Pilot Study Final Phase I Report

Evaluation of Ambulance Based Troponin Measurements

A Feasibility and Impact Pilot Study of the Utility of pre-hospital POC testing of Cardiac Biomarkers on Patients Presenting with Acute Chest Pain

Sponsored by:

NHS 24 **NHS Borders Hospital,**

Scottish Centre for Telehealth and Telecare **Scottish Ambulance Service**

Samsung Electronics Co. Ltd, HME Global Business Unit

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TABLE OF CONTENTS

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1.1 LIST OF ABBREVIATIONS

A&E Accident and Emergency
ACS acute coronary syndrome
AHA- American Heart Association
AMI acute myocardial infarction
BGH Borders General Hospital
CABG coronary artery bypass graft
CHD coronary heart disease
CI confidence interval
cTnI – cardiac Troponin I
CV coefficient of variation
ECG electrocardiogram
ED emergency department
ESC European Society of Cardiology
GCP Good Clinical Practice
GP general practitioner
MI myocardial infarction
NICE National Institute for Health and Clinical Excellence
NSTEMI non-ST-elevation myocardial infarction
OR odds ratio
PCI percutaneous coronary intervention
POCT point of care testing
RATPAC Randomised Assessment of Treatment using Panel Assay of Cardiac markers
RCT randomised controlled trial
RIE Royal Infirmary of Edinburgh
SAS Scottish Ambulance Service
SD standard deviation
SE standard error
STEMI ST-elevation myocardial infarction
TAT Turn-Around-Time
TIMI thrombolysis in myocardial infarction (risk score)
UA unstable angina
WHF – World Heart Federation
All abbreviations that have been used in this report

2. Background

This final report is a Summary of a Phase 1 Program to determine the feasibility and logistics of performing Cardiac Biomarker measurements in the ambulance setting with paramedics. Specifically the report presents the findings and a list of recommendations relative to the measurement of cardiac TnI (cTnI) from patients presenting with chest pain prior to and during transit to a primary care hospital (Borders General Hospital-BGH) via the Scottish Ambulance Service. (SAS).

The immunoassay system used to quantitatively determine cTnI was the Samsung LABGEO^{IB10} (BCA-IB10). While patients presenting with chest pain suggestive of myocardial infarction (MI) can be diagnosed by paramedics almost immediately via 12 lead ECG telemetry, that subset of patients with no significant and persistent ST segment elevation (NSTEMI) or normal ECG are not eligible for administration of thrombolytic agents and are routinely dispatched according to the current chest pain pathway to the Borders General Hospital in Melrose. STEMI patients are immediately rerouted to a secondary or tertiary hospital with interventional cardiology capability to perform angiography, PCI or more complicated procedures to identify and resolve cardiac ischemia (Royal Infirmary of Edinburgh).

Patients with NSTEMI or acute coronary syndrome (ACS) require, as part of their differential diagnosis, at least 1 elevated concentration of cTnI which may include serial measurements if the initial concentration is near or just below the designated cut –off, usually defined as the 99th percentile concentration of an apparently healthy reference population. Every cTnI assay establishes it's own cut point and they may vary significantly. Elevated cTnI levels correlate with the risk of mortality, MI or increased probability of ischemic events, requiring urgent revascularization. The recently published Third Universal Definition of Myocardial Infarction approved by an International Task Force endorsed by the European Society of Cardiology (ESC), American College of Cardiology Federation (ACCF), World Heart Federation (WHF) and the American Heart Association (AHA) requires at least one elevation of cTnI above the 99 percentile of a reference population (Table 1) with 2-3 samples taken over a period up to 12 h.[1]

Several previous studies using quantitative point of care devices (POC) in the Emergency Department have demonstrated total turn around times (TAT) of 30 minutes or less compared to cTnI report times from the central lab of > 1 h.[2] One such study found a TAT reduction of 50-60% in both urban and community based hospitals for reporting ED cardiac marker test results compared to cTnI results reported submitted to the laboratory. A more recent report from a randomized study comprising 6 ED departments in the UK ,with approximately 1130 patients in each arm (ED cardiac marker testing compared to standard laboratory based reporting), was undertaken to assess the possibility of earlier dismissal from the hospital compared to the current National Institute for Health and Clinical Excellence guidelines of 10-12 h[3] The RATPAC (Randomized Assessment of Treatment using a Panel Assay of Cardiac Markers) protocol was based on POC testing at presentation and a second test 90 minutes later. Main outcome measures for RATPAC were:

- Successful discharge by 4 hr after attendance -32% vs 13% (rapid rule out)
- Reduced median length of initial hospital stay
- Greater use of coronary care unit

Table 1. Third Definition of Myocardial Infarction (Thygesen et al (2012)

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

2.1 NHS Borders General Hospital/NHS Telehealth Goals

The goals of this Phase 1 program were to:

Evaluate the feasibility of obtaining accurate and precise measurements in a moving ambulance including assessment of training proficiency of paramedics performing the test in a moving vehicle as compared to testing in a central laboratory environment with trained laboratory personnel.

Examine the impact of introducing point of care testing to the Scottish Ambulance Service. The data will explore variables including:

- Reduction in time of first cTnI measurement
- Reduced length of stay in the ED
- Improved triage to appropriate onward care
- Reduced length of stay
- Increased productivity
- The potential impact of pre-hospital cTnI testing on subsequent patient pathways

The initial Pilot Outline (version 4.0) was distributed on October 1, 2012 and contained the current chest pain and proposed modified pathway [4] (Fig. 1and 2). The pilot commenced in mid November 2012 and ran until mid-May 2013. Results of an interim study were published by Scotland et al in February 2013 [5] Both outline and interim reports are attached as appendices. The main objective of the current report is focused on performance and logistics of measurement of cTnI in an ambulatory environment with paramedics given basic training in the operation and use of the Samsung LABGEO^{IB10} Analyzer and LABGEO ^{IB} Troponin I.

To date, there are few published studies utilizing a quantitative cardiac biomarker system in an ambulance environment. This might be unnecessary in an urban setting where time from ambulance dispatch to hospital arrival may be less than 30 minutes. In addition, urban environments typically have close proximity to multiple facilities with interventional care.

However in a rural environment, where transit times to secondary care hospitals may exceed a number of hours, the potential exists that significantly elevated cTnl as measured on a NSTEMI/ACS patient may influence where that patient is subsequently dispatched to. These patients are the ones who will likely benefit most from early cTnI measurements.

The second relevant aspect of early baseline measurements is that the prevalence of patients presenting with chest pain who ultimately have an ACS event is low. As the majority of patients with chest pain are low risk for MI or early ACS presenters whose symptoms are < 6-8 h from onset, most baseline patient values are negative. The AHA has recently defined guidelines for testing low risk patients presenting with chest pain and cited studies that only 2.5% of the low risk group with a 30 day major cardiovascular event could be recognized in the ED[6.]

cTnI adds value in ruling out cardiac events and helps to differentiate low from high risk individuals. Due to its specificity for cardiac muscle damage, the negative predictive value (NPV) of successive cTnI levels below the cut off is high. The earlier the 1st measurement can

be taken to establish baseline, the earlier the second measurement can be taken to rule out most chest pain patients and discharge those who would otherwise remain in the chest pain unit waiting additional unnecessary time for discharge.

