicating a higher-quality study. The methodological quality of systematic reviews will be evaluated using the measurement tool for the "assessment of multiple systematic reviews" (AMSTAR, Appendix 6).[5] AMSTAR is an 11-item checklist that has been developed to ensure reliability and construct validity. The same tool will be used for the assessment of systematic reviews or meta-analyses included in identified HTA reports.

The methodological quality of cost-effectiveness studies will be assessed using the guidelines for the appraisal of economic studies by Drummond and Jefferson[6] Any disagreements will be resolved through discussion until consensus is reached.

The results of quality assessments will be used to summarize strengths and limitations of the included studies.

3.6 Data Analysis Methods

The population, interventions, and outcome measures will define the comparability of the studies. When two or more comparable studies with quantitative outcomes are identified, pooled estimates of the outcome measures will be performed through meta-analysis. When the studies are not comparable in terms of population, interventions, or outcome measures, or if there is variation in the reporting of clinical outcomes, a formal meta-analysis will not be performed. Instead, the individual studies will be described and synthesized using a narrative approach.

3.7 Statistical Analyses

3.7.1 Outcomes

There are three types of comparative outcomes between one test and the other test(s) that will be derived from the data abstraction process to estimate comparative effectiveness: diagnostic test performance, differences in change in continuous measures, and differences in rates of binary outcomes.

Comparative diagnostic test performance include sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, AUC, positive predictive value, negative predictive value, rates of false-positive tests, and rates of false-negative tests. Details on how each of these methods will be derived are provided in Appendix 7. The analysis will be conducted without the pre-specification of a reference gold standard. This dictates that the diagnostic test performance will be presented as the lower performing test relative to the higher performing test.

Differences between tests for changes in continuous measures such as quality of life will be analyzed as a weighted mean difference. Difference between tests for changes in binary measures (thromboembolic events such as, VTE, DVT, PE), acute cardiovascular events (e.g., ACS, AMI), chronic/non-acute cardiovascular events (e.g., coronary artery stenosis/narrowing seen on angiogram), revascularization procedures (e.g., angiograms, PCI, CABG), heart failure, death, 30-day readmission rate, 30-day recurrence rate, 30-day mortality, and any harm outcomes) will be reported as relative risks.

3.7.2 Comparisons

Each of these outcomes will be provided for the comparison between four possible tests: hs-cTnT assay, hs-cTnI assay, cTnT assay, and cTnI assay. The focus of the comparisons will be:

- hs-cTnT assay versus cTnT assay
- hs-cTnI assay versus cTnI assay
- hs-cTnT assay versus any non–high-sensitivity cTn assay
- hs-cTnI assay versus any non–high-sensitivity cTn assay
- hs-cTnT assay versus hs-cTnI assay.

3.7.3 Direct and Indirect Comparisons

Direct and indirect comparisons will be used to analyze the data depending on the availability of the evidence obtained in the data abstraction process. The outcomes to be estimated will be reported as the estimate and the 95% confidence interval (CI) (direct comparison) or 95% credibility interval (CrI) of the posterior distribution (indirect comparison). Based on the scoping of the literature, direct evidence on the relative performance between the two high-sensitivity assays is absent and indirect methods to derive the comparative effectiveness are required.

3.7.4 Direct Comparisons

Pooled estimates of the comparison between tests will be calculated using Review Manager 5.1.[7] Fixed and random-effects models will be conducted based on the degree of homogeneity. Homogeneity with each comparator and across each comparator will be assessed with I2, with greater than 50% being moderate heterogeneity and greater than 70% being considerable heterogeneity, as suggested by the Cochrane Handbook of Systematic Reviews.[8] In addition, Cochran's Q statistic (based on chi-squared, where I2 = (Q-df)/Q) will be used to test for the presence of heterogeneity based on a level of significance of 10%. The causes of the considerable heterogeneity with I2 above 75%, or $p < 0.10$ will be carefully investigated to determine if unadjusted pooling is appropriate[8] or if heterogeneity can be explained by differences in patient characteristics (e.g., inclusion criteria). For this latter purpose, meta-regression techniques may be used to test for and to adjust for any reported differences between studies.[9] This involves estimating the effect measures using classical meta-analysis with meta-regression, with the log of the outcome as the dependent variable, and dummy variables for each of the types of tests. Following the unadjusted results, we will adjust the indirect estimates with meta-regression to include the covariates of study level and patient level summary measures for baseline characteristics. Meta-regressions will be conducted with Stata version 11.0, using the command metareg.[10]

3.7.5 Indirect Comparisons (including mixed treatment comparisons [MTCs])

In the absence of head-to-head evidence, indirect and mixed treatment comparisons will be used to provide information on the comparative effectiveness between tests. Indirect comparisons involve pooling studies that are without head-to-head evidence, while MTCs involves pooling both head-to-head studies and the indirect comparisons. The primary method for indirect comparison (in which we include MTC) will be based on Bayesian techniques [11-14] to allow the simultaneous analysis of multiple comparators at one time. With Bayesian techniques, random-effects, "non-informative" priors that produce final estimates that are not affected (i.e., informed) by the prior, will be used such that the final estimates will be generated solely by the data.

The benefit of the Bayesian method is that the data are derived from Monte Carlo methods to simulate relative effect estimates for all tests simultaneously. The main assumption in this type of analysis is that there is no interaction between covariates defining subgroups of patients (such as inclusion criteria) and the magnitude of the treatment effect. In particular, the assumption is that the studies that compare the tests have the same patient population. To assess the possible lack of similarity among the patient populations, the relative rates of binary outcomes and the relative rates of levels of continuous outcomes will be compared to determine outliers. Sensitivity analyses were conducted to exclude those outlier studies.

The Bayesian estimates will be compared with pair-wise comparisons derived from the publicly available indirect treatment comparison software (http://www.cadth.ca/index.php/en/itc-user-guide) developed for CADTH by Wells et al. (2009).[15] In this non-Bayesian approach, indirect comparisons will be conducted by evaluating the differences between two tests. Indirect and mixed treatment comparisons will be conducted using Bayesian methods in WinBUGS software version 1.4.3, which performs Bayesian analysis using Markov Chain Monte Carlo methods.[16] A hierarchical model using random effects mixed models in WinBUGS[14] will be used and differences between estimates versus Wells' CADTH software will be resolved.

