Institution: The University of Manchester		
Unit of Assessment: 1 (Clinical Medicine)		
Title of case study: Rapid diagnostic pathways reduce unnecessary hospital admissions for suspected acute coronary syndromes		
Period when the underpinning research was undertaken: January 2010 – July 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Richard Body	Clinical Professor of Emergency Medicine Honorary Lecturer Clinical Lecturer in Cardiac Medicine	2017 – present 2012 – 2017 2010 – 2011
Kevin Mackway-Jones	Honorary Lecturer	2006 – present
Garry McDowell	Honorary Lecturer	2011 – present
Period when the claimed impact occurred: 1 January 2016 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Manchester (UoM) researchers developed and validated three new methods to obviate the need for inpatient investigation of chest pain, a common reason for emergency hospital admission. UoM research involving >4,000 patients, led to improved diagnostic technologies. Two applications of high-sensitivity cardiac troponin assays are now incorporated in the National Institute for Health and Care Excellence (NICE), and European Society of Cardiology guidelines. A third, the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid is being implemented across Greater Manchester allowing quicker, more effective diagnosis and treatment. It has been used for >30,000 patients, leading to reduced hospital admissions and savings of approximately GBP2,000 per patient. UoM research has supported roll-out of high-sensitivity cardiac troponin testing in England, Wales and the United States.

2. Underpinning research

Cardiac Troponin T (cTnT) is a protein released into the blood when heart muscle is damaged. It is an indicator of acute coronary syndromes (ACS) where decreased blood flow through narrowed arteries to the heart causes muscle damage. Traditionally patients with suspected cardiac chest pain, only approximately 30% of whom have ACS, were routinely admitted into hospital for up to three days to allow sufficient time for blood levels of cTnT to rise to detectable levels and to inform management decisions.

Researchers at UoM began expediting earlier diagnosis of ACS through high-sensitivity cardiac troponin assays in 2010 and analysed stored samples from a previous study (2006-7) for a novel high-sensitivity cardiac troponin (hs-cTn). Analysis of samples from 804 patients yielded two key outputs:

(1) Derivation of the Manchester Acute Coronary Syndromes (MACS) decision aid, subsequently refined and simplified to become the T-MACS decision aid [1]. T-MACS combines high-sensitivity cardiac troponin T (hs-cTnT) concentrations with details of patients' symptoms and electrocardiogram (ECG) results to optimise clinical decision making, soon after presentation. UoM research showed T-MACS has 99.3% negative predictive value and 98.7% sensitivity for ACS. It could therefore rule out ACS in 40.4% of patients whilst ruling in 4.7% at highest risk, offering greater diagnostic efficiency and the potential to conserve healthcare resources [1].

(2) The first report of very low cardiac troponin concentrations (set at the Limit of Detection (LoD) of an hs-cTn assay) being used to 'rule out' the diagnosis of acute myocardial infarction (AMI) with a single blood test in the Emergency Department [2]. This method is referred to as 'LoD strategy'. Further UoM research into LoD strategy confirmed that patients who presented with non-ischaemic ECG results and undetectable hs-cTnT had a very low

probability of AMI. Of 17.3% of patients (n=80) with hs-cTnT below LoD and no ECG ischemia, none had AMI [3].

In 2011-13, Body was the UK Chief Investigator for an international diagnostic accuracy study (TRAPID-AMI) at 14 international centres sponsored by Roche Diagnostics. The study of 1,282 patients validated the accuracy of an algorithm to 'rule out' the diagnosis of AMI with serial blood tests for hs-cTnT drawn one hour apart [4]. TRAPID-AMI demonstrated that this '1-hour algorithm' had a negative predictive value of >99% for AMI. In a pre-planned secondary analysis, LoD strategy was found to have a negative predictive value of 99.6% [5]. The results were presented at the European Society of Cardiology Annual Congress 2017.

In 2015-18, Body was Chief Investigator for the Bedside Evaluation of Sensitive Troponin (BEST) study, which recruited >1,500 patients with suspected acute coronary syndromes at 18 Emergency Departments nationally (funded by EU-H2020 scheme, Abbott Point of Care and the Royal College of Emergency Medicine, with in-kind support from Siemens Healthineers, Singulex, Alere, FABPulous BV and Beckman). The key primary output of the BEST study has been to validate the T-MACS decision aid with additional troponin assays including two point of care troponin assays [6], increasing external validity and enabling adoption of T-MACS in a wider variety of healthcare settings.

