High-sensitivity troponin for the early rule out of acute myocardial infarction (provisional title)

Draft scope consultation

Who	Section	Comment	NICE Response
Beckman Coulter	Technologies 2.Are the descriptions of the technologies accurate?	2.2.2 Access hsTnI assay (Beckman Coulter): The turnaround time of the assay is to be confirmed by the company. Beckman Coulter confirms: Results are available within 17 minutes	Thank you for your comment. The scope has been updated.
British Cardiovascular Society endorsed by Royal College of Physicians	Technologies 3.Are each of the technologies in use in the NHS and relevant to the evaluation?	I'm not sure if you call it a technology, but there are widely used risk scoring tools in this area (EDACS, Heart SCORE TIMI and others). I'm not sure what the added value of using these scores is in conjunction with hs troponin testing	Thank you for your comment. This assessment will focus only on high sensitivity troponin, therefore risk scoring tools are not included as an adjunct to troponin testing, Assessing clinical risk scores would require an in-depth assessment of their underlying prediction models and validation to enable the added value of the high-sensitivity troponin to be quantified, and would be best addressed as a separate clinical question. Some of the variables which are included in the clinical risk scoring tools are likely to be documented as baseline characteristics of the populations included in diagnostic accuracy studies and will be extracted and documented where they are reported.
British Cardiovascular Society endorsed by Royal College of Physicians	Technologies 4.Are there any other technologies with a similar purpose in use in the NHS?	Not in everyday use, but there are other biomarkers that have been the subject of ongoing research in this area. I don't know the specifics. There are portable troponin/combined biomarker devices – these would allow for pre-hospital triage of some of these patients by ambulance teams. I	Thank you for your comment. This assessment will focus only on troponin tests used in the emergency department, therefore other biomarkers and settings are not included. Alternative biomarker tests can be notified to NICE for consideration via HealthTech Connect.

Who	Section	Comment	NICE Response
		don't believe there are as yet any hs troponin assays that can be usd in this way.	
British Cardiovascular Society endorsed by Royal College of Physicians	Technologies 5.Given the stated performance characteristics of the included assays, are all of them suitable for use to rule-out within 4 hours irrespective of the time since symptom onset?	Yes	Thank you for your comment.
British Cardiovascular Society endorsed by Royal College of Physicians	Population 6.Is the population defined appropriately?	Yes, all such patients will have had an ECG at baseline. One problem encountered in the CG94 group I sat on was that many trials have a mixed population that includes ST elevation patients. Such patients would not be considered as here.	Thank you for your comment. This will be considered further during the assessment.
British Cardiovascular Society endorsed by Royal College of Physicians	Comparator 8.Is this the most appropriate comparator for the assessment?	No, I don't think many NHS units have a 10-12 hour rule out system any more. Most will use 4or 6 hours any many have moved to much shorter 1 or 2 hour rule out algorithms. So the comparator would need to be, say, a 6 hour rule out v a 1-2 hour rule out.	Thank you for your comment. The comparator of serial cardiac troponin testing with a 10-12 hour peak measurement test strategy was used in the first NICE diagnostics assessment of troponins (DG15). The comparator will remain the same in the update so that the new tests included can be assessed on the same terms as the older high sensitivity troponin assays. Where high sensitivity troponin has been adopted there is wide variation in how the tests and protocols have been implemented. This assessment aims to consider different protocols and provide clarity on those that can be adopted nationally.