Bayesian-based results will be reported according to the Reporting of Bayes used in clinical Studies (ROBUST) criteria in which the outcomes estimated were reported as the mean and the 95% CrI of the posterior distribution of the effect measure.[17] For Bayesian analysis, priors must be pre-specified for both the mean and standard deviation of the effect estimate. Each of these priors has both a mean and a precision. Non-informative priors will be predefined for the mean relative risk as a normal distribution with a mean of zero and a precision of 0.001. The prior for the standard deviation of the relative risk effect estimate was defined as a uniform distribution with a mean of zero and a precision equal to 10, where precision is equal to 1/variance. Both of these distributions of priors indicate weak information. The priors defined for the relative risks will also allow the estimation of diagnostic test performance to be driven only by the data. For each outcome, we will perform enough simulations to reach burn-in, and two chains were run simultaneously. Convergence will be assessed using all of the Geweke, Raftery-Lewis, Gelman-Rubin and Heidelberger-Welch tests, each of which identifies convergence using different criteria. All the base-case Bayesian analyses will use a random effects model, and a sensitivity analysis will be conducted to test the impact of this assumption.

3.7.6 Missing data

When necessary, missing data for effect estimates as well as for standard deviations will be derived from the papers according to the methods suggested in The Cochrane Handbook for Systematic Reviews of Interventions. These methods include estimating missing standard deviations in the continuous outcomes, from which the standard deviation can be derived from the 95% CI or from Buck's regression, which assumes a constant mean/standard deviation ratio across similar studies.

Similarly, when measuring the pooled relative risk for a dichotomous variable, Review Manager excludes studies that report zero events for both tests. The exclusion of these studies may bias the estimates. Therefore, for pooled analyses that have zero event studies, a sensitivity analysis will be conducted assuming a 0.5 continuity correction. Because Review Manager does not allow a 0.5 continuity correction for zero event studies, the sensitivity analysis will be conducted in an alternate software package (Stata).

3.8 Primary Economic Analysis

3.8.1 Overview

An economic model will be developed to compare the cost-effectiveness of different laboratory testing strategies for patients admitted to ED with chest pain or other symptoms leading to the suspicion of MI or ACS. The four testing strategies to be evaluated are: hs-cTnT, hs-cTnI, cTnT, cTnI. The lifetime costs and outcomes for each strategy will be estimated by the economic model. Costs will include those for each troponin test, subsequent diagnostic tests during the acute episode, and those related to AMI/ACS treatment (e.g., PCI, CABG, medications). The primary clinical outcome will be the number of QALYs accrued during a lifelong time horizon.

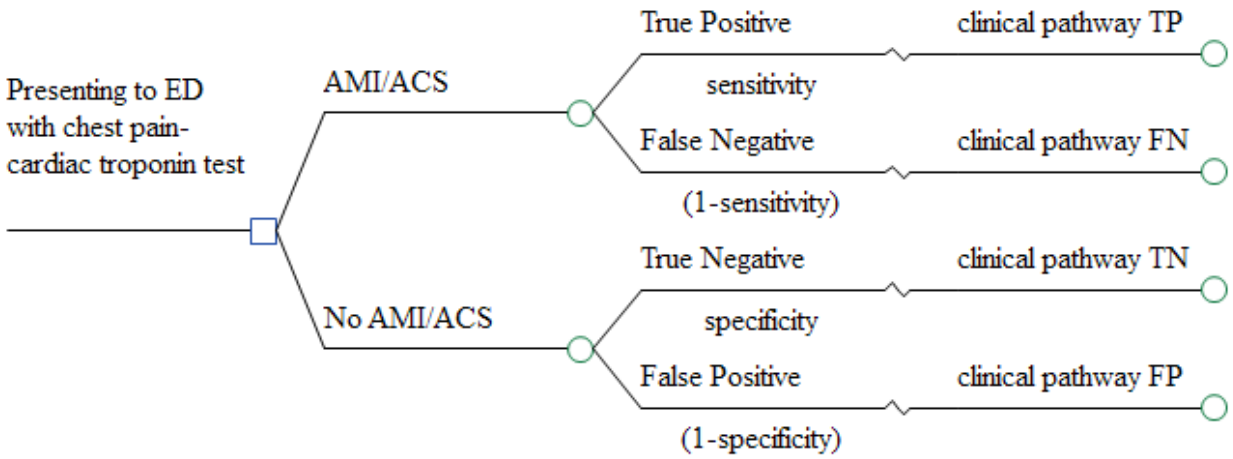
A lifelong time horizon is proposed because the testing strategies may have different impacts on short-term mortality. Any short-term mortality differences will lead to differences in lifetime accumulated QALYs, which can only be properly captured using a lifelong time horizon.

3.8.2 Model Structure

The first step in developing the economic model will be the determination of its structure. The beginning of the structure of the model is illustrated in Figure 1. As shown, the model will begin with patients presenting to an ED with chest pain who are suspected of having AMI or ACS. Patients are given a troponin laboratory test to help diagnose the presence of AMI or ACS.

A proportion of patients will truly be experiencing an AMI or ACS, while a proportion will not. The sensitivity and specificity of the troponin test along with the prevalence of AMI or ACS will determine the proportion of patients in each of four diagnostic categories: true positive (TP), false negative (FN), true negative (TN), and false positive (FP).

