A LONGITUDINAL ASSESSMENT OF EXTERNAL QUALITY ASSURANCE PERFORMANCE OF HAEMATOLOGY AND COAGULATION ANALYTES AT AN ACADEMIC LABORATORY

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in part fulfilment of the requirements for

the degree of Master of Medicine in the branch of Haematology

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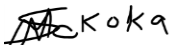
DECLARATION

I, Ngwanatala Sophia Mokoka declare that this research report is my own, unaided work. It is submitted for the Degree of Master of Medicine in the branch of Clinical Pathology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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11th day of April 2024 in Parktown, Johannesburg

ABSTRACT

Participation in external quality assurance (EQA) is a requirement of the South African National Accreditation System. The main purpose of EQA is to monitor quality from sample collection to authorizing of results in order to improve laboratory performance. This study evaluated the EQA performance of the haematology and coagulation test parameters on the Royal College of Pathologists of Australasia program from December 2016 to December 2020 at Charlotte Maxeke Johannesburg Academic Hospital. The following tests were assessed from the EQA reports, the full blood count, differential, and reticulocyte (Sysmex XN haematology analysers, Roche Diagnostics, Kobe, Japan); erythrocyte sedimentation rate (StaRRsed, Mechatronics, Zwaag, the Netherlands); and lupus anticoagulant, von Willebrand factor, prothrombin time, international normalised ratio, fibrinogen, activated partial thromboplastin time (aPTT), thrombin time, d-dimer and coagulation factors (STA-R/Max evolution coagulation analysers, Diagnostica Stago, Paris, France). The test performance was determined from analytical quality specification (APS) and/or z-scores. Bias and imprecision were used to calculate sigma (σ) metric scores. Specifications from European Federation of Laboratory Medicine and/or biological variation were applied. The laboratory achieved a satisfactory mean testing score of at least 80% over the 4-year study period. All the haematology and coagulation test parameters evaluated achieved an acceptable APS. The mean z-scores, however, were >2 and unacceptable for the mean cell volume and haematocrit. On investigation, this was attributed to a pre-survey issue. The median σ value was ≥ 6 for white cell count, haemoglobin, aPTT, thrombin time, fibrinogen, and d-dimers. EQA participation assisted the laboratory in maintaining a quality system. Ageing of the analytical platforms with a decline in test performance was not observed during the study period. Six sigma may be a beneficial quality management system tool for haematology laboratories with multiple analysers.

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NOMENCLATURE

APS:	Analytical performance specifications
aPTT:	Activated partial thromboplastin time
CLIA:	Clinical laboratory improvement amendments
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
CV:	Coefficient of variation
DIFF:	Differential count
DRVVT:	dilute Russell's viper venom time
EFLM:	European Federation of Laboratory Medicine
EQA:	External Quality Assurance
ESR:	Erythrocyte sedimentation rate
FBC:	Full blood count
HB:	Haemoglobin
HCT:	Haematocrit
INR:	International Normalised Ratio
IQC:	Internal Quality Control
IQR:	Interquartile range
MCH:	Mean cell haemoglobin
MCHC:	Mean cell haemoglobin concentration
MCV:	Mean cell volume
MPV:	Mean platelet volume
NHLS:	National Health Laboratory Service
PT:	Prothrombin time
RCC:	Red cell count
RCPA:	Royal College of Pathologists of Australasia

RDW:	Red cell distribution width
RETIC:	Automated reticulocyte
SANAS:	South African National Accreditation System
SD:	Standard deviation
TEa:	Allowable total error
VWF:	von Willebrand Factor
WCC:	White cell count

1. INTRODUCTION

1.1 Background

1.1.1 Quality assurance

Quality assurance is a system used to monitor and evaluate a laboratory's pre-analytical, analytical and post-analytical performance with the analysis of quality control material. This can be subdivided into internal quality control (IQC) and external quality control (also known as proficiency testing). IQC is an internal process that monitors the accuracy and precision of laboratory testing on a day-to-day basis. External quality assurance (EQA) is defined as a system of objectively checking laboratory results by an external agency (1). Since the establishment of the first EQA programme more than 60 years ago, the scope of EQA has increased significantly. Currently, EQA is an essential component of the laboratory quality system as well as a requirement for laboratory accreditation (2).