Who	Section	Comment	NICE Response
British Cardiovascular Society endorsed by Royal College of Physicians	Outcomes 9. Will these outcome measures capture the most important benefits (and harms) of the technology	They are all reasonable endpoints, but there have been publications questioning the value of hs troponin in terms of long term outcome – does it make any difference to survival etc if hs troponin used as opposed to conventional troponin testing regimes? Does it make any difference to outcomes if a lower threshold for the diagnosis of MI is used?	Thank you for your comment. This will be considered further during the assessment.
British Cardiovascular Society endorsed by Royal College of Physicians	Provisional stakeholder list 11.Are there any other stakeholders who should be invited to participate in the assessment? Please refer to appendix c for a full list of invited stakeholders.	I believe there is a research group in Edinburgh who are very interested in this area – Professor Nick Mills for example runs the “High-sensitivity Troponin in the Evaluation of patients with Acute Coronary Syndrome (HighSTEACS): A randomised controlled trial” which seems to cover exactly the area you are interested in.	Thank you for your comment. The University of Edinburgh have been contacted regarding the assessment. NICE is aware of the HighSTEACS study.
Ortho Clinical Diagnostics	Technologies: 2. Are the descriptions of the technologies accurate?	2.1 “older (non-high-sensitivity) troponin assays (hereafter referred to as standard”. The literature refers to these assays as contemporary assays - “contemporary troponin assays” terminology should be considered for consistency.	Thank you for your comment. To avoid confusion between contemporary and contemporary sensitive assays the scope defines any non-high sensitivity assay as ‘standard’. NICE is aware that there is variation in this group of assays. This terminology was used in the previous assessments and for consistency will be used in this assessment.
Ortho Clinical Diagnostics	Technologies: 2.Are the descriptions of the technologies accurate?	2.1 “These are able to detect lower levels of troponin in the blood earlier than older standard assays, leading to improved early detection of acute MI. Using these high-sensitivity assays enables earlier detection of changes in troponin levels. ” Consider changing this to: “These are able to detect lower levels of troponin and absolute	Thank you for your comment. In this background section of the scope we aim to keep the description clear and simple so that it can be easily understood by a wide range of stakeholders. Further technical details about the performance of high-sensitivity troponin assays will be provided in the diagnostics assessment report.

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		troponin changes with an enhanced precision compared with the contemporary assays, leading to improved early detection of acute MI and facilitating early differentiation of acute myocardial infarction from a chronic myocardial injury." (REF: http://www.onlinejacc.org/content/accj/early/2018/08/22/j.jacc.2018.08.1038.full.pdf) 2.2 We request VITROS Immunodiagnostic Products hs Troponin, manufactured by Ortho Clinical Diagnostics, be added to the Troponin I assays section of the draft scope document, in a new paragraph (2.2.8) We request the table of characteristics (Table 1) be updated to reflect the addition of the Ortho Clinical Diagnostics hs Troponin. Please see proposed language insertion. (IFU also attached).  HsTnI assay_Ortho_201908´  hsTnI_GEM1320_XUS_EN_I.pdf	Thank you for your comment. The VITROS High Sensitivity Troponin I assay has been added to the scope.
Ortho Clinical Diagnostics	Technologies: 3.Are each of the technologies in use in the NHS and relevant to the evaluation?	"the comparator for this assessment will remain standard troponin testing over 10–12 hours to capture the benefit of high sensitivity troponin assays used in combination with early rule-out protocols." In paragraph 2.1, the '10-12 hours' refers to the time from chest pain onset. It is not clear if this is also the case at paragraph 3.0, (or does this refer to the time from presentation)?	Thank you for your comment. This has been clarified in the scope.

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Ortho Clinical Diagnostics	Technologies: 4.Are there any other technologies with a similar purpose in use in the NHS?	Table 2: Please add VITROS hs cTnI assay to the list of assays listed in table 2.	Thank you for your comment. The VITROS High Sensitivity Troponin I assay has been added to the scope.
Ortho Clinical Diagnostics	Technologies: 5.Given the stated performance characteristics of the included assays, are all of them suitable for use to rule-out within 4 hours irrespective of the time since symptom onset?	Similar to the other troponin assays, for the VITROS hscTnI assay, this information is listed in the package insert. The VITROS cTnI assay performance at the 99th percentile (male, female and overall) is shown at 0,1,2, and 3 hours.	Thank you for your comment. The VITROS High Sensitivity Troponin I assay has been added to the scope.
Ortho Clinical Diagnostics	Comparator 8.Is this the most appropriate comparator for the assessment?	Yes, if the comparator troponin assay has the CE mark.	Thank you for your comment.
Siemens Healthineers	Introduction/product properties 1. Are these sections accurate and complete?	Siemens Healthineers are comfortable with the Introduction/product properties	Thank you for your comment.
Siemens Healthineers	Technologies 2. Are the descriptions of the technologies accurate?	Corrections for Siemens Healthineers assays: 2.2.4 ADVIA Centaur high-sensitivity troponin I assay (Siemens Healthineers) Sex specific cut offs of 36.99 ng/L for females and 57.27 ng/L for males in lithium heparin are provided. Sex specific cut offs of 39.59 ng/L for females and 58.05 ng/L for males in serum are provided. 2.2.5 Atellica IM High-sensitivity troponin I assay (Siemens Healthineers) Sex specific cut offs of 34.11 ng/L for females and 53.48 ng/L for males in lithium heparin are provided. Sex specific cut offs of 38.64 ng/L for females and 53.53 ng/L for males in serum are provided.	Thank you for your comment. These details have been added to the scope.