3. References to the research

1. **Body R,** Carlton E, Sperrin M, Lewis PS, Burrows G, Carley S, **McDowell G**, Buchan I, Greaves K, **Mackway-Jones K**. Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts. *Emergency Medicine Journal*. 2017 Jun;34(6):349–56. DOI:10.1136/emermed-2016-205983
2. **Body R,** Carley S, **McDowell G**, Jaffe AS, France M, Cruickshank K, Wibberley C, Nuttall M, Mackway-Jones K. Rapid Exclusion of Acute Myocardial Infarction in Patients With Undetectable Troponin Using a High-Sensitivity Assay. *Journal of the American College of Cardiology.* 2011 Sep;58(13):1332–9. DOI:10.1016/j.jacc.2011.06.026
3. **Body R**, Burrows G, Carley S, Cullen L, Than M, Jaffe AS, Lewis PS. High-Sensitivity Cardiac Troponin T Concentrations below the Limit of Detection to Exclude Acute Myocardial Infarction: A Prospective Evaluation. *Clinical Chemistry*. 2015 Jul 1;61(7):983–9. DOI:10.1373/clinchem.2014.231530
4. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, **Body R**, Panteghini M, Jernberg T, Plebani M, Verschuren F, French J, Christenson R, Weiser S, Bendig G, Dilba P, Lindahl B; TRAPID-AMI Investigators. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T. *Annals of Emergency Medicine*. 2016 Jul;68 (1):76-87.e4. DOI:10.1016/j.annemergmed.2015.11.013
5. **Body R**, Mueller C, Giannitsis E, Christ M, Ordonez-Llanos J, de Filippi CR, Nowak R, Panteghini M, Jernberg T, Plebani M, Verschuren F, French JK, Christenson R, Weiser S, Bendig G, Dilba P, Lindahl B; TRAPID-AMI Investigators. The Use of Very Low Concentrations of High-sensitivity Troponin T to Rule Out Acute Myocardial Infarction Using a Single Blood Test. *Academic Emergency Medicine*. 2016;23(9):1004-1013 DOI:10.1111/acem.13012
6. **Body R**, Almashali M, Morris N, Moss P, Jarman H, Appelboam A, Parris R, Chan L, Walker A, Harrison M, Wootten A, McDowell G. Diagnostic accuracy of the T-MACS decision aid with a contemporary point-of-care troponin assay. *Heart*. 2019 Jan 12;heart jnl-2018-313825. DOI: 10.1136/heartjnl-2018-313825

4. Details of the impact

Impact of the Limit of Detection (LoD) strategy on European guidelines

Through original research led from UoM, validated by collaborative meta-analyses, LoD's use is now advocated in UK NICE and European guidelines. NICE evaluated hs-cTn assays

for early diagnosis of AMI in October 2014, concluding LoD strategy may provide an effective/cost-effective approach compared with current standard of care [A]. In 2016 an updated NICE Clinical Guideline 95 (Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis) recommended implementing LoD strategy in clinical practice "*For people at low risk…consider performing a single high-sensitivity troponin test only at presentation…if the first troponin test is below the lower limit of detection*" [B]. This recommendation was unchanged at 2019 review. In 2016, European Society of Cardiology (ESC) recommended employing LoD strategy clinically, extending impact reach [C].

Impact of the 1-hour algorithm on international practice

In 2016, ESC recommended the 1-hour algorithm for clinical use stating "*A rapid rule-out and rule-in protocol at 0hr and 1hr is recommended if a high-sensitivity cardiac troponin test with a validated 0hr/1hr algorithm is available"* [C,2]. Economic analysis found UK use of the 1-hour algorithm saves >GBP2,000/patient, representing significant potential healthcare savings if applied to approximately 350,000 UK patients and 39,000,000 world-wide [D].

Since ESC's recommendations, further European validation has demonstrated patient benefits in participating countries:

- Northern Ireland: 71% of patients discharged early after having AMI safely ruled out within 1 hour. No cardiac deaths within 6 months [Ei].
- Netherlands: 46.7% patients had diagnosis of AMI rapidly ruled out. No deaths or AMIs within 6 weeks follow up [Eii].
- Sweden: Reduced: hospital admissions (59% to 33%, adjusted odds ratio 0.33 [95% confidence interval 0.25-0.42]); length of hospital stay (median 23.2 hours to 4.7 hours); and healthcare costs (USD1,748 to USD1,079/patient) [Eiii].
- Thailand: Reduced time to 'rule in'/'rule out' AMI from mean of 238 minutes pre-implementation to 134 minutes post-implementation ($p<0.001$) [Eiv].
- Switzerland and Argentina: 2019 study of 2296 patients concluded in real-world settings *"excellent applicability, short time to ED* [emergency department] *discharge, and low rate of 30-day* [major cardiac events]" from routine clinical use of the ESC 0/1-h algorithm for management of patients presenting to the ED [Ev].