Figure 1: Current chest pain pathway at BGH

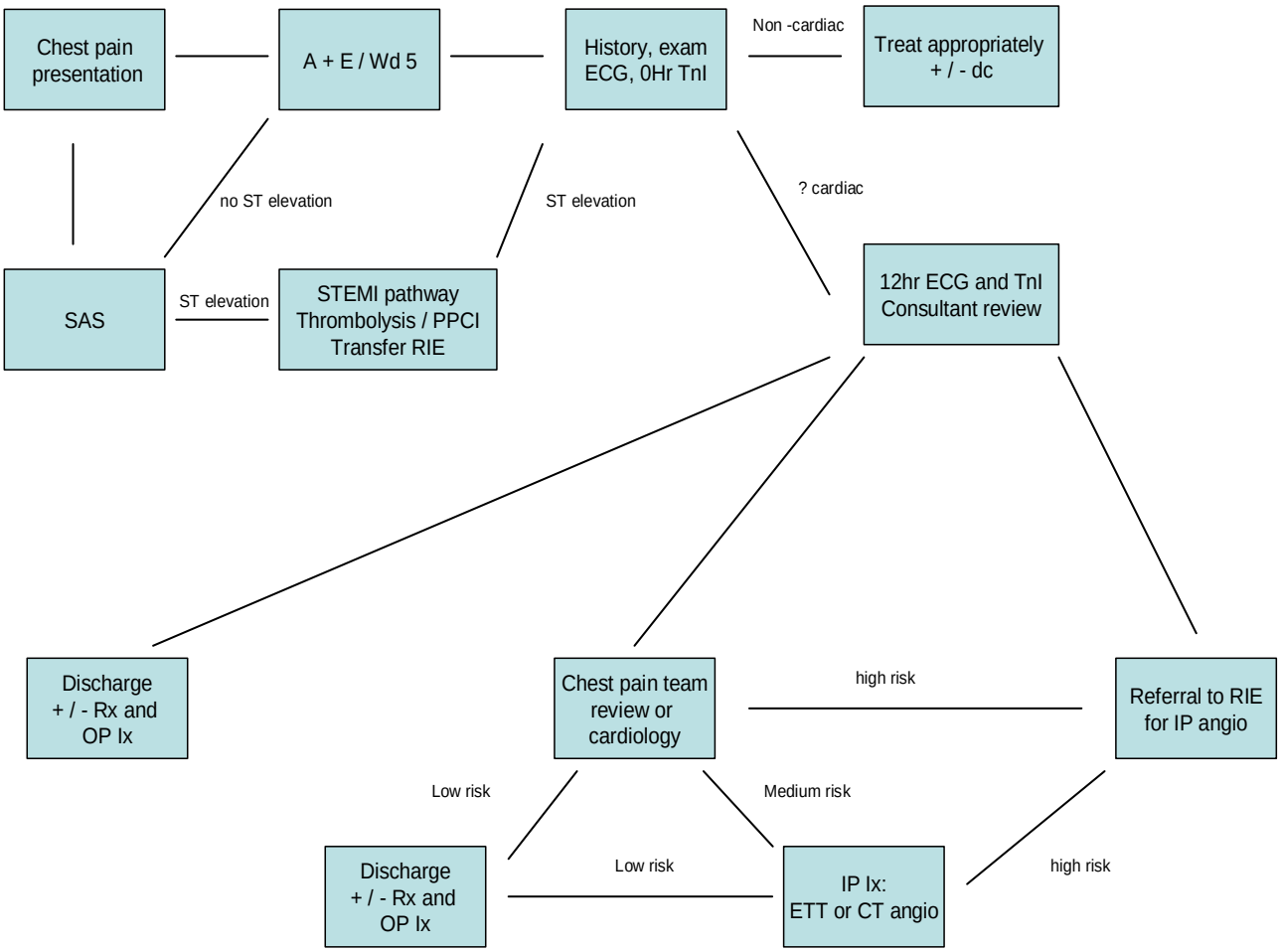
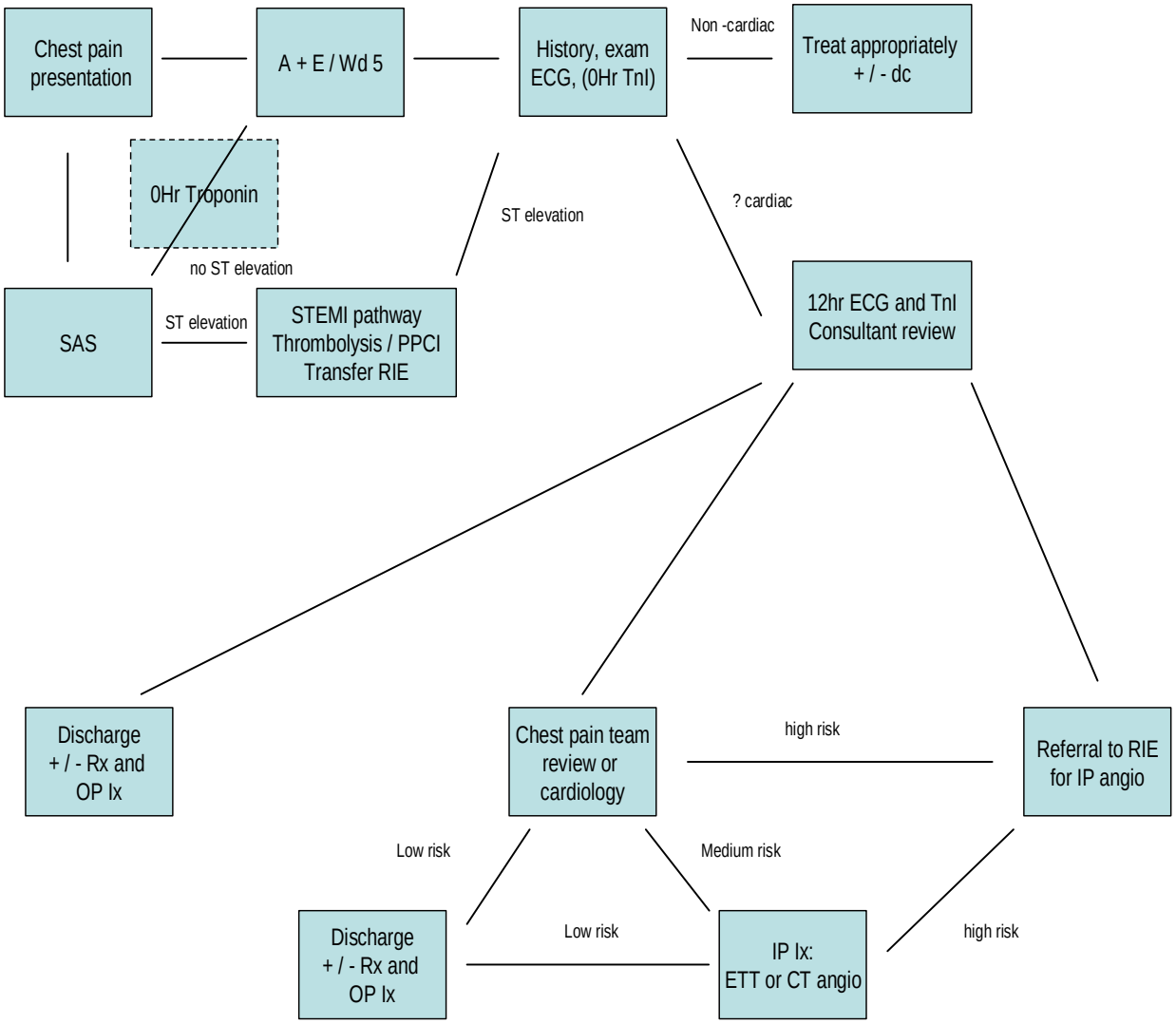