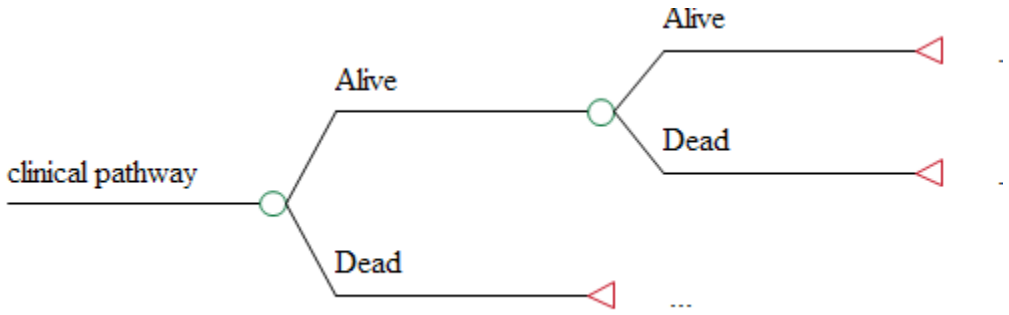
Figure 1: Structure of the Beginning of the Economic Model



The structure of the next part of the model will be developed through consultation with emergency physician(s) and cardiologists who are part of the current project team. Specifically, clinical experts will be consulted on what occurs in clinical practice after a positive or negative troponin test result is received in the ED. We have referred to this as the “clinical pathways” after diagnosis in Figure 1. For example, clinical experts will be asked whether patients with negative troponin tests are immediately discharged or whether other diagnostic tests are performed before discharge. Similarly, experts will be consulted on what confirmatory tests and treatments (i.e., PCI, CABG, medications) would be undertaken after a positive cTn test. Experts will also be consulted on whether the sequence and number of diagnostic tests may differ if hs-cTnT is used instead of non–hs-cTnT in the ED.

The last part of the model structure is shown in Figure 2. Because of the high mortality rate after MI, the acute phase of the model will end with a proportion of patients surviving the episode, while a proportion will not. The probability of death will differ according to diagnostic status (i.e., TP, FN, TN, FP). A Markov phase of the model will be added in which patients are at risk of dying in each yearly model cycle.

Figure 2: End of Model Structure



a) Sources for Model Parameters:

Various sources will be used to populate the model. Results of the clinical review of the model will be used for sensitivity and specificity for each of the four troponin tests. The prevalence of AMI and ACS among patients presenting to an ED with chest pain will likely be obtained from the literature. General population mortality rates will be based on Canadian life tables, while AMI and ACS-related mortality will be based on findings from published literature sources.

The costs of each specific type of troponin test will likely have to be obtained from individual hospital costing databases; costs for other relevant diagnostic tests and cardiac procedures will be derived from costing databases (Ontario Case Costing Initiative [OCCI], Alberta Health), from individual hospitals, or from published literature. Utility weights will be based on literature sources.

b) Analysis Plan

The expected lifetime costs and QALYs for each of the four treatment strategies will be estimated in the model. Next it will be determined which, if any, strategies are dominated by other strategies. The non-dominated strategies will make up the efficiency frontier. The incremental cost-effectiveness will be calculated moving sequentially from one strategy to the next most effective strategy on the efficiency frontier. Results will be presented on the cost-effectiveness plane. The model will be fully probabilistic. Parameter uncertainty will be expressed using cost-effectiveness acceptability curves along with cost-effect pairs from the simulation plotted for each strategy on the cost-effectiveness plane. Structural uncertainty and model validity will be assessed using one-way and two-way sensitivity analysis. If there is insufficient information in the literature to allow for the completion of a full economic evaluation, a cost-minimization analysis will be undertaken.

3.9 Budget Impact Analysis

A budget impact analysis will be undertaken to assess the resource implication of the adoption of hs-cTnT or hs-cTnI in EDs across Canada. The budget impact will be conducted in a number of steps. First an estimation of the annual number of visits made to EDs in Canada for chest pain will be made. This estimate will be based on published literature. Next, an estimate of the current mix of types of cTn tests (i.e., hs-cTnT, hs-cTnI, cTnT, cTnI) used in Canadian EDs will be made. These data will be based upon findings of an Environment Scan looking at patterns of types of cTn tests currently used in Canadian EDs.

In the next step, the costs pretest for each of the cTn tests of interest will be made. These unit costs will be derived from hospital databases with which the clinical experts of the project are associated. Since cTnI has not yet been approved for use in Canada, it is unlikely that costs for this test will be attainable. Therefore, it may be necessary to assume the same costs for cTnI as for cTnT.

The unit costs for the various cTn tests will be applied to estimates of the current mix of types of cardiac tests used in Canada along with the number of ED visits for chest pain to generate an approximate total annual cost of cTn tests in Canadian EDs. Finally, annual costs of cTn tests in Canadian EDs will be made assuming that high-sensitivity tests are used exclusively in Canadian EDs.

4 DELIVERABLES

- List of selected studies
- Draft reports
- Final report

REFERENCES

1. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, 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. Circulation. 2007;116(7):e148-304.
2. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007;50(22):2173-95.
3. Alpert JS, Thygesen K, Jaffe A, White HD. The universal definition of myocardial infarction: a consensus document: ischaemic heart disease. Heart. 2008;94(10):1335-41.
4. 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. Ann Intern Med [Internet]. 2011 [cited 2012 Sep 13];155(8):529-36. Available from: http://www.annals.org/content/155/8/529.full.pdf+html
5. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2012 Oct 5];7:10. Available from: http://www.biomedcentral.com/content/pdf/1471-2288-7-10.pdf
6. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ [Internet]. 1996 [cited 2012 Oct 5];313(7052):275-83. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2351717
7. Review Manager (RevMan). Version 5.1 [computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

8. Imputing standard deviations [Internet]. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions 5.1.0 [updated March 2011]. London: The Cochrane Collaboration; 2011. Chapter 16 [cited 2012 Oct 29]. Available from: www.cochrane-handbook.org.
9. Sharp S. Meta-analysis regression [Internet]. In: Stata technical bulletin STB-42. College Station (TX): Stata Press; 1998. p. 16-22. Chapter sbe23 [cited 2012 Sep 13]. Available from: http://www.stata.com/products/stb/journals/stb42.pdf.
10. StataCorp. Stata statistical software. Release 11 [computer program]. College Station (TX): StataCorp LP; 2009.
11. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2005;331(7521):897-900.
12. Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. Health Technol Assess [Internet]. 2005 [cited 2012 Sep 13];9(26):1-134, iii-iv. Available from: http://www.hta.ac.uk/execsumm/summ926.htm
13. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ. 2003;326(7387):472.
14. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23(20):3105-24.
15. Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect treatment comparison. Version 1.0 [computer program]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2009.
16. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS: a Bayesian modelling framework: concepts, structure, and extensibility. Stat Comput. 2000;10(4):325-37.
17. Sung L, Hayden J, Greenberg ML, Koren G, Feldman BM, Tomlinson GA. Seven items were identified for inclusion when reporting a Bayesian analysis of a clinical study. J Clin Epidemiol. 2005;58(3):261-8.
18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 [cited 2012 Oct 5];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf
19. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol. 1991;44(8):763-70.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	OvidSP
Databases:	Embase <1980 to 2012 Week 19>, emez Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1946 to current>, prmz **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 16, 2012
Alerts:	Monthly search updates began May 16, 2012 and will run until TBD.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; cross-over studies; case control studies; comparative studies; diagnostic studies; costs and cost analysis studies, economic literature.
Limits:	English language Humans, where possible