Impact of the T-MACS decision aid on patient care

While simplicity of LoD and 1-hour algorithms comes from reliance solely on biomarker concentrations, the more elaborate T-MACS decision aid (combining biomarkers, symptoms and ECG findings using a computer algorithm), offers greater diagnostic efficiency [1]. T-MACS has been used by Manchester University NHS Foundation Trust (MFT) since June 2016, after developing local solutions for algorithm implementation to capture data electronically. By November 2020, 11,250 MFT patients had been assessed with T-MACS [Fi]. Whereas over 80% of patients were previously admitted to inpatient wards for investigation, 66% are now managed in reclining chairs, in an ambulatory care environment [Fii]. Low risk patients (62%) have 95% probability of going home on the same day, with no adverse events reported. The project won 'Trust Transformation Prize 2016' and gained adoption as a Health Innovation Manchester exemplar project [Fii]. T-MACS was implemented at 6 hospitals across Greater Manchester (GM) by December 2020, with 6 more in progress [Fi]. To date, T-MACS has guided care of >30,000 GM patients and, once fully operational, will guide care of approximately 30,000 patients/year throughout GM.

National implementation of rapid rule-out protocol

In 2019, NHS's Accelerated Access Collaborative (AAC) initiated a project to implement high-sensitivity troponin rule-out pathways nationally. Implementation was incentivised through NHS's Innovation & Technology Payment [Gi], leading to adoption by Commissioning for Quality and Innovation scheme (CQUIN) for 2020-2021. CQUIN highlights NHS delivery goals for financially incentivised initiatives. 'Rapid rule out protocol for Emergency Department patients with suspected AMI' was included as a best practice pathway [H]. NHS England stated, *"this could lead to overall national benefits upwards of £20m as a direct result of this improved rule out"* [H]. Body was appointed as one of two

NHS England Clinical Champions supporting national implementation. In March 2020 Body was invited to present the first AAC/Innovation Agency webinar about adoption of high-sensitivity cardiac troponin testing in NHS trusts through the COVID-19 emergency, supporting implementation [Gii].

Roche and introduction of high-sensitivity cardiac troponin assays in US

In Europe, Roche Diagnostics, used RAPID-AMI findings to market its hs-cTn assay, citing UoM studies in product information [Ii,3,4,5]. In January 2017, Roche's Elecsys Troponin-T Stat Assay became the first hs-cTnT assay approved by US Food and Drug Administration. Clinician education was vital for transition to high-sensitivity testing in US. Roche stated, *"Professor Body has worked with Roche Diagnostics as part of advisory boards to plan the implementation of high-sensitivity cardiac troponin in England and Wales; and in the United States. He has presented at our international symposium…and participated in a Roche-sponsored webinar…produced by Medscape*" [Iii]. The webinar was commissioned to support US implementation and was co-authored by Body [Ji]. Roche confirmed UoM research, "*has played a pivotal role in getting these diagnostic pathways into clinical practice*" [Iii]. Among the first to begin high-sensitivity testing in 2018 were San Diego Health Center and Massachusetts General Hospital. Campbell County Health, Wyoming, confirmed they began using high-sensitivity testing in 2019 stating in August 2020 that afterwards "*a number of our regional hospitals followed suit, …it is quickly becoming the standard of care across the United States, helping us provide better, safer care for our patients*"[Jii]. In 2019, American College of Cardiology recommended transition to hs-cTn for all hospital services, publishing their expert panel recommendations for institutions transitioning to high sensitivity troponin testing. Body was an expert panel member [Jiii,1].

5. Sources to corroborate the impact

A. Report commissioned for NICE: High-sensitivity troponin assays for the early rule-out or diagnosis of AMI in people with acute chest pain: a systematic review and cost-effectiveness analysis- Westwood M, van Asselt, T, Ramaekers B et al. *Health Technology Assessment* 2015 Jun;19(44):1-234. DOI: 10.3310/hta19440 – ***confirmed there was evidence that hs-cTn testing may provide an effective/cost-effective approach and that LoD may be sufficient to rule out NSTEMI (non-ST segment elevation myocardial infarction), cites UoM reference 2.***

B. NICE Clinical Guideline CG95: Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis (last updated November 2016) & Appendices A-U https://www.nice.org.uk/guidance/cg95 - ***guidance updated to consider performing a single high-sensitivity troponin test if the first test is below the lower limit of detection (negative). Body listed as topic expert, UoM reference 2 listed in A.2 and Appendix U references.***

C. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 *European Heart Journal*. 2016 Jan 14;37(3):267–315. DOI:10.1093/eurheartj/ehv320 - ***Recommends use of LoD strategy and 0/1 hour algorithm- cites UoM reference 2.***