Figure 2: Revised Chest Pain- reduction of time zero cTnI availability in ambulance versus BGH Clinical Laboratory



3. METHODS

3.1. NHS BORDERS/NHS 24/ SAS Pilot Study (Borders)

3.1.1. Patient population

The Scottish Borders Pilot covers all patients carried by emergency ambulance within the Scottish Borders with a provisional diagnosis of cardiac chest pain and who do not have ST elevation ECG changes. The Scottish Borders is a large sparsely populated rural area with a population of 108,000. There is no single major conurbation or urban agglomeration and the largest town has a population of 16,000, with over 20% of people living out with settlements of 500 people.

In 2011/2012 in Scotland 12,103 people suffered an MI with 299 confirmed in NHS Borders. ISD Scotland http://www.isdscotland.org/Health-Topics/Heart-Disease/Topic-Areas/Audits/

In Scotland, death rates from all heart disease have fallen by around 40 per cent over the last 11 years (from 216.8 to 129 deaths per 100,000 population), and death rates from heart attacks have fallen by almost 50 per cent (from 107.4 to 55.7 deaths per 100,000 population).

The recent Healthcare Improvement Scotland review of clinical standards for heart disease highlights that good care provision has contributed to this fall.

The SAS has been a key player in providing this care reaching 78.3% of patients with a suspected heart attack within eight minutes. (Source: Scottish Ambulance Service Annual Report 2011/12)

Patient inclusion/exclusion criteria for the Scottish Borders Pilot study included the following:
Inclusion criteria:

- Patients complaining of cardiac chest pain according to SAS protocol
- Patients attended by Scottish Ambulance Service paramedic
- Patients who are conscious and aware
- Patients who are able to give verbal consent to taking of blood

Exclusion criteria

- Patients with ST elevation on ECG
- Patients who are not conscious
- Patients who are unable to give verbal consent to taking of blood
- Patients with other conditions requiring transport to hospital
- Patients who do not require transport to hospital

3.1.2. Paramedic Training Program

All A & E ambulances in NHS Borders were fitted with Samsung LABGEO ^{IB10}analysers and 57 paramedics were trained to operate this instrument and to test for cTnI using the Samsung LABGEO ^{IB} Troponin test. Training involved a refresher course in cannulation and use of blood vacutainer tubes. It also instructed operators to learn the various LCD touch screens on the

instrument and what information to enter on the touch keypad. Paramedics were also trained in the use of a simple pipette to draw 0.5 mL from the patient blood tube and to dispense it into the cTnI test disc.

The training was collaboratively designed and provided by the Scottish Ambulance Service Learning and Development Department, NHS Borders Training and Development Department, Scottish Centre for Telehealth and Telecare and Samsung. Topics covered also included the aetiology of Coronary Heart Disease and the production of cardiac markers such as cTnI.

The evaluation from the training was extremely positive with 94% of attendees rating it as extremely helpful.

3.1.3. Management of Instruments/Data at Borders SAS Stations

All A & E ambulances in NHS Borders were fitted with a Samsung analyzer.

At the conclusion of the study, all cumulated data was downloaded from each Analyzer onto a USB flash drive and sent to Samsung for analysis and archive as source data. A total of 11 instruments were used. Additionally, each station was given a small bar refrigerator in which to store the Liquid External QC materials and cTnI test discs.

A protocol was established wherein, instruments would be tested daily with dry optical EQC disc and at periodic intervals with the liquid QC materials (see next section for detailed information on the Analyzer, cTnI tests and performance QC) in order to maintain operator proficiency as well as to develop a statistical data base of precision performance including all components of variance (instruments, operators, cTnI device lots). In addition, each site was provided with blood analyzer log sheets, one for each instrument to be filled in on a weekly basis. An example blood analyzer spreadsheet is presented in Table 2 below.

3.2. LABGEO ^{Ib10} Instrument, Quality Control, and Troponin Testing

3.2.1. External Liquid QC Material

Paramedics tested routinely for cTnI contained in a liquid Cardiac Marker Quality Control Material (CLINIQA CO., San Marcos, CA). Liquid control testing was performed by paramedics on a frequent basis to maintain proficiency as the process steps of adding sample and measuring is identical to the steps used in measuring patient's whole blood. Although quite simple to use, any alterations in instructions for sample addition to the disc could result in a liquid QC result outside the acceptable range of cTnI concentration determined by Samsung at the time of cTnI disc manufacture of each lot of new discs. In some cases, if a sample is added improperly, the Analyzer may report an "insufficient sample error code" and an inability to complete the test for either the liquid control or the patient sample.

3.2.2. Dry Reusable Optical QC (EQC disc)

In addition to a liquid QC, the operators were required to perform a dry optical EQC composed of three strips of different color intensity. These reusable strips assure that the Analyzer is performing correctly in it's ability to read a colored signal proportional to the concentration of cTnI contained in the patient sample.

3.2.3. Patient Sample cTnI Measurement in the Ambulance

To test for cTnI, a 5mL sample of venous blood was taken from the patient's cannula site and transferred to the analyser. The Samsung LABGEO ^{IB10} provides the cTnI result within 20 minutes and the blood is analysed when the patient is in transit to Borders General Hospital (BGH).To protect patient anonymity, thermal paper print out results with patient data were deposited in a lock box at BGH with reconciliation performed by a third party at the conclusion of the study. In this manner, no patient data could be extrapolated during the course of the study for use in decision making. Additionally, blood samples drawn in the ambulance were not considered as the baseline sample as they were redrawn upon arrival at BGH A&E. This lag interval, between the ambulance sampling and the A&E sampling may have some significance if an MI was evolving and the time interval between samplings was extensive.