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.mp	In MEDLINE=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier In Embase=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.kw	In MEDLINE=Keyword Heading; this field contains the Keyword Headings assigned by the indexers at NLM to describe the content of an article In Embase=Keyword; this field contains keywords defined by the author of the article
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.dm	In Embase=Device Manufacturer; this field contains the full name of the manufacturer of a drug or device discussed in an article. Manufacturer names are listed in their brief form, for example, Lilly for "Eli Lilly"
.dv	In Embase=Device Trade Name; this field contains the medical device trade names assigned to the records
.pt	Publication type

Multi-Database Strategy		
#	Searches	Results
1	exp Ambulances/ use prmz	6199
2	Early Diagnosis/ use prmz	9538
3	Emergencies/ use prmz	32447
4	Emergency Medical Services/ use prmz	28994
5	Emergency Medical Technicians/ use prmz	4630
6	Emergency Medicine/ use prmz	8929
7	exp Emergency Service, Hospital/ use prmz	42011
8	exp Emergency Treatment/ use prmz	86409
9	Evidence-Based Emergency Medicine/ use prmz	113
10	Time Factors/ use prmz	922909
11	Triage/ use prmz	7040
12	((acute or urgent*) adj2 care).ti,ab,kw.	31995
13	(ambulance* or emergencies or emergency* or first response or first responder* or out-of-hospital or paramedic* or prehospital or pre-hospital).ti,ab,kw.	350868
14	(earl* or rapid*).ti.	568953
15	((earl* or rapid*) adj (diagnos* or detect*)).ab,kw.	183038
16	(trauma center* or trauma centre* or triage or rescue personnel).ti,ab,kw.	33659
17	Ambulance/ use emez	7053
18	Early Diagnosis/ use emez	55156
19	Emergency/ use emez	28817
20	Emergency Care/ use emez	13977
21	Emergency Health Service/ use emez	57398
22	Emergency Medicine/ use emez	19352
23	Emergency Medical Services Education/ use emez	171
24	Emergency Nurse Practitioner/ use emez	144
25	Emergency Nursing/ use emez	4574
26	Emergency Patient/ use emez	798
27	Emergency Physician/ use emez	3213
28	Emergency Surgery/ use emez	11364
29	Emergency Treatment/ use emez	13372
30	Emergency Ward/ use emez	40558
31	Evidence Based Emergency Medicine/ use emez	106
32	First Aid/ use emez	8910
33	Rescue Personnel/ use emez	4970
34	Time/ use emez	405776
35	Acute Coronary Syndrome/ use prmz	4979
36	(Chest Pain/ or Heart Failure/ or Heart Injuries/ or Myocardial Infarction/) and acute*.mp.	130285
37	((coronary syndrome? or (heart adj2 infarct*) or (myocardial adj2 infarct*) or (myocardium adj2 infarct*) or chest pain?) and acute*).ti,ab,kw.	162704

Multi-Database Strategy		
#	Searches	Results
38	((cardiac* or myocardial injur*) and acute*).ti.	11153
39	Acute Coronary Syndrome/ use emez	18139
40	Acute Heart Failure/ use emez	3936
41	Acute Heart Infarction/ use emez	39916
42	(Heart Failure/ or Heart Infarction/ or exp Heart Injury/ or Thorax Pain/) and acute*.mp.	82891
43	or/1-42	2726587
44	Troponin/	10651
45	Troponin I/	13765
46	Troponin T/	11047
47	(troponin* or cTn* or TnI* or TnT*).ti,ab,kw,dm,dv.	38908
48	or/44-47	46521
49	(high sensitivity or highsensitivity or high sensitive or highsensitive or HS or highly sensitive or highlysensitive or ultra high* or ultrahigh* or ultra sensitiv* or ultrasensitiv* or new assay* or newer assay* or emerging assay* or new sensitive or increased sensitivity or next generation or new generation or newer generation or better sensitivity).ti,ab,kw,dm,dv.	246042
50	more sensitiv*.ti,ab,kw,dm,dv.	115393
51	or/49-50	355576
52	48 and 51	2673
53	(cTnIhs* or cTnI-hs* or cTnIultra* or cTnI-ultra* or TnIultra* or TnI-ultra* or hsTnI* or hs-TnI* or hscTnI* or hs-cTnI*).ti,ab,kw,dv.	139
54	(cTnThs* or cTnT-hs* or cTnTultra* or cTnT-ultra* or hsTnT* or hs-TnT* or hscTnT* or hs-cTnT*).ti,ab,kw,dv.	393
55	(Architect* adj10 (troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.	89
56	(Access* and Beckman* and (AccuTnI* or troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.	136
57	(Vista* and (troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.	12
58	((Cobas e601 or Cobas e411 or Elecsys) adj10 (troponin* or cTn* or TnI* or TnT*)).ti,ab,kw,dm,dv.	172
59	or/52-58	2967
60	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	406311
61	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	482007
62	Multicenter Study.pt.	143235
63	Randomized Controlled Trial/	648245
64	Randomized Controlled Trials as Topic/	95609
65	Controlled Clinical Trial/	472561
66	Controlled Clinical Trials as Topic/	5535
67	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/	1350352