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		2.2.6 Dimension EXL High-sensitivity troponin I assay (Siemens Healthineers) Sex specific cut offs of 51.4 ng/L for females and 76.2 ng/L for males in lithium heparin are provided. Sex specific cut offs of 47.8 ng/L for females and 71.8 ng/L for males in serum are provided 2.2.7 Dimension Vista high-sensitivity troponin I assay (Siemens Healthineers) Sex specific cut offs of 53.7 ng/L for females and 78.5 ng/L for males in lithium heparin are provided.	
		Sex specific cut offs of 51.1 ng/L for females and 74.9 ng/L for males in serum are provided **Table 1 – Summary of key high-sensitivity cTnI and cTnT assay characteristics** Please correct column re CE marking as follows: Siemens Healthineers Atellica IM CE Marked YES Siemens Healthineers Dimension EXL CE Marked YES Siemens Healthineers Dimension Vista CE Marked YES Siemens Healthineers ADVIA Centaur Systems CE Marked YES Please correct column re CV at 99th percentile as follows: Siemens Healthineers Atellica IM as per table <4% Siemens Healthineers Dimension EXL <5% Siemens Healthineers Dimension Vista <5%	

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		Siemens Healthineers ADVIA Centaur Systems <4.9%	
Siemens Healthineers	Technologies 3. Are each of the technologies in use in the NHS and relevant to the evaluation?	Yes	Thank you for your comment.
Siemens Healthineers	Technologies 4. Are there any other technologies with a similar purpose in use in the NHS?	Not known	Thank you for your comment.
Siemens Healthineers	Technologies 5. Given the stated performance characteristics of the included assays, are all of them suitable for use to rule-out within 4 hours irrespective of the time since symptom onset?	Yes	Thank you for your comment.
Siemens Healthineers	Population 6. Is the population defined appropriately?	Yes	Thank you for your comment.
Siemens Healthineers	Population 7. Are there groups within this population that should be considered separately?	Siemens Healthineers only consider sex to be required as a separate group	Thank you for your comment. Clinical advice suggests that, in addition to sex, people who may have chronically elevated troponin are an important subgroup to consider within the context of ruling out NSTEMI.
Siemens Healthineers	Comparator 8. Is this the most appropriate comparator for the assessment?	Although serial cardiac troponin testing with a 10-12 hour peak measurement test strategy is no longer standard of care, it is probably the most consistent comparator	Thank you for your comment.

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Siemens Healthineers	Outcomes 9. Will these outcome measures capture the most important benefits (and harms) of the technology?	Siemens Healthineers would like to propose an amendment as follows: Diagnostic accuracy including at 99th percentile cut-off levels, limit of detection and limit of quantitation and considering delta change 'Diagnostic accuracy including at 99th percentile cut-off levels, limit of detection, limit of quantitation and **optimised low concentration cutoff** and considering delta change' Proportion of people diagnosed with NSTEMI Siemens Healthineers would like to propose an amendment as scope of the guidance is for early rule out rather than rule in: Maintenance of diagnostic sensitivity for people diagnosed with NSTEMI/AMI	Thank you for your comment. The purpose of the guidance update is to review the evidence available for early rule out protocols which has been developed since the publication of NICE diagnostics guidance 15. Data will be extracted on the cut-off values used for each assay within these early-rule out protocols where this is reported.
Siemens Healthineers	Provisional stakeholder list 11. Are there any other stakeholders who should be invited to participate in the assessment? Please refer to appendix c for a full list of invited stakeholders.	There are no entries under Associated guideline groups. Siemens Healthineers ask whether European Society of Cardiology (ESC) should be included?	Thank you for your comment. The European Society of Cardiology have now been invited to register as a stakeholder.
St George's University Hospitals NHS Foundation Trust	Introduction/product properties 1. Are these sections accurate and complete?	This section is fundamentally correct although not up to date in respect of the CE marked status and potential range of technologies. The Ortho diagnostics hs assay and Biomerieux assay are not included although both have clinically published studies and are CE marked. For a comprehensive and up to date account of assay performance see	Thank you for your comment. The VITROS High Sensitivity Troponin I assay and the VIDAS High sensitive Troponin I assay have been added to the scope.