This data will be reported in the Results section of this report.

Table 2: Blood Analyzer Log Sheet

Samsung LABGEOIB10/Operation Log
(Unit I.D. Code: KELSO 01)

Samsung LABGEO ^{IB10} Analyzer SN: _____

Week Commencing: 6/5/13

Model /Part Number and Name of Test: IVR-IB05 Troponin I

Cliniqa Liquid QC Cardiac Marker Control Complete, Level 2 Lot # 12110818

Cliniqa Cardiac Marker Control Complete, Level 2
Samsung LABGEO ^{IB10} Troponin I, Assay Value Sheet

Mean	Range
.89	0.50 – 1.78

Day	Paramedic	Unit Check	EQC Test	Pass	Cliniqa Control Actual Value	Within Range Y/N	Test Disc Lot #	Patient Blood Testing Y/N	Problem	Error Code
Monday	T. HARKIN									
	E0022754	✓	✓	✓	0.77	Y	R5001C98			
Tuesday	RMcEwen	✓	✓	✓	—	—	R9000D2Q			
	E0003514									
Wednesday	[illegible]	/	/	/		Y	R9000D2Q			
	E0013382	/	/	/						
Thursday	A Graham	✓	✓	✓			R9000D2Q			
	E0013352									
Friday										
Saturday	MNewins	✓	✓	✓			R9000 D2Q			
	E0150IX.									
Sunday	L Lee	✓	✓	✓			R9000 D2Q			
	E0010782									

3.2.4. Samsung LABGEO ^{IB10} Analyzer and LABGEO ^{IB} Troponin I Test

The LABGEO ^{IB10} Analyzer is an in-vitro immunology analyzer that quantitatively measures antigens or antibodies in whole blood or plasma samples on a dedicated proprietary disc format. This disc is comparable in size and shape to a DVD compact disc. Utilizing an immunochromatographic assay (ICA) method, the LABGEO ^{IB10} measures and analyzes results with a built-in sensor, reports them on a paper print out and stores the data for future or immediate electronic download to flash drives, direct computer link or LIS interfacing.

The Samsung immunochemistry system combines chemistry with microfluidics and centrifugal flow to rapidly prepare cell free plasma from whole blood that can then be moved through a channel to rehydrate, solubilize and mix with freeze dried immunoconjugates. Using a combination of active flow and capillary action, the test sample is quantitatively measured in 20 minutes with an optical signal level proportional to the analyte(s) concentration.

After addition of the patient sample, the entire test is performed within the Samsung LABGEO ^{IB10} Analyzer which provides control of the temperature of the disc, as well as the analysis process sequence, centrifugal flow, mixing, incubation time, final signal measurement, quantitation and reporting of results. The Test disc includes a positive internal control to ensure that the test has operated properly. Each lot is calibrated to ensure that lot-to-lot variability is minimized. Lot specific calibration along with additional information such as the lot expiration date is contained on a QR code label affixed to each disc. It is recommended that external controls be tested at appropriate time intervals to confirm that the system and test lot are performing within acceptable limits. Photos of the instrument and test disc are shown in Figures 3a-3c

The features of the LABGEO^{IB10} Analyzer and cTnI test are listed in Table 3 and meet or exceed the requirements of POC Analyzers. For operator interaction, the Analyzer has a 4.3 inch LCD touchscreen with which system configuration and other information such as patient and user ID may be entered. For ease of use and to minimize transcription errors, information may be entered via a bar code scanner. In addition, the Analyzer provides a number of data interface alternatives for printing, data output or exchange with the Laboratory Information System (LIS).

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Table 3: Performance characteristics of the SAMSUNG LABGEO ^{IB10} Analyzer and Troponin I Test

Feature of POC systems	**Benefits of SAMSUNG LABGEO ^{IB10} Analyzer**
Light weight and compact	Weight: **2.4 kg (~ 5 lbs),** self contained handle, battery backup
Test results in< 30 minutes	Results reported in 20 minutes
Barcode reader/ computer connectivity	Bar code enabled, USB and Ethernet connectivity, built in thermal printer,
Self contained reagents	Single or multiple assays on a single disc ; on board centrifugation for whole blood
No sample pretreatment	Analyzer is capable of measuring whole blood without precentrifugation processing
Electronic and optical QC	Self test electronics and 3 level reusable QC Test disc (1 min run time)
Analyte test menus	Tests to measure cardiac cell necrosis/hemodynamic function/aid in differential diagnosis; provide prognostic and adverse risk assessment measurement
LABGEO^{IB} Troponin I Test	**Cardiac troponin I (cTnI)**
cTnI test is fully quantitative	Dynamic range from 0.05 – 30 ng/mL
Harmonized to other cTnI tests	Calibrated to Ortho Clinical Diagnostics VITROS® Troponin I ES assay
cTnI test is ***Clinically Usable***	99th reference population percentile precision is less than 15% CV at 0.1 ng/mL

Figure 3a: LABGEO ^{B10} Analyzer

Figure 3b- Sample Disc

Figure 3c – Sample Disc with Whole Blood Dispensing

3.3. Analytical Considerations of different cTnI tests -Relation to Clinical cut-offs

For cTnI measurements, it is essential to know which commercial assay is being used as different assays have different cut off values at the ***99th percentile of a reference population.*** MI guideline recommendations specify that the test result report both the manufacturer of the test and the 99th percentile cut off.[1,7] A list of major manufacturer 99th percentile reference cut-off is given in Table 4.

For the purposes of the current study the cut off values are 0.1 ng/mL for the Samsung LABGEO IB Troponin test and 0.05 ng/mL for the BGH Lab Beckman UniCel DxI cTnI. This information will have additional relevance if the patient is transferred to RIE and they were to use a different cTnI system.

Additionally, it must be taken into consideration that patient's with test results around the cut off are subject to added complexity and possible repeat testing based on the 95% confidence interval(CI) surrounding the result. As an example, a patient test result of 0.1 ng/mL at 15% CV scrutinized at a 95% CI could have an actual value of 0.07 to 0.13 ng/mL. However, numerous clinical studies have determined that tests with CV's between 10-20% have clinical sensitivity and specificity that are identical and have been designated as guideline acceptable/ clinically usable. [8-10]

After much debate, unified International Organizations dedicated to cardiac biomarkers have agreed that: "…harmonization of cTnI measurement aims to establish consensus values for cTnI in 'real' patient specimens by a normalization or realignment process to minimize between method variability. "[11] Both the Samsung LABGEO[IB] Troponin Test[12] and Beckman UniCel DxI cTnI tests[13] took these points into consideration during development. It is important for clinicians to understand what assays are being used as a patient is dispatched between hospitals or sites within a single facility that may have their own near patient / ancillary site chemistry systems.