Multi-Database Strategy		
#	Searches	Results
68	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/	185123
69	Clinical Trials/	13386
70	Multicenter Study/ or Multicenter Study as Topic/	241078
71	Randomization/	132189
72	Random Allocation/	132189
73	Random Sampling/	61
74	Double-Blind Method/	223195
75	Double Blind Procedure/	108636
76	Double-Blind Studies/	180886
77	Single-Blind Method/	31912
78	Single Blind Procedure/	15834
79	Single-Blind Studies/	31912
80	Placebos/	228588
81	Placebo/	197741
82	Control Groups/	34151
83	Control Group/	34151
84	Cross-Over Studies/ or Crossover Procedure/	63194
85	(random* or sham or placebo*).ti,ab,hw.	1875115
86	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	341906
87	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	619
88	(control* adj3 (study or studies or trial*)).ti,ab,hw.	4735983
89	(clinical adj3 (study or studies or trial*)).ti,ab,hw.	3380165
90	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti,ab,hw.	52025
91	(phase adj3 (study or studies or trial*)).ti,ab,hw.	189081
92	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.	76537
93	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.	315563
94	(allocated adj "to").ti,ab,hw.	71131
95	trial.ti.	234036
96	Epidemiologic Methods/	164691
97	Epidemiologic Studies/	141527
98	Cohort Studies/	255436
99	Longitudinal Studies/	123244
100	Prospective Studies/	519599
101	Follow-Up Studies/	1055815
102	Retrospective Studies/	689936
103	Case-Control Studies/	196263
104	Cross-Sectional Study/	212504
105	Evaluation Studies.pt.	164637

Multi-Database Strategy		
#	Searches	Results
106	Evaluation Studies as Topic/	296162
107	Comparative Study.pt.	1575215
108	Observational Study/	28496
109	Cohort Analysis/	255436
110	exp Case Control Study/	621077
111	Cross-sectional Study/	212504
112	Quasi Experimental Study/	1019
113	exp Longitudinal Studies/	819547
114	Prospective Studies/	519599
115	Retrospective Studies/	689936
116	Followup Studies/	443191
117	Pretesting/	7
118	exp Program Evaluation/	1719819
119	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.	112922
120	(cohort adj7 (study or studies or design or analysis or analyses)).ti,ab,hw.	363109
121	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab,hw.	761265
122	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,hw.	594554
123	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab,hw.	348524
124	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab,hw.	864369
125	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,hw.	276336
126	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.	1133
127	(population adj3 (study or studies or analysis or analyses)).ti,ab,hw.	191462
128	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.	4079
129	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,hw.	312809
130	((natural adj experiment) or (natural adj experiments)).ti,ab,hw.	1638
131	(quasi adj (experiment or experiments or experimental)).ti,ab,hw.	9506
132	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.	1357
133	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,hw.	41015
134	((comparison or comparative*) adj3 (study or studies or analysis	2420034

Multi-Database Strategy		
#	Searches	Results
	or analyses)).ti,ab,hw.	
135	((before-after or (before* adj after)) adj3 (study or studies or design?)).mp.	1958
136	((follow up or followup) and (base line* or baseline*)).ti,ab,hw.	141384
137	exp "Sensitivity and Specificity"/	522335
138	False Positive Reactions/	62864
139	False Negative Reactions/	55244
140	Diagnostic Techniques, Cardiovascular/	2637
141	Troponin/du	41
142	Troponin T/du	26
143	Troponin I/du	48
144	Validation Studies.pt.	55413
145	sensitivit*.ti,ab.	1015659
146	specificity.ti,ab.	607810
147	predict*.ti,ab.	1696867
148	distinguish*.ti,ab.	349185
149	differentiat*.ti,ab.	950135
150	enhancement.ti,ab.	285248
151	identif*.ti,ab.	3485311
152	detect*.ti,ab.	3054507
153	diagnos*.ti,ab.	3233436
154	accura*.ti,ab.	859830
155	precision.ti,ab.	129775
156	prognos*.ti,ab.	714572
157	false positive*.ti,ab.	81551
158	false negative*.ti,ab.	48352
159	exp Diagnosis/	9846087
160	Diagnostic Procedures/	287
161	Acute Coronary Syndrome/di or Acute Heart Failure/di or Acute Heart Infarction/di or Chest Pain/di or Heart Failure/di or Heart Infarction/di or Heart Injury/di or Heart Injuries/ or Myocardial Infarction/di or Thorax Pain/di	81522
162	or/60-161	23604499
163	exp animals/	17745548
164	exp animal experimentation/	1514487
165	exp models animal/	1006759
166	exp animal experiment/	1514487
167	nonhuman/	3836843
168	or/163-167	21821748
169	exp humans/	25703002
170	exp human experiment/	300383
171	or/169-170	25704394

Multi-Database Strategy		
#	Searches	Results
172	168 not 171	8371991
173	43 and 59 and 162	1599
174	173 not 172	1557
175	Diagnostic Techniques, Cardiovascular/	2637
176	biomarker*.ti.	42953
177	Cardiovascular System Examination/	1768
178	or/175-177	45574
179	Meta-Analysis.pt.	33494
180	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/	157901
181	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.	91566
182	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.	9731
183	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.	18400
184	(data synthes* or data extraction* or data abstraction*).ti,ab.	24191
185	(handsearch* or hand search*).ti,ab.	9462
186	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.	23130
187	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.	5400
188	(meta regression* or metaregression* or mega regression*).ti,ab.	3544
189	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	222375
190	(medline or Cochrane or pubmed or medlars).ti,ab,hw.	150738
191	(cochrane or health technology assessment or evidence report).jw.	21838
192	Meta Analysis/ or Systematic Review/ or Biomedical Technology Assessment/	142896
193	or/179-192	368086
194	43 and (59 or 178) and 193	148
195	174 or 194	1686
196	limit 195 to english	1532
197	remove duplicates from 196	1016=clinical studies
198	*Economics/	21250
199	*Economics, Medical/	20698
200	*Economics, Pharmaceutical/	4495
201	exp "Costs and Cost Analysis"/	384954
202	exp Health Care Costs/	215217
203	exp Decision Support Techniques/	61840
204	Economic Value of Life/	103479
205	exp Models, Economic/	97413