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		http://www.ifcc.org/media/477441/high-sensitivity-cardiac-troponin-i-and-t-assay-analytical-characteristics-designated-by-manufacturer-v08232018.pdf Although the Emergency Department (ED) is named these patients are also seen in Chest Pain Units and may be sent there directly or transferred there for evaluation.	
St George's University Hospitals NHS Foundation Trust	Technologies 2. Are the descriptions of the technologies accurate?	See comments above	Thank you for your comment.
St George's University Hospitals NHS Foundation Trust	Technologies 3. Are each of the technologies in use in the NHS and relevant to the evaluation?	Yes although the user base for Biomerieux and Ortho is small. However this does not mean they will not be used in the future particularly in dedicated emergency labs.	Thank you for your comment. The VITROS High Sensitivity Troponin I assay and the VIDAS High sensitive Troponin I assay have been added to the scope.
St George's University Hospitals NHS Foundation Trust	Technologies 4. Are there any other technologies with a similar purpose in use in the NHS?	See comment above	Thank you for your comment.
St George's University Hospitals NHS Foundation Trust	Technologies 5. Given the stated performance characteristics of the included assays, are all of them suitable for use to rule-out within 4 hours irrespective of the time since symptom onset?	This is a strongly debated topic. There are clinical concerns that patients presenting with symptoms <3 hours (early presenters) may not be detected with adequate sensitivity. Crea F, Jaffe AS, Collinson PO, et al. Should the 1h algorithm for rule in and rule out of acute myocardial infarction be used universally? Eur Heart J 2016 Nov 21;37(44):3316-23.	Thank you for your comment. This will be considered further during the assessment.

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St George's University Hospitals NHS Foundation Trust	Population 6. Is the population defined appropriately?	This is appropriate but these patients are also managed in chest pain units.	Thank you for your comment. Chest pain units have been added as a setting.
St George's University Hospitals NHS Foundation Trust	Population 7. Are there groups within this population that should be considered separately?	There are concerns that different reference ranges are not being used for men and women potentially underdiagnosing myocardial infarction in women.	Thank you for your comment. Sex is included as a subgroup and males/females will be assessed separately if data allows.
St George's University Hospitals NHS Foundation Trust	Comparator 8. Is this the most appropriate comparator for the assessment?	Although diagnosis based on a predicate consensus hs troponin test is used this is in some sense a circular argument as it assumes one troponin test is the gold standard. Where studies have included hard end points (death or major adverse cardiac events - MACE - at follow up) they are much more significant. Please note that tests using limit of detection or a low diagnostic discriminant are predictive and NOT diagnostic. They predict the likelihood of prevalent myocardial infarction during the period of admission or MACE typically up to 30 days from admission.	Thank you for your comment. This will be considered further during the assessment.
St George's University Hospitals NHS Foundation Trust	Outcomes 9. Will these outcome measures capture the most important benefits (and harms) of the technology?	See comments above.	Thank you for your comment.
St George's University Hospitals NHS Foundation Trust	Equality 10. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and	See comments above re under diagnosis in women [Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the underdiagnosis	Thank you for your comment. Sex is included as a subgroup and males/females will be assessed separately if data allows.

Who	Section	Comment	NICE Response
	others. Please let us know if you think that the proposed scope may need changing in order to meet these aims.	of myocardial infarction in women: prospective cohort study. BMJ 2015;350:g7873.]	
St George's University Hospitals NHS Foundation Trust	Provisional stakeholder list 11. Are there any other stakeholders who should be invited to participate in the assessment? Please refer to appendix c for a full list of invited stakeholders.	Singulex is no longer trading. See comments above on Biomerieux and Ortho	Thank you for your comment.
St George's University Hospitals NHS Foundation Trust	General 12. Please tell us if there are any other key points that are important and relevant to consider for this assessment that are not currently included in this draft scope.	The literature review should consider patients presenting to the Emergency Department and Chest Pain units Please feel free to contact me directly for clarification on any of the above.	Thank you for your comment. Chest pain units have been added as a setting.
Quidel	Introduction/product properties 1. Are these sections accurate and complete?	Yes	Thank you for your comment.
Quidel	Technologies 2. Are the descriptions of the technologies accurate?	Yes	Thank you for your comment.
Quidel	Technologies 3. Are each of the technologies in use in the NHS and relevant to the evaluation?	Yes	Thank you for your comment.
Quidel	Technologies	Yes	Thank you for your comment.