3.4. Point of Care Performance Compared to the Central Laboratory

In order to evaluate the performance of the Samsung LABGEO [IB10] Analyzer and LABGEO[IB]Troponin I Test as performed by both paramedics versus skilled laboratory personnel, one LABGEO[IB10] analyzer was allocated to the central laboratory of BGH under the supervision of Gordon Nicoll. (Section Manager- Clinical Chemistry Laboratory). In addition to multiple liquid QC runs by different Biomedical Scientists, a method comparison was also performed versus the central laboratory floor model immunoassay system, Beckman-Coulter Unicel Dxl Access system using the AccuTnI test. According to the Beckman –Coulter Accu TnI Instructions for Use (IFU) the 99th percentile of a reference population is 0.04 ng/mL with a total CV of 14%. BGH uses the upper limit of 95% confidence for a reference population as a cut of at 0.05 ng/mL.

Table 4: 99th percentile cut off for various commercial cTnI assays

Assay Reference Code	MANUFACTURER ASSAY NAME TROPONIN I	99th Percentile Medical decision cut off (ng/mL) (CV<20%)	
1	***Samsung LABGEO*** *IB10*	***0.10***	***(14%)***
2	**Abbott** *AxSYM ADV*	0.04	(15%)
3	**Abbott** *ARCHITECT*	0.03	(15%)
4	**Abbott** *i-STAT*	0.08	(17%)
5	**Alere** *Triage Cardio 3*	0.06	(17%)
6	***Beckman Coulter*** *Access AccuTnI*	***0.04***	***(14%)***
7	**bioMerieux** *Vidas Ultra*	0.01	**(>20%)**
8	**Mitsubishi** *PATHFAST*	0.03	(5%)
9	**Ortho** *Vitros ECi ES*	0.03	(10%)
10	**Radiometer** *AQT90 FLEX cTnI*	0.02	(18%)
11	**Roche** *Elescys TnI*	0.16	(10%)
12	**Siemens** *Centaur Ultra*	0.04	(10%)
13	**Siemens** *Dimension RxL*	0.07	(20%)
14	**Siemens** *Stratus CS*	0.07	(10%)
15	**Siemens** *Vista*	0.05	(10%)
16	**Tosoh** *ST AIA-PACK*	0.06	(8.5%)
	TROPONIN T		
17	**Roche** *E170/Elecsys 2010*	0.01	(18%)
18	**Roche** *hs-TnT*	0.01	(8%)
19	**Radiometer** *AQT90 FLEX cTnT*	0.02	(18%)

4. Results and Conclusions

4.1. Analytical Performance

4.1.1. Instrument Placement and Identification

A total of 11 Instruments were placed at SAS ambulance stations with an additional instrument placed in the BGH Clinical Chemistry Laboratory. The instruments, serial numbers and number of tests are given in Table 5. Where identifiable, the instruments are also listed by Station Site. Location was checked via weekly testing feedback summaries, and blood Analyzer log sheets. All instruments were tested with dry EQC and routinely passed optics qualification. In some cases the sites EQC discs outdated and were not replaced by Samsung in a timely fashion. Samsung needs to extend the shelf life of these discs from 6 months to ~ 1 year so that POC QC criteria can be certified without having to run liquid QC on a frequency basis of more than once a week (or month). Daily liquid QC is not an economically viable option for customers given the added costs of extra cTnI test discs that would have to be amortized across the number of patient samples tested in addition to the extra costs associated with the volumes of CLINIQA liquid QC material.

4.1.2. LABGEO ^{IB10} instrument failures, root cause analysis and resolution

The original environmental design specifications of the LABGEO^{IB10} were based on the assumption that the instruments would be used in a temperature environment between 15°C to 32 °C and did not anticipate the effects of leaving the ambulances(and hence the instruments) in unheated or minimally heated garages such as ambulance stations or parked outside for extended periods. As a result during the early stages of instrument implementation by SAS, 3 analyzers generated heating error codes designed to protect the electronics in harsh environmental conditions.

Investigation by Samsung engineers found that the heating modules needed to be retrofitted to be more robust to lower temperatures. All Borders Analyzers were upgraded in February 2013 to operate in conditions below 15°C. No incidents have been reported since retrofitting.

Table 5: Instrument ID, SAS Station, # cTnI tests performed, # cTnI tests valid.

Inst #	serial #	SAS station	# TnI tests Pts + QC	(insufficient volume)208402	.CSV file
1	H005M3ACA00001T	Hawick-01	34	8	120505
2	H007M3ACA00006A	Chirnside-02	55	11	120910
3	H007M3ACA00005Y	Chirnside-01	53	9	130516
4	H007M3ACA00007P	Galashiels-02	52	7	104940
5	H007M3ACA00008D	Galashiels-01	58	7	115342
6	H007M3ACA00003K	Peebles (upgrade)	10	0	115406
7	H007M3ACA00002B	Peebles -01	15	6	120055
8	H007M3ACA00001T	Hawick-01	51	4	140211
9	H007M3ACA00009X	Hawick-02	53	8	140735
10	H007M3ACA00004Z	Kelso-01	33	6	154837
11	H005M3ACA00002B	Kelso -02	55	6	155259
	Totals - ambulance		469	72	
	Total TnI's -net tests		397	-	
12	H007M3ACA00001M		41	1	LAB

From this data it was determined that a total of 469 troponin tests were run which included live patient tests and liquid cTnI QC tests. Of these 397 had no error code and provided results. Unfortunately, during training, operators were not clearly instructed to enter patient ID's for every sample so they could be tracked on the instrument logs. Also, paramedics were not

clearly instructed to identify the QC control material with an “alias” patient ID designation such as **QC** with additional identifiers for the QC lot such as the last 4 characters (e.g **QC103B**).

Fortunately, patient identification and differentiation from liquid QC has been substantially reconciled via the 3rd party anonymous evaluation sheet from lock box thermal paper entries deposited at BGH. Of 397 tests, 112 were patients who could be traced by incident report numbers and then cross checked by date stamps on the individual instrument logs. Analysis of patient data with 3rd party de-identified codes is summarized in the patient analysis section.

4.1.3. Comparison of LABGEO Operator Precision between BGH and SAS

Using CLINIQA QC control material Lot number 1111103B, a total precision analysis was derived based on 234 measurements. % CV for Ambulances and paramedics are given in Tables 6a, 6b, 6c. The cTnI value of this material as supplied by the manufacturer was 0.89 ng/mL cTnI with a range of 0.5 to 1.78 ng/mL.