Multi-Database Strategy		
#	Searches	Results
206	Markov Chains/	59043
207	Monte Carlo Method/	33617
208	Decision Trees/	12621
209	Uncertainty/	9460
210	exp "Quality of Life"/	303699
211	Quality-Adjusted Life Years/	14689
212	exp Health Care Cost/	215217
213	exp Health Economics/	540871
214	exp Economic Evaluation/	183265
215	exp Pharmacoeconomics/	154826
216	exp Economic Aspect/	979886
217	Quality Adjusted Life Year/	14689
218	(econom* or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget* or afford* or pharmacoeconomic or pharmaco-economic*).ti,ab.	958592
219	(cost* adj1 (util* or effective* or efficac* or benefit* or consequence* or analy* or minimi* or saving* or breakdown or lowering or estimate* or variable* or allocation or control or illness or sharing or life or lives or affordabl* or instrument* or technolog* or day* or fee or fees or charge or charges)).ti,ab.	200517
220	(decision adj1 (tree* or analy* or model*)).ti,ab.	19162
221	((value or values or valuation) adj2 (money or monetary or life or lives or costs)).ti,ab.	6721
222	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.	59072
223	(sensitivity analys*s or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc*).ti,ab.	36678
224	(unit-cost or unit-costs or markov).ti,ab.	23889
225	or/198-224	2280281
226	43 and (59 or 178) and 225	547
227	limit 226 to english	518
228	remove duplicates from 227	378=economic studies

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
The Cochrane Library Issue 5 of 12, May 2012; Issue 2 of 4, Apr 2012	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types, human and language restrictions. Syntax adjusted for The Cochrane Library databases.
Health Economic Evaluations Database (HEED)	Same keywords and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for HEED database.

APPENDIX 2: TITLE AND ABSTRACT SCREENING CHECKLIST

Reviewer: _____ **Date:** _____

Ref ID: _____ **First Author (year):** _____

	Include	Exclude
1. What is the study population in this article?	□ Patients presenting in the ED with chest pain □ Patients with suspected ACS or AMI □ Can't tell	□ Patients in non-ED hospital setting; i.e., regular hospital wards, intensive care unit (ICU), coronary care unit (CCU) □ Community-based/non-institutional care settings
2. What is the intervention?	□ hs-cTnT □ hs-cTnI	□ Conventional/sensitive (i.e., non-high sensitivity) cTn assays.
3. What is the type of study reported in this article?	□ RCT □ Non-RCT □ Meta-analysis, systematic review, or HTA □ Comparative observational study □ Economic evaluation □ Can't decide	□ Before after trial □ Non-comparative observational study □ Qualitative study
Include for full text review	□ **Yes**	□ **No**

ACS = acute coronary syndrome; AMI = acute myocardial infarction; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; HTA = health technology assessment; ID = identification; RCT = randomized controlled trial.

APPENDIX 3: FULL TEXT SCREENING CHECKLIST

a) Clinical Review

1. **Did this article include patients presenting in the ED with chest pain who are suspected to have ACS or AMI?**
   - ☐ Yes (include)
   - ☐ No (exclude)
   - ☐ Maybe (include)

2. **Is the article the primary report of the final results from a:**
   - ☐ RCT (include)
   - ☐ Non-RCT (include)
   - ☐ Meta-analysis / systematic review, or HTA (include)
   - ☐ Comparative observational study (include)
   - ☐ All other study types (exclude)
   - ☐ Can't decide (include)

3. **What comparator is used in the study?**
   - ☐ cTnT (include)
   - ☐ cTnI (include all non–point-of-care assays or Siemens Stratus CS point-of-care assay))
   - ☐ Cardiac ischemia biomarkers other than troponin (exclude)
   - ☐ No comparator (exclude)

4. **Include if the outcome of interest in the study is one of the following:**
   - ☐ Diagnostic test performance (including sensitivity, specificity, positive or negative likelihood ratios, positive or negative predictive values, AUC, rates of false-positive or false-negative tests, and test accuracy)
   - ☐ Thromboembolic events (e.g., VTE, DVT, PE)
   - ☐ Acute cardiovascular events (e.g., ACS, AMI)
   - ☐ Chronic / non-acute cardiovascular events (e.g., coronary artery stenosis/narrowing seen on angiogram)
   - ☐ Revascularization procedures (e.g., angiograms, PCI, CABG)
   - ☐ ED time until diagnosis or detection of abnormal concentration
   - ☐ Heart failure
   - ☐ Quality of life
   - ☐ Death
   - ☐ 30-day readmission rate
   - ☐ 30-day recurrence rate
   - ☐ 30-day mortality
   - ☐ Any harm outcomes reported
   - ☐ None of the above (exclude)

5. Final Decision

- ☐ Include
- ☐ Exclude
- ☐ Non-English or unable to translate

Reason for Exclusion:

- ☐ Inappropriate study population
- ☐ Not study types of interest
- ☐ Not primary report of study
- ☐ Study description only
- ☐ No intervention of interest
- ☐ No/inappropriate control group
- ☐ No relevant outcomes

b) Economic Review

Author (Year): _____ **REF ID:** _____

Level 2 Screening Questions	Circle One	
Q1. Is this a primary economic evaluation?	Yes	No
Q2. Are costs measured?	Yes	No
Q3 Is effectiveness measured	Yes	No
Q4. Does the study evaluate laboratory testing for patients admitted to an ED who are suspected of having MI or ACS?	Yes	No
Q5. Is one of treatment comparators: a) hs-cTnT (Abbott ARCHITECT, Beckman Access, Siemens Vista) **or** b) hs-cTnI (Roche Cobas E, Roche Elecsys)	Yes Yes	No No
Q6. Is one of the treatment comparators: a) hs-cTnT (Abbott ARCHITECT, Beckman Access, Siemens Vista) **or** b) hs-cTnI (Roche Cobas E, Roche Elecsys) **or** c) Sensitive Troponin T (Roche Cobas H232, Roche, Elecsys TnT Gen 4, Roche Cardiac Reader cTnT) **or** d) Sensitive Troponin I (Abbott AxSYM ADV, Abbott ARCHITECT, Alere Triage Cardio2, Alere Triage Cardio3, Beckman Access AccuTnI, bioMérieux Vidas Ultra, Ortho Vitros ECi ES, Siemens Centaur XP Ultra, Siemens Dimension RxL, Siemens Dimension Vista, Siemens Immulite 2500, Siemens Stratus CS)	Yes Yes Yes Yes	No No No No
Include study for review	Yes	No

Reason for Exclusion:

Check One if Study Was Excluded	
1. Neither costs or effects evaluated	
2. Cost-study only (no effectiveness measured)	
3. hs-cTnI or hs-cTnT were not comparators	
4. Other	