1.1.2 External Quality Assurance

The main purpose of EQA is to monitor quality from sample collection to reporting and authorising of results in order to improve laboratory testing and performance (1). EQA survey material is sent to participating laboratories at least twice per year. The EQA samples are incorporated into the laboratory's routine analytical workflow and the analysis is performed by the routine technical staff i.e. mimicking patient sample handling in the laboratory. Laboratories analyse the samples and then return the results to the scheme for comparison and incorporation into the statistical analysis of all results received from participating laboratories. Laboratories respond to unacceptable EQA results by investigating the root cause of the testing error, correcting procedures that contributed to the error and implementing preventive measures. In this way, EQA allows each laboratory to assess and compare their performance against other participating laboratories using the same analytical method, instrument or reagents (3). Moreover, EQA provides the opportunity for monitoring of analytical accuracy with changes in testing platforms and identifies inter-laboratory discrepancies. EQA samples can also be used for validation of new methods and instruments in the laboratory (4).

1.1.3 The Royal College of Pathologists of Australasia External Quality Assurance scheme

In South Africa, participation in a recognized EQA scheme is a requirement of the South African National Accreditation System (5). The laboratory at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) has been participating in the Royal College of Pathologists of Australasia (RCPA) EQA scheme for 30 years. Currently, the RCPA scheme offers their EQA programme in over 80 countries worldwide (6). The CMJAH laboratory receives six to twenty-four EQA samples per haematology and coagulation analyte per year. The EQA material matrix is non-commutable i.e. not equivalent to but representative of a clinical sample. The RCPA scheme also provides an end-of-year cycle report to assess accuracy and precision of each analyte over the cycle period of one year. The laboratory uses its performance in the RCPA EQA scheme in conjunction with IQC to monitor the quality of its overall testing process.

1.1.4 Analytical methods

EQA schemes define analytical performance specification (APS) criteria in order to assist laboratories in objectively establishing quality planning strategies and to assess if testing processes require improvement (7). Consensus with regards to global APS in laboratory medicine was reached at the Stockholm expert conference (8) and subsequently updated at the Milan expert conference in 2014 (9). Consequently, the European Federation of Laboratory Medicine (EFLM) has described the required characteristics and specifications with regards to EQA schemes (Table 1S Appendix 1) (10). These include the nature of the EQA material, the procedure used to establish the assigned value, the data set for application of APS, the applicable analytical quality being assessed, the rationale for the selection of the APS and the type of model used. APS is determined in accordance with the following models: clinical decision applications (Milan model 1b), biological variation (Milan model 2) or state-of-the-art criteria (Milan model 3) (11).

The RCPA EQA scheme establishes the assigned target value from the enrolled laboratories' submitted results. The results are categorized according to peer groups with similar analytical methods, reagents, instruments or manufacturer. With regards to clinical limits, the desirable or minimal APS value is the laboratory result minus peer group mean and indicates whether the difference from the target value is acceptable (Table 2S Appendix 1) (12, 13).

According to the state-of-the-art criteria, the RCPA scheme assesses the laboratory performance with a z-score. The z-score is calculated from the following equation: $z= (x-\mu)/ \sigma$, where x is the laboratory result, μ is the peer group mean and σ is the standard deviation (SD). Assessment of z scores is based on the following: $z \leq -1.49$ or $z \leq 1.49$ is acceptable; z of -1.5 to -1.99 or z of 1.5 to 1.99 requires trouble-shooting; and $z \geq -2.0$ or $z \geq 2.0$ is unacceptable (1). The performance of the laboratory is compared to the results obtained by the participants in the peer group. As such, the assigned target value is influenced by the number of participants and result variability. In addition, the RCPA EQA assesses the imprecision, bias and allowable total error (TEa). This is calculated from several measurements and presented in the end of cycle report. Sigma metric is a quality assurance tool which combines the TEa, bias and imprecision (14, 15). The measured sigma metric provides guidance for establishing acceptability levels and frequencies of IQC runs in the clinical laboratory (16, 17). Briefly, the sigma metric is scored from 0 to 6. Westgard proposes that parameters with a sigma (σ) of ≥ 6 should be evaluated with one alternating level of IQC per day and applying a simple 1_3S rejection rule. Parameters with σ of 4-6, should be evaluated with two levels of IQC once per day and a combination of multi-rejection rules namely,1_3S, 2_2S and R_4S. A σ of 3-4 indicates a poor performance, requiring at least two levels of controls twice per day and a combination of multi-rejection rules namely1_3S, 2_2S, R_4S and 4_1S. Lastly, parameters with $\sigma < 3$ should be investigated to determine the root cause of the unacceptable parameter performance.