Variables included:

- 11 Instruments
- multiple paramedics
- Multiple sites
- 2 Lots of LABGEO cTnI Test Discs (R5001C98/ R5001CBR)

QC performance testing in the BGH Laboratory was almost identical to SAS results (Table 7)

Table 6a: % CV from SAS with all components of variation

Ambulance alone				**Count**	
Average cTnI (ng/mL)	1.00			234	
SD	0.140				
CV, %	**13.92%**				
1SD +/- range		**2SD +/- range**		**3SD +/- range**	
0.87	1.15	0.73	1.29	0.59	1.43

Table 6b: % CV from SAS for device lot R5001C98

Device Lot			**R5001C98**	**Count**
Average cTnI (ng/mL)	1.00			172
SD	0.14			
CV, %	**14.25%**			

Table 6c: % CV from SAS for device lot R5001CBR

Device Lot			**R5001CBR**	**Count**
Average cTnI (ng/mL)	1.02			62
SD	0.13			

CV, %	**13.11%**			

Table 7: % CV from BGH Clinical Chemistry Laboratory using Liquid QC material

BGH Laboratory				**Total repetitions**
Average cTnI (ng/mL)	**1.04**			**23**
SD	**0.14**			
CV, %	**13.56%**			

Table 8: % CV pooled from both BGH Clinical Chemistry and paramedics

BGH and Ambulance				**Total repetitions**
AveragecTnI (ng/mL)	**1.01**			**257**
SD	**0.14**			
CV, %	**13.93%**			

In summary, precision between minimally trained paramedics and highly skilled Biomedical Scientists is identical. No outliers have been removed (except for insufficient sample code errors) which prevent a result from being reported. These data confirm precision performance as reported in the Samsung LABGEO ^{IB} Troponin Test IFU which states

Reproduced from Samsung LABGEO ^{IB} Troponin Test IFU[12]

PRECISION

The precision of Samsung LABGEO ^{IB} Troponin I Test was determined using samples where cTnI was added to normal human plasma at three concentrations (Table 3). The within-day and total precision were performed in two runs per day, in replicates of 4 per run at each concentration level over a 15 day period for a total number of repetitions of 120 at each concentration level. The within-run, total variances and coefficients of variation (CVs) were computed according to CLSI guideline EP5-A2.[14]

Table 3.

Sample	Mean level (ng/mL)	Within-run		Total	
		Std. dev. (ng/mL)	CV (%)	Std. dev. (ng/mL)	CV (%)
1	0.46	0.06	12.6	0.06	12.6
2	0.95	0.11	12.0	0.12	13.0
3	4.43	0.41	9.4	0.45	10.1

4.1.4. Method comparison- Beckman Unicel DxI and LABGEO ^{IB} Troponin

Out of 18 patient samples tested on both instruments in the BGH Clinical Chemistry Laboratory, six were below the cut off for each respective assay. Analytical concordance assessed in a 2X2 contingency table gave results of 89% (Tables 9.10). These samples were drawn at the same time followed by testing of the Lithium Heparin plasma sample on the Beckman Unicel DxI and on the LABGEO Test, with minimal delay between processing.

Table 9: Paired data, same patient sample

	Plasma cTnI Comparison	
	LABGEO	Beckman DxI
1/16/2013	<0.05	0.011
1/17/2013	<0.05	0.018
1/24/2013	1.42	1.264
1/25/2013	<0.05	0.003
1/25/2013	<0.05	0.044
1/25/2013	0.12	0.071
1/25/2013	<0.05	0.004
1/25/2013	4.90	4.379
1/31/2013	**<0.05**	**0.058**
1/31/2013	<0.05	0.007
1/31/2013	**<0.05**	**0.174**
2/8/2013	0.1	0.147
2/27/2013	1.88	2.86
2/6/2013	0.66	0.763
3/19/2013	0.14	0.368
3/20/2013	10.19	15.795
3/20/2013	0.1	0.145
3/20/2013	0.82	0.872

Table 10: Contingency table for the same sample drawn and tested at BGH

Beckman Unicel DxI Access TnI

Values > 0.05 ng/mL

Samsung LABGEO^{IB} TnI Values > 0.1 ng/mL

Values > 0.1 ng/mL

	Positive	Negative	Total
Positive	10	0	10
Negative	2	6	8
Total	12	6	18

% Analytical Concordance: 16/18 = 89%

4.1.5. Regression Analysis Correlation on Paired Patient Samples at BGH

Although a small sample set, the correlation between the LABGEO and Beckman Dxl was acceptable in the low end of the assay, where the key medical decision points reside. Although the dynamic range of the LABGEO assay is 30 ng/mL and 100 ng/mL for the Beckman DxI, cut-offs using a 99th percentile values of apparently healthy reference populations have shifted clinically relevant cTnI concentrations to lower ranges, with a sharper focus on dynamic range between > 0 to 5 ng/mL).

Given that both assays were “harmonized” (standardized) by setting calibration to a cTnI reference assay (originally the Dade Stratus II cTnI) after adjustment by measuring large numbers of patient samples, a comparison of cTnI concentration values within a 20-25% value range is quite routine amongst commercial assays. Using the Passing-Bablok method, the following regression and correlation was observed on the limited sample set tested at BGH.

Samsung LABGEO ^{IB} Troponin = 0.83(Beckman Dxl Access Accu TnI) -0.009 ng/mL; N=17,

Correlation coefficient, r =0.97

This result is comparable to a larger method comparison performed by Samsung where LABGEO was compared to another high performance commercial clinical analyzer/test, the Ortho Clinical Diagnostics Vitros TnI ES. As reported in the IFU for the Samsung LABGEO ^{IB} Troponin Test.

Samsung LABGEO ^{IB} Troponin = 0.80 (Ortho Vitros Troponin I ES) -0.009 ng/mL; N=253,

Correlation coefficient, r =0.92

4.2. Time to Result SAS vs BGH Clinical Chemistry Lab based cTnI

4.2.1. Parameters for Consideration

As part of this pilot study, meticulous attention was paid to collection of time based parameters for numerous variables. This has been accumulated into a database comprising 40 columns of information. The scope of this Phase I Report is focused upon parameters related specifically to cTnI measurements, but ancillary appendices will be compiled as time permits to capture other parameters addressed but not directly related to the impact or effect of cTnI testing.

A list of parameters recorded is presented in Table 11. The interim report of February 2013 focused on a number of these variables based on 42 patients. While data from a total of 118 patients were compiled at the May 2013 conclusion of this study, sufficient data for complete analysis is only available on 80. Parameters for exclusion included 7 samples where the ambulance test failed due to insufficient volume, 6 samples where the BGH Clinical Chemistry laboratory reported sample not taken at BGH on arrival either in the ED or ward (total available =105) and up to 30 samples with no discharge diagnosis. Given this limitation, some compilations have various numbers of patients depending on the availability of data to perform a particular analysis.