APPENDIX 4: DATA ABSTRACTION FORMS

a) Clinical Review

Study	
Ref ID	
Author	
Publication year	
Country	
Funding	

Methodology	
Study type	☐ **RCT** ☐ **non-RCT**
Study design	
Setting	
Total sample size	
Number of eligible participants	
Number of randomized participants	
Number of participants who completed the study	
Number evaluated	
Sampling procedure	
Randomization procedure	

Inclusion/Exclusion	
Inclusion criteria	
Exclusion criteria	

Intervention/Comparator				
	hs-cTnT ☐ **reference standard** ☐ **index test**	**hs-cTnI** ☐ **reference standard** ☐ **index test**	**Comparator 1** ☐ **reference standard** ☐ **index test**	**Comparator 2**
Product / Manufacturer				
Sample size				
Time since chest pain onset				
Time since ED admission				

Population Characteristics					
		hs-cTnT	hs-cTnI	Comparator 1	Comparator 2
Mean age, year (SD)					
Gender (% female)					
Ethnicity (% white)					
Prior diagnosis of ischemic heart disease					
Cardiac treatments **1. _____ (%)** **2. _____ (%)** **3. _____ (%)**					
Cardiac risk factors	**BMI**				
	Waist to hip ratio				
	Smoking (% current)				
	Smoking (% former)				
Pre-existing conditions	**Hypertension (%)**				
	Diabetes (%)				
	Hyperlipidemia (%)				
	Angina				
	MI				
ECG Results	**ST-segment elevation (%)**				
	ST-segment depression (%)				
	T inversion (%)				
	Left to right bundle branch block (%)				
	Other----------				
Other biomarkers (unit) **1. _____ ( )** **2. _____ ( )** **3. _____ ( )**					

Reported Outcomes	
Primary	
Secondary	
Timing of assessment (days)	

Results				
Outcome	**hs-cTnT**	**hs-cTnI**	**Comparator 1**	**Comparator 2**
Diagnostic test performance				
Sensitivity				
Specificity				
Positive likelihood ratio				
Negative likelihood ratio				
Positive predictive value				
Negative predictive value				
AUC				
% false-positive tests				
% false-negative tests				
Test accuracy				
Thromboembolic events (%)				
VTE **DVT** **PE**				
Acute cardiovascular events				
ACS **AMI**				
Revascularization procedures (e.g., angiograms, PCI, CABG) (%)				
Heart failure (%)				
30-day readmission rate (%)				
30-day recurrence rate (%)				
30-day mortality (%)				
Overall mortality (%)				
Adverse events: _____ (%)				

ACS = acute coronary syndrome; AMI = acute myocardial infarction; AUC = area under the receiver operating characteristic curve; BMI = body mass index; CABG = coronary artery bypass graft;
DVT = deep vein thrombosis; ECG = electrocardiogram; ED = emergency department; hs-cTnI = high-sensitivity cardiac troponin T; hs-cTnT = high-sensitivity cardiac troponin I; ID = identification;
MI = myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism;
RCT = randomized controlled trial; SD = standard deviation; VTE = venous thromboembolism.

b) Economic Review

Ref ID	
Citation	
Industry sponsorship	
Study perspective	
Population	
Interventions and comparators	
Study design	
Location	
Outcome and sources	
Currency and year	
Estimate of cost-effectiveness	
Conclusions	

APPENDIX 5: DOWNS AND BLACK CHECKLIST[18]

REPORTING	Yes/No/Partially	Score
1. Is the objective of the study clear?	Yes = 1, No = 0	
2. Are the main outcomes clearly described in the Introduction or Methods?	Yes = 1, No = 0	
3. Are characteristics of the patients included in the study clearly described?	Yes = 1, No = 0	
4. Are the interventions clearly described?	Yes = 1, No = 0	
5. Are the distributions of principal confounders in each group of subjects clearly described?	Yes = 2 Partially = 1 No = 0	
6. Are the main findings of the study clearly described?	Yes = 1, No = 0	
7. Does the study estimate random variability in data for main outcomes?	Yes = 1, No = 0	
8. Have all the important adverse events consequential to the intervention been reported?	Yes = 1, No = 0	
9. Have characteristics of patients lost to follow-up been described?	Yes = 1, No = 0	
10. Have actual probability values been reported for the main outcomes except probability < 0.001?	Yes = 1, No = 0	
11. Is the source of funding clearly stated?*	Yes = 1, No = 0	
EXTERNAL VALIDITY	**Yes/No/Unclear**	**Score**
12. Were subjects asked to participate in the study representative of the entire population recruited?	Yes = 1, No = 0, Unclear = 0	
13. Were those subjects who were prepared to participate representative of recruited population?	Yes = 1, No = 0, Unclear = 0	
14. Were staff, places, and facilities where patients were treated representative of treatment most received?	Yes = 1, No = 0, Unclear = 0	
INTERNAL VALIDITY	**Yes/No/Unclear**	**Score**
15. Was an attempt made to blind study subjects to the intervention?	Yes = 1, No = 0, Unclear = 0	
16. Was an attempt made to blind those measuring the main outcomes?	Yes = 1, No = 0, Unclear = 0	
17. If any of the results of the study were based on data dredging was this made clear?	Yes = 1, No = 0, Unclear = 0	
18. Was time period between intervention and outcome the same for intervention and control groups or adjusted for?	Yes = 1, No = 0, Unclear=0	
19. Were statistical tests used to assess main outcomes appropriate?	Yes = 1, No = 0, Unclear = 0	
20. Was compliance with the interventions reliable?	Yes = 1, No = 0, Unclear = 0	
21. Were main outcome measures used accurate? (valid and reliable)	Yes = 1, No = 0, Unclear = 0	

INTERNAL VALIDITY-CONFOUNDING (SELECTION BIAS)	Yes/No/Unclear	Score
22. Were patients in different intervention groups recruited from the same population?	Yes = 1, No = 0, Unclear = 0	
23. Were study subjects in different intervention groups recruited over the same period of time?	Yes = 1, No = 0, Unclear = 0	
24. Were study subjects randomized to intervention groups?	Yes = 1, No = 0, Unclear = 0	
25. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	Yes = 1, No = 0, Unclear = 0	
26. Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	Yes = 1, No = 0, Unclear = 0	
27. Were losses of patients to follow-up taken into account?	Yes = 1, No = 0, Unclear = 0	
POWER	**Size of Smallest Intervention Group Score 0 to 5**	**Score**
28. Was the study sufficiently powered to detect clinically important effects where probability value for a difference due to chance is < 5%?		