Who	Section	Comment	NICE Response
	4. Are there any other technologies with a similar purpose in use in the NHS?		
Quidel	Technologies 5. Given the stated performance characteristics of the included assays, are all of them suitable for use to rule-out within 4 hours irrespective of the time since symptom onset?	Yes	Thank you for your comment.
Quidel	Population 6.Is the population defined appropriately?	Yes	Thank you for your comment.
Quidel	Population 7. Are there groups within this population that should be considered separately?	No further comments or additions	Thank you for your comment.
Quidel	Comparator 8.Is this the most appropriate comparator for the assessment?	Yes	Thank you for your comment.
Quidel	Outcomes 9.Will these outcome measures capture the most important benefits (and harms) of the technology?	Yes	Thank you for your comment.
Quidel	Equality 10. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think	No changes or comments	Thank you for your comment.

Who	Section	Comment	NICE Response
	that the proposed scope may need changing in order to meet these aims. In particular, please tell us if the proposed scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. • Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts		
Quidel	Provisional stakeholder list 11. Are there any other stakeholders who should be invited to participate in the assessment? Please refer to appendix c for a full list of invited stakeholders.	No further comments	Thank you for your comment.

Who	Section	Comment	NICE Response
Quidel	General 12. Please tell us if there are any other key points that are important and relevant to consider for this assessment that are not currently included in this draft scope.	No comments	Thank you for your comment.
Randox	Introduction/product properties 1. Are these sections accurate and complete?	Due to the short timeframe for reviewing the information we are unable to examine all the facts in detail or provide publications as evidence of the facts. It is unclear with regards CE marking what "awaiting confirmation" means. Does this mean the supplier has not given you the information or that the test is still awaiting CE approval in which case the test is not available to the NHS. Should the Singulex troponin be included?	Thank you for your comment. The scope has been updated with information received from companies.
Randox	Technologies 2. Are the descriptions of the technologies accurate?	Table 1 – "99th percentile" column should include figures for overall, male and female troponin levels "CV at 99th percentile" should also include figures for overall, male and female CVs. Also the actual CVs should be stated. Furthermore, the 99th percentile in both serum and plasma should be included for each test. In addition, is the LoD and LoQ values the same for each matrix (serum or plasma)? Turnaround time for Beckman should be known and inserted.	Thank you for your comment. The scope has been updated with these details where this has been received from companies.
Randox	Technologies 3. Are each of the technologies in use in the NHS and relevant to the evaluation?	If the tests are not CE marked then they are unlikely to be used	Thank you for your comment. Companies providing tests included in the scope have now confirmed their tests are CE marked.

Who	Section	Comment	NICE Response
Randox	Technologies 4. Are there any other technologies with a similar purpose in use in the NHS?	No, however, Randox have developed heart-type fatty acid-binding protein (HFABP) test. H-FABP is released into the blood stream 30minutes after an ischaemic event. Numerous studies have shown that elevated H-FABP detected in patients at the time of presentation of patients with chest pain of suspected cardiac origin to the emergency department can identify individuals at higher risk of MI and rule-out false negatives (Navarro et al., J Clin Exp Cardiolog 2018, 9:8).	Thank you for your comment. This assessment will focus on troponin only. Alternative biomarker tests can be notified to NICE for consideration via HealthTech Connect.
Randox	Technologies 5. Given the stated performance characteristics of the included assays, are all of them suitable for use to rule-out within 4 hours irrespective of the time since symptom onset?	We believe they are.	Thank you for your comment.
Randox	Population 6. Is the population defined appropriately?	The population is defined appropriately	Thank you for your comment.
Randox	Population 7. Are there groups within this population that should be considered separately?	Age-dependent cut-offs for troponin should be investigated to reduce any potential bias. Also, troponin levels in high risk patient subgroups e.g. BMI, smokers, diabetics should also be investigated.	Thank you for your comment. The scope states that the analysis should consider subgroups with low and high pre-test probabilities for NSTEMI, for example people with a history of previous AMI.
Randox	Comparator 8. Is this the most appropriate comparator for the assessment?	Currently this is the most appropriate comparator	Thank you for your comment.
Randox	Outcomes	The outcomes have all been covered	Thank you for your comment.

Who	Section	Comment	NICE Response
	9. Will these outcome measures capture the most important benefits (and harms) of the technology?		
Randox	Equality	We are not knowledgeable in this area	Thank you for your comment.
Randox	Provisional stakeholder list 11. Are there any other stakeholders who should be invited to participate in the assessment? Please refer to appendix c for a full list of invited stakeholders.	These are fine	Thank you for your comment.
Randox	General 12. Please tell us if there are any other key points that are important and relevant to consider for this assessment that are not currently included in this draft scope.	We are not aware of any	Thank you for your comment.