Table 11: List of performance variables identified for the Phase I study

#	Information/performance variables
1	Date
2	Samsung LABGEO Analyzer Serial No.
3	Incident Report No.
4	**Time of ambulance test result availability**
5	Test available on arrival at hospital
6	Samsung LABGEO cTnI test result (ng/mL)
7	Issues/Failed tests- error codes-other
8	Time from onset of symptoms to ambulance call
9	Time from onset of symptoms to ambulance arrival
10	Time from call to arrival
11	Time to transport patient to hospital
12	Arrival time at hospital
13	**Time from test result to hospital**
15	Time of prescription Clopidigrel
16	Time of administration Clopidigrel
17	Time of anticoagulant therapy
18	Patient taken direct to ward 4 & 5
19	**Time of test drawn in ED/Ward**
20	BGH Lab Beckman DxI Accu cTnI Test Result (ng/mL)
21	Time test received in BGH Lab
22	**Time test result available**
23	**Time result accessed**
24	BGH Lab Beckman DxI -12 hour sampling cTnI test result (Concentration)
25	Time test received in labs- 12 hr sampling
26	Time test result available- 12 hr sampling
27	Time result accessed-12 hr
28	Time of first assessment
29	Admission date/time
30	Discharge date/time
31	Length of Stay (LOS)
32	0 day/23 hr stay?
33	Discharge Diagnosis
34	Discharge code
35	**Time of onset of symptoms to SAS result – baseline cTnI**
36	**Time of onset of symptoms to BGH results- baseline cTnI**
37	Time of onset to time of first assessment
38	Time of call to SAS result

4.2.2. Time based characteristics of SAS baseline vs BGH Laboratory baseline patient measurements

Data from the interim study (February 2013) indicated a time differential of 2 h 27min based on a sample size of ~ 40 patients. Analysis of the full data base suggests that this time differential continues to be maintained (average time 2h:21 min, N=97) . Table 12 shows the availability of results to clinicians by either the ambulance or Clinical Chemistry laboratory (not accession time which varied considerably).

Additional analysis of the database indicates that the mean/median time of transport to the hospital by the SAS is approximately 30 minutes. This is the approximate time it takes to measure cTnI on LABGEO including sample addition and data entry but not including canullation and phlebotomy (Table 13).The interim study presented findings that an additional 7-9 minutes was required at the patient scene which was used to draw blood, set up the test disc, enter key data via touch screen, aliquot the sample into the test disc and initiate the run prior to putting the vehicle in motion. Once initiated the test result is available in 20 minutes. A numeric ordering of 107 data points quantifying transit time indicates that 80% of the cTnI results would be available on arrival at A&E.

Use of LABGEO for cTnI measurement in transport makes the baseline result available to clinicians about 2 ½ h earlier than the current clinical pathway. To understand the Laboratory's role in this delay, time from sample draw to result availability by the BGH Clinical Chemistry laboratory was evaluated on 12 h cTnI requests. Table 14 provides evidence indicating that on a STAT request, the Clinical Chemistry Laboratory is capable of a mean and median turn around time of 30 minutes. The additional 2 h delay likely resides in the logistical pathways of patient processing in A&E and the delay in time before a physician can evaluate a chest pain patient, perform an ECG, assess the results, order the test, wait for sample phlebotomy, sample transport, sample preparation (centrifugation), sample testing, result consult validation and final report.

Table 12 : Availability of baseline cTnI measurement result

	Time difference -baseline TnI result availability
	SAS result vs BGH result
	(hh:mm)
Average	2:21
median	2:07
max diff	6:09
min diff	0:23
count	97

Table 13: Transport time to BGH by SAS

	Transport time to Hospital
	(hh:mm)
Average time	0:28
Median time	0:27
max transport	1:11
min transport	0:03
Count	107

Table 14: Lab turn around on requests for cTnI at 12 h post baseline

	Clinical Chemistry Laboratory TAT on 12 Hr TnI's
	hh:mm
Mean	00:32:
Median	00:27:
Count	74

4.3. Concordance of Patient Results – baseline cTnI

4.3.1. Method of Analysis – low frequency events

As anticipated based on numerous studies [3,6,14] demonstrating the low prevalence of true MI's or ACS amongst patients presenting to ED's with chest pain symptoms, the majority of SAS samples and BGH Clinical Chemistry Laboratory baseline cTnI's are negative. Additionally, those identified by ECG as STEMI were not tested for cTnI by SAS paramedics. This eliminated availability of ~ 50% of possible MI's. from biomarker testing. Due to established public awareness, patients experiencing chest pain are accessing medical services earlier and the likelihood of finding an elevated cTnI on first measurement is low as it takes at least 3-6 h after chest pain onset for cTnI to enter the peripheral blood system as an indicator of cardiac necrosis.

Also contributing to a low frequency of positive cTnI's is that the SAS response time is excellent. In this study an average response time for ambulances was 11 minutes from call to arrival (N=107). This rapid response coupled with a transit time averaging less than 30 min means better medical care and a better chance of survival for patients who have NSTEMI/ACS. Additionally, patients with significantly elevated cTnI's on baseline measurement should be immediately considered as candidates for aggressive anti-platelet therapy and interventional revascularization. Since serial measurements are necessary, especially when baseline values are within the 95-99% confidence interval of the cut point, a 3, 6 and, if necessary, 12 h additional measurement(s) may be required. Current NICE recommendations are 0 and 10-12 h[14] and are in practice at BGH as part of the current chest pain pathway (Figure 1). The RATPAC UK study addressed the issue of reducing serial measurement to baseline and 2 h [3]

A 2 x 2 contingency table was constructed to measure the concordance of positive and negative findings of BGH patients that were sampled and tested for cTnI by LABGEO while in transit compared to those who were resampled at varying times after arrival at A&E (Table 15). One of the major limitations of this study is that there are variable differences in the timing of each patient when comparing ambulance vs BGH blood sampling. The implication is that in some cases a negative LABGEO result in the ambulance may be positive by the time it was re-sampled at BGH. Collection of data establishing the time interval of blood draw at A&E to determine an interval between the ambulance blood draw and the BGH blood draw is insufficient and needs to be re-evaluated.

Table 15: Contingency Table TnI LABGEO Ambulance vs baseline at BGH using Beckman

Beckman Unicel DxI Access TnI

Values > 0.05 ng/mL

Samsung LABGEO^{IB} TnI Values > 0.1 ng/mL

	>0.05 ng/mL	<0.05 ng/mL	Total
>0.1 ng/mL	9	2	11
<0.1 ng/mL	14	79	93
Total	23	81	1

% Analytical concordance: 88/104 = 84.6 %

Of the 104 samples with sufficient information available including correct time stamps and separate blood samples drawn twice, both at presentation to SAS and again at BGH in A&E or Ward 4/5, the negative frequency was **89%** using LABGEO and **76%** using the hospital based measurements from the samples re-drawn when the ambulance arrived at BGH. Given that Table 13 demonstrates that the ambulance result is available about 2 ½ h before the Clinical Chemistry Laboratory result and that Clinical Chemistry Laboratory result TAT is only 30 minutes, there is a possibility that some sample draws are up to 2 h later than the ambulance draw and could contribute in part to the 14 samples that were "negative" on LABGEO and "positive on the BGH Lab Beckman system. A second possibility is that the Beckman Unicell DxI Access Accu cTnI assay is more sensitive then LABGEO.