In summary, EQA test performance on the RCPA scheme is determined from APS, z-scores, imprecision, bias and TEa. However, few studies have evaluated the influence of participation in EQA on ongoing improvement of the laboratory's quality system.

1.2 Study Aim and Objectives

Aim

The aim of this study was to review the EQA performance of haematology and coagulation test analytes at the CMJAH laboratory over four years (December 2016 - December 2020).

Objectives

The specific objectives of the research were:

1. To review the performance of the haematology and coagulation test analytes in the RCPA EQA programme. The test performance was determined from APS, z-scores, imprecision and bias.

2. To describe the laboratory's response to unacceptable EQA results. This included investigation of the root cause of the testing error, correction of the procedure which produced the error and implementation of preventive measures. In addition, the effect of the implementation of the preventative measures on subsequent EQA performance, was assessed.

3. To compare the yearly EQA performance over the four year cycle in order to evaluate the performance as the analytical platforms ages.

4. To assess the performance of the haematology and coagulation analysers and test methods on the sigma scale. Performance specifications from EFLM and/or biological variation were applied.

2. METHODS

2.1 Study design

This retrospective study reviewed the RCPA EQA performance of haematology and coagulation test analytes at the CMJAH laboratory over four years (December 2016- December 2020). The EQA schedule is provided in Table 3S - Appendix 1.

2.2 Study protocol

Inclusion criteria: RCPA EQA reports for quantitative, automated haematology and coagulation analyte analysis at CMJAH between 1 December 2016 and 31 December 2020

Exclusion criteria: RCPA EQA reports for qualitative/manual tests

Data collection: Data were collected from the RCPA EQA reports for all the respective analytes. These were retrieved from the RCPA website (My EQAP: https://rcpaqap.secure.force.com/login). The following data as per the data collection sheet were entered from the cycle reports: APS values and the z-scores per analyser and analytical methodology. The assigned z-scores were available on RCPA reports after March 2019. In addition, the bias and imprecision were collected from the end of cycle report for each analyte to calculate the TEa. The calculated TEa was then used to assess the laboratory's performance according to the EFLM biological variation database.

For non-conforming EQA results the laboratory investigation into the root cause of the testing error was retrieved from the National Health Laboratory Service (NHLS) Q-pulse database. The criteria used for classifying testing errors was according to the proposed classification by Kristensen et al. (18). This classification details a step-by-step approach to troubleshooting unacceptable EQA results. The testing errors were broadly classified as transcription error, pre-survey issue, sample receipt/handling, test performance, data handling by EQA provider and reporting and interpretation (18). An error was classified as random if no cause was identified and repeat testing yielded an acceptable within consensus result. The corrective and preventive measures were recorded. The effect of the implementation of the preventative measures on the APS- and z-scores achieved by the laboratory on subsequent EQA sample analysis was assessed.

Analytical methods: The analytical methods of the respective analysers are detailed in Table 4S Appendix 1. Full blood count (FBC) parameters namely; white cell count (WCC), red cell count (RCC), haemoglobin (HB), haematocrit (HCT), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin

concentration (MCHC), red cell distribution width (RDW), platelet count and mean platelet volume (MPV); differential (DIFF) parameters namely % neutrophils, % lymphocytes, % monocytes, % basophils and % eosinophils and automated reticulocyte (Retic) parameters were measured using each of the laboratory's three Sysmex XN® haematology analysers (Roche®Diagnostics, Kobe, Japan) (referred to as XN10-1; XN10-2 and XN20). The erythrocyte sedimentation rate (ESR) was measured on the StaRRsed® (Mechatronics®, Zwaag, the Netherlands) analyser. The coagulation parameters namely; Lupus sensitive partial thromboplastin time screen and screen ratio, dilute Russell viper venom test (DRVVT) screen and screen ratio, von Willebrand factor (VWF) antigen and Ristocetin cofactor activity, prothrombin time (PT), international normalised ratio (INR), fibrinogen, activated partial thromboplastin time (aPTT), thrombin time, d-dimer and coagulation Factors (II, V, VII, VIII, IX, X, XI and XII) were measured using the laboratory's two STA-R/Max Evolution® coagulation analysers (Diagnostica Stago®, Paris, France). The reagents were supplied by the respective manufacturers and the analysers were installed and in routine use at the CMJAH laboratory since 2016.

2.3 Data Analysis

Data was captured on an Excel® spreadsheet (Microsoft Office® 2010, Redmond) and analysed using Statistica® 13.2 software (Palo Alto, California, the United States). Descriptive statistics was applied. Normally distributed, continuous data (z-scores and APS values) was presented as mean ± SD and variables with non-Gaussian distribution as medians with interquartile ranges [IQRs]. Categorical data was presented in frequency distribution tables. Testing scores were values between 0 and 100 and represented the percentage of acceptable results per cycle for each test analyte. The EQA performance for all test analytes during the 4 years was compared using the chi-squared test for testing scores and the one-way Anova for the z-scores and APS value. A p-value of less than 0.05 was considered significant.

Calculation equations:

The APS values were calculated according to the equation:

APS value = Target median – Participating laboratory median

The z-score was determined according to the equation:

$z\text{-score} = (x-\mu)/\sigma$

where x is the laboratory result, μ is the peer group mean and σ is the SD (5).

Precision was expressed as % coefficient of variation (CV) and was calculated according to the equation:

% CV = standard deviation/ mean x 100

Bias was calculated according to the equation:

Bias = mean of peer group participants – CMJAH laboratory mean/ mean of all laboratories x 100

TEa was calculated according to the equation:

TEa = Bias + 1.65 x SD

and the results were compared to the biological variation data from EFLM and other databases (18).

The sigma metric was calculated according to the equation:

Sigma (σ) = TEa - Bias /CV

and was calculated for WCC, RCC, haemoglobin, platelet count, Retic parameters, PT, INR, aPTT, thrombin time, fibrinogen, d-dimers and coagulation factors.

The performance values for σ was considered at the following levels:

$\sigma \geq 6$, σ 4-6, σ 3-4 and $\sigma < 3$

2.4 Ethics

The protocol was approved the Human Research Ethics Committee of the University of the Witwatersrand (M210713)

3. RESULTS

Table 3.1 contains the APS and z-scores of the submitted EQA results of 18 haematology and 20 coagulation tests over the four year study period. All EQA testing scores for the haematology tests were within acceptable limits with the exception of the z-scores for the MCV, MCHC and HCT. The z-scores for the MCHC on all three Sysmex® analysers were in the range of 1.45-1.99 and therefore required trouble shooting. The z-scores for MCV and HCT on all three analysers were, however, above 2 and unacceptable. The EQA testing scores for the coagulation tests were all within acceptable limits.