*Criteria were added for the current systematic review.

APPENDIX 6: AMSTAR MEASUREMENT TOOL TO ASSESS SYSTEMATIC REVIEWS[5]

1. Was a priori design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, Embase, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? A priori methods of assessment should be provided (e.g., for effectiveness studies if the author[s] chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

APPENDIX 7: DETAILS OF OUTCOME MEASURES / TESTS OF ACCURACY

	+ Test 2	– Test 2	Total
+ Test 1	True Positive (A)	False Positive (B)	A + B
- Test 2	False Negative (C)	True Negative (D)	C + D
Total	A + C	B + D	A + B + C + D

True positives (A) will be identified when the positive Test 1 agrees with the positive Test 2. False positives (B) will be identified when the positive Test 1 disagrees with the negative Test 2. False negatives (C) will be identified when the negative Test 1 disagrees with the positive Test 2.

True negative (D) will be identified when the negative Test 1 agrees with the negative Test 2.

From this 2 x 2 table, several tests of accuracy can be made with confidence intervals.[19]

Sensitivity: TP/(TP+FN): the proportion of persons with the disease who are correctly identified by a test. That is, a test with a high sensitivity is useful for ruling out a disease if a person tests negative.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TP+FN}}$

Specificity: TN/(TN+FP): the proportion of persons without a disease who are correctly identified by a test. High specificity is important when the treatment or diagnosis is harmful to the patient.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TN+FP}}$

Positive Predictive Value (PPV): TP/(TP+FP): the proportion of patients with positive test results who are correctly diagnosed.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TP+FP}}$

Negative Predictive Value (NPV): TN/(TN+FN): the proportion of patients with negative test results who are correctly diagnosed.

Confidence interval: $p \pm Z * \sqrt{\frac{p*(1-p)}{TN+FN}}$

Positive Likelihood Ratio (LR+): indicates how much more likely it is to get a positive test in the diseased group as opposed to the non-diseased group.

Confidence interval: $LR+ = \exp(\ln \frac{sensitivity}{1-specificity} \pm 1.96 * \sqrt{\frac{1-sensitivity}{TP} + \frac{specificity}{FP}})$

Negative Likelihood Ratio (LR–): indicates how much more likely it is to get a negative test in the non-diseased group as opposed to the diseased group.

Confidence interval: $LR- = \exp(\ln \frac{1-sensitivity}{specificity} \pm 1.96 * \sqrt{\frac{sensitivity}{FN} + \frac{1-specificity}{TN}})$

Area Under the Receiver Operating Characteristic Curve

AUC analysis will be performed for the patient-level analysis. Because the estimates of sensitivity and specificity will be constructed for the full patient population, only one estimate of sensitivity and one estimate of specificity will be generated. With only one estimate the sensitivity/specificity graphical methods to derive AUC are not applicable. Instead, the accepted method of estimating AUC will be determined by the non-parametric Wilcoxon approximation of the 2 x 2 table (which is statistically equivalent to the AUC generated with the trapezoid rule, and the Mann-Whitney U Test).

The degree of precision of the AUC estimated will be reported by generating the standard error and 95% confidence interval around the estimate.

Area Under the Receiver Operating Characteristic Curve (AUC): represents the probability that a randomly chosen diseased patient is correctly diagnosed with greater suspicion than a randomly chosen non-diseased patient.

$$\text{Wilcoxon AUC} = \frac{TN \times TP + 0.5 \times TN \times FN + 0.5 \times FP \times TP}{N_N \times N_A}$$

Standard error (Hanley and McNeil method):

$$SE(A) = \sqrt{\frac{A(1-A) + (N_A - 1) * (Q_1 - A^2) + (N_N - 1) * (Q_2 - A^2)}{N_A * N_N}}$$

where A = AUC
N_A = number of positive disease cases
N_N = number of negative disease cases

$$Q1 = \frac{TN \times [TP^2 + TP \times FN + \frac{1}{3} \times FN^2] + FP \times [\frac{1}{3} \times TP^2]}{N_N \times N_A^2}$$

$$Q2 = \frac{FN \times [\frac{1}{3} \times TN^2] + TP \times [TN^2 + TN \times TP + \frac{1}{3} xFP^2]}{N_A \times N_N^2}$$

Example:

Overall			**Total**
	CICA: D+	**CICA: D-**	
64 CT: + test	183	22	205
64 CT: - test	2	219	221
Total	185	241	426

CT = computed tomography; TP = 183, FP= 22, FN = 2, TN = 219.

AUC = (219 x 183 + 0.5 x 219 x 2 + 0.5 x 22 x 183) / (185 x 241) = 0.9490.
Similarly, Q1 = 0.9287, Q2 = 1.5051, SE = 0.0581.
95% CI = (0.9490 – 1.96*0.0581, 0.9490 + 1.96* 0.0581) = (0.8351, 1).

Kappa Coefficient:
Cases of disagreement between the two observers will be resolved by consensus, and the interobserver variability in identifying disease will be calculated and expressed using the Cohen's kappa-coefficient (κ).

According to Landis and Koch[20] a kappa (*κ)* value of 0 indicated poor agreement; 0.01 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, good agreement; and 0.81 to 1.00, excellent agreement.

		Rater # 1		
		Positive	**Negative**	**Total**
Rater # 2	Positive	P11	P12	P1 (rater 2)
	Negative	P21	P22	P2 (rater 2)
	Total	P1 (rater 1)	P2 (rater 1)	1

In percentages:
Po = probability of observed agreement = P11 + P22.
Pe = probability of expected agreement = P1 (rater 1) * P1 (rater 2) + P2 (rater 2) * P2 (rater 2)
Kappa = (Po – Pe)/(1 – Pe).

Example with Counts:

		Rater # 1		
		Positive	**Negative**	**Total**
Rater # 2	Positive	48	6	54
	Negative	8	30	38
	Total	56	36	92

Kappa = ((48/92+30/92) – (56/92*54/92 + 36/92 * 38/92)) / (1– (56/92*54/92 + 36/92*38/92) = 0.6837.