4.3.2. Concordant Samples Positive on first measurement by both systems

There were 9 samples that were positive by both LABGEO and Beckman cTnI tests on baseline measurement (Table 16). Of these 6 had confirmation of elevation based on the 12 h measurement of cTnI according to BGH protocol. Of most significance was the high value determined on the patient with an acute subendocardial myocardial infarction (1.61 ng/mL LABGEO/1.83 ng/mL. While infrequent in occurrence, samples such as these may be used to justify an alteration of protocol wherein such patients are immediately rerouted in transit from BGH to RIE for immediate interventional procedures or CT angiography.

Table 16: Samples positive by both methods on baseline sampling and 12 h (if available)

Samsung Test result	Clin Chem Test result	Clin Chem 12 hr result	Discharge Diagnosis
1.61	1.83	no sample taken	Acute subendocardial myocardial infarction
0.19	0.37	no sample taken	Dizziness and giddiness
0.76	0.80	11.67	NSTEMI
0.24	0.62	1.54 (haemolysed)	Chest pain unspecified
0.17	0.90	0.96	Chest pain unspecified
0.1	0.56	5.77(haemolysed)	Chest pain unspecified
0.96	0.32	0.29	Chest pain unspecified
0.22	0.41	3.56	Chest pain unspecified
1.83	1.84	no sample taken	Unspecified

4.3.3. Analytical/Clinical Evaluation of Discordant Samples

Of the 16 discrepant samples, 2 were positive on LABGEO and negative on the Beckman system. One sample was diagnosed as ***Diarrhea and gastroenteritis of infectious origin*** and the other was ***unspecified chest pain*** with no reported follow-up.

Of the 14 samples positive by Beckman and negative by LABGEO, 3 are within the upper confidence limit of the Beckman cut-off of 0.05 ng/mL which infers they cannot be discriminated as statistically different than the Beckman 0.05 ng/mL. The remaining 12 are tabularized in Table 17. Without more detailed discharge diagnoses and time intervals between the ambulance and BGH cTnI, it cannot be determined if these patients were NSTEMI/ACS9 i.e chest pain unspecified is insufficient.

Table 17: Discordant Samples – positive by BGH / negative by LABGEO baseline and 12 h

Samsung Test result	Clinical Chemistry Test result	Clinical Chem 12 hr result	Notes Discharge Diagnosis
<0.05	0.73	3.45	*Chest pain unspecified*
<0.05	0.15	admission >12h	STEMI
<0.05	0.23	1.09	Chest pain unspecified
<0.05	0.21	1.17	Chest pain unspecified
<0.07	0.33	1.57	Chest pain unspecified
<0.05	0.24	0.48	Chest pain unspecified
0.06	8.30	11.56	Chest pain unspecified
<0.05	0.10	7.93	Dyskinesia of oesophagus ??
0.0.7	0.45	20.93	no diagnosis
<0.05	0.11	0.10	No diagnosis
<0.05	0.32	no result	No diagnosis

5. Summary and Recommendations

Many of the recommendations listed in the interim report (February 2013) are relisted here with additional observations. They can most succinctly be characterized with one or two sentences and various stake-holders are free to expand upon these items in detail of most relevance is that the ambulance measurement of cTnI, while low in frequency of positive cTnI events sets back the timeline for baseline cTnI documentation by almost two hours. Therefore, the current NICE [14] recommendations of 10-12 h wait time for the second measurement can be reduced by at least 2 h. This should have an immediate effect in reducing the number of low risk patients waiting in A&E for their second cTnI measurement to be taken.

- This pilot study has demonstrated that the LABGEO^{IB} is simple enough to operate that non-laboratory personnel are capable of obtaining the same results and precision as skilled lBiomedical Scientists. Good training is essential with a focus on key steps or technique that may induce errors.

- A more comprehensive method comparison needs to be carried out between the BGH reference system and the LABGEO analyzer using the same sample specimens (time of draw). The precision of the Beckman analyzer is superior to the LABGEO analyzer. However, at the respective medical decision point of the 99th percentile of a healthy reference population, they are nearly identical (14 and 15%).

- Samples near the upper and lower 99% Confidence Interval (CI) need to be repeated at a later timepoint to confirm that the value is not just within the limits of the analytical performance of the device. Serial samplings will always be required. The focus is to move the sampling intervals down and improve assay sensitivity.

- Highly elevated values on LABGEO cTnI (> 10x the reference limit of 0.1 or greater than 1.0 ng/mL should be considered highly significant in making triage decisions if results are available in transit or immediately upon arrival in the ED.

- A formal Research Ethics Committee clinical trial protocol (adhering to Scottish research governance) should be developed in conjunction with a detailed Case Report Form.

- The RATPAC study could be used as a model as their charter was to discharge patients from the ED within 4 h of arrival and serial marker testing at presentation and 2 h later was a significant indicator of safe rule/out in the study.

- Since ambulance based measurements were available 2 ½ h sooner than measurements made in the Clinical Chemistry Laboratory and the Clinical Chemistry Laboratory has demonstrated a “STAT” TAT capability of approximately 30 minutes, BGH should review it’s chest pain pathway and logistics to better understand the approximate 2 h delay when patients arrive. It may likely be due in part to the initial processing of patients and preliminary clinical exam and ECG. However, blood is typically drawn very shortly after a physician orders laboratory tests. If testing ECG STEMI patients with cTnI at baseline is contraindicated, the Laboratory may have the blood for other testing but does not have to run cTnI.

- Samsung should strive to make improvements in the robustness of the LABGEO^{IB} instrument and develop, under formal software design control, systems to allow secure telemonitoring of the resultant test data and additional information.

- A better system is needed to assure that paramedics enter some form of patient ID into the system. If bar code labels are used for patients, the system is capable of using a linear bar code scanner. This is preferable to hand entering on a touch screen identifiers that may be more than 10 characters.

- Although large numbers of liquid QC samples were run in this study, in principal, a quality POC instrument only requires liquid QC once a week or even once a month. It is not economically feasible to run liquid QC every day. The dry strip EQC is for that purpose.

- Any new protocol should specify that ambulance systems run EQC daily and external liquid QC only once a week. This data should be compiled and maintained by a qualified Biomedical Scientist or else have a designee at each Station act as the POC representative. After undergoing an extensive POC training program as established in the UK ,the EC and US.[15]

- There were 16 discordant samples where the two tests did not agree. 14 of these were based on the LABGEO value being negative while the BGH Clinical Laboratory test was positive. This could be due to several factors including : 1) values too close to the cut off zone falling arbitrarily over the +/- cut point line,2) an earlier sampling by the SAS versus the time of a second blood draw at the hospital. If there was an instance of evolving MI, increases in concentration by the time the baseline hospital measurement was made would result in elevated levels. Discordant findings need to be investigated in detail in all future studies.

- Pre-hospital Troponin testing appears to significantly reduce time from symptom onset to Troponin result. Further studies are required to determine whether this could be of significance in clinical management of patients.

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