Table 3.1 Testing scores on the Royal College of Pathologists of Australasia External Quality Assurance scheme, 2016-2020					
Instrument	**Test parameter**	**z-score (median [IQR])**	**z-score interpretation**	**APS value (median [IQR])**	**APS value interpretation**
Sysmex XN10-1	white cell count	-0.52 [0.39]	acceptable	-0.01 [0.16]	acceptable
	red cell count	-0.07 [0.19]	acceptable	-0.01 [0.10]	acceptable
	haemoglobin	0.55 [2.11]	acceptable	-0.10 [0.21]	acceptable
	haematocrit	2.14 [6.10]	unacceptable	-0.08 [0.22]	acceptable
	mean cell volume	0.51 [2.32]	unacceptable	-0.07 [2.57]	acceptable
	mean corpuscular haemoglobin	0.97 [1.16]	acceptable	0.03 [0.16]	acceptable
	mean cell haemoglobin concentration	-1.65 [4.85]	requires troubleshooting	-0.08 [0.31]	acceptable
	red cell distribution width	1.39 [4.49]	acceptable	-0.25 [0.25]	acceptable
	platelet count	-0.83 [0.39]	acceptable	-0.13 [0.07]	acceptable
	mean platelet volume	-0.35 [0.58]	acceptable	0.03 [0.08]	acceptable
	%neutrophil	0.50 [0.92]	acceptable	0.07 [0.34]	acceptable
	%lymphocytes	0.46 [1.14]	acceptable	-0.10 [0.22]	acceptable
	%monocytes	-0.95 [2.78]	acceptable	0.11 [0.27]	acceptable
	%eosinophil	0.26 [0.44]	acceptable	0.07 [0.04]	acceptable
	%basophil	0.03 [0.44]	acceptable	0.01 [0.04]	acceptable
Sysmex XN10-2	white cell count	-0.47 [0.27]	acceptable	-0.06 [0.09]	acceptable
	red cell count	-0.15 [0.36]	acceptable	0.02 [0.08]	acceptable
	haemoglobin	1.42 [1.53]	acceptable	0.01 [0.30]	acceptable
	haematocrit	2.46 [5.23]	unacceptable	-0.01 [0.26]	acceptable
	mean cell volume	0.53 [2.23]	unacceptable	-0.03 [2.87]	acceptable
	mean corpuscular haemoglobin	1.09 [1.91]	acceptable	-0.03 [0.21]	acceptable
	mean cell haemoglobin concentration	-1.67 [4.18]	requires troubleshooting	-0.02 [0.34]	acceptable
	red cell distribution width	1.38 [4.78]	acceptable	-0.25 [0.37]	acceptable

	platelet count	-0.09 [0.09]	acceptable	-0.03 [0.07]	acceptable
	mean platelet volume	-0.28 [0.22]	acceptable	-0.01 [0.12]	acceptable
	%neutrophil	0.50 [0.92]	acceptable	0.07 [0.34]	acceptable
	%lymphocytes	0.28 [2.21]	acceptable	0.13 [0.49]	acceptable
	%monocytes	-0.59 [2.80]	acceptable	-0.01 [0.41]	acceptable
	%eosinophil	0.08 [0.56]	acceptable	-0.19 [0.28]	acceptable
	%basophil	-0.29 [0.66]	acceptable	-0.01 [0.05]	acceptable
	automated reticulocyte count (%)	0.25 [5.04]	acceptable	0.10 [0.10]	acceptable
	automated reticulocyte count (absolute)	-0.06 [0.33]	acceptable	0.32 [0.27]	acceptable
Sysmex XN10-3	white cell count	-0.11 [0.45]	acceptable	0.03 [0.12]	acceptable
	red cell count	-0.16 [0.53]	acceptable	-0.04 [0.08]	acceptable
	haemoglobin	0.64 [2.65]	acceptable	-0.05 [0.18]	acceptable
	haematocrit	2.26 [5.04]	unacceptable	-0.05 [0.20]	acceptable
	mean cell volume	0.53 [3.35]	unacceptable	-0.08 [2.86]	acceptable
	mean corpuscular haemoglobin	0.77 [2.75]	acceptable	-0.04 [0.16]	acceptable
	mean cell haemoglobin concentration	-1.94 [3.50]	requires troubleshooting	0.04 [0.28]	acceptable
	red cell distribution width	1.25 [4.60]	acceptable	-0.26 [0.46]	acceptable
	platelet count	-0.92 [0.38]	acceptable	-0.15 [0.07]	acceptable
	mean platelet volume	-0.23 [0.21]	acceptable	-0.03 [0.05]	acceptable
	%neutrophil	0.33 [0.98]	acceptable	0.01 [0.19]	acceptable
	%lymphocytes	0.23 [0.15]	acceptable	0.10 [0.24]	acceptable
	%monocytes	-0.91 [1.45]	acceptable	-0.11 [0.27]	acceptable
	%eosinophil	