D. Economic evaluation of the one-hour rule-out and rule-in algorithm for acute myocardial infarction using the high-sensitivity cardiac troponin T assay in the emergency department: Ambavane A, Lindahl B, Giannitsis E, et al. [published correction appears in *PLoS One*. 2018 Jan 11;13(1):e0191348]. *PLoS One*. 2017;12(11):e0187662. Published 2017 Nov 9. DOI:10.1371/journal.pone.0187662 - ***found use of the 1-hour algorithm in UK saves >GBP2,000/patient.***

E. Clinical trials following ESC recommendation of 0/1 hour algorithim - ***bringing patient benefits***:

   i. Use of a one hour high-sensitivity troponin t measurement in the initial assessment of patients presenting with cardiac chest pain to emergency departments in the Belfast

Trust. Linden K, Swales L, Davenport S, et al. 26;*Heart* 2017;**103:**A15-A16 - ***Belfast, Northern Ireland.***

ii. Safety of a 1-hour Rule-out High-sensitive Troponin T Protocol in Patients With Chest Pain at the Emergency Department. Röttger E, de Vries – Spithoven S, Reitsma JB, et al. *Critical Pathways in Cardiology*. 2017 Dec;16(4):129–34 - ***Utrecht, The Netherlands.***

iii. A Rule-Out Strategy Based on High-Sensitivity Troponin and HEART Score Reduces Hospital Admissions. Ljung L, Lindahl B, Eggers KM, et al. *Annals of Emergency Medicine*. 2019;73(5):491-499 ***Stockholm & Uppsala, Sweden.***

iv. The feasibility of the 1-h high-sensitivity cardiac troponin T algorithm to rule-in and rule-out acute myocardial infarction in Thai emergency patients: an observational study. Ruangsomboon O, Mekavuthikul P, Chakorn T, et al. *International Journal of Emergency Medicine* 2018;11(1):43. Published 2018 Oct 22 - ***Bangkok, Thailand.***

v. Outcome of Applying the ESC 0/1-hour Algorithm in Patients With Suspected Myocardial Infarction. Twerenbold R, Costabel JP, Nestelberger T, et al. *Journal of the American College of Cardiology*. 2019;74(4):483-494 – ***real world data from Basel, Switzerland and Buenos Aires, Argentina.***

F. T-MACS implementation supported by Health Innovation Manchester

i. HIM Annual Report 2017-2018- ***detailing benefits of T-MACS.***

ii. Email from HIM project manager 25 November 2020– ***detailing roll-out of T-MACS across Greater Manchester and successes to date.***

G. Implementation of High-Sensitivity Cardiac Troponin testing nationally

i. 'NHS England announcement of 2019/2020 ITP funding programme', April 2019 – ***includes high-sensitivity cardiac troponin testing.***

ii. First AAC/Innovation Agency webinar to support trusts in adopting high-sensitivity testing through Covid-19 period- ***Body was one of three presenters, March 2020.***

H. NHS England's CQUIN Guidance for 2020-2021, February 2020. ***Rapid rule out protocol for ED patients with suspected acute myocardial infraction (excluding STEMI) listed as best practice pathways in CQUIN scheme.***

I. Roche pocket guide and testimonial letter:

i. Pocket guide for Elecsys Troponin T-high sensitive- Faster diagnosis of Acute Myocardial Infarction, published 2018 - ***cites UoM references 3, 4 and 5.***

ii. Testimonial letter from Roche Diagnostics Head of Medical Affairs and Senior International Medical Affairs Lead, 21 January 2021 – ***confirms the role of UoM research in getting diagnostic pathways into clinical practice and Body's work with Roche***.

J. Introduction of high-sensitivity testing in US, guidance and education for clinicians:

i. Medscape Education Activity 'Lessons Learned: A Master Class in High-Sensitivity Troponin. A Global perspective. Released 15th May 2017, - ***Co-authored by Body who appeared as a panellist to support implementation in the US***.

ii. Press releases from UC San Diego Health 7 March 2018, Massachusetts General 5 Jun 2018 and Campbell County Health, Wyoming 4 August 2020- ***confirming implementation of high-sensitivity testing in US hospitals.***

iii. American College of Cardiology Recommendations for Institutions Transitioning to High-Sensitivity Troponin Testing: JACC Scientific Expert Panel. Januzzi JL Jr, Mahler SA, Christenson RH, et al. *Journal of American College of Cardiology*. 2019;73(9):1059-1077 – ***Body was on the expert panel, providing recommendations for implementation in US, cites UoM reference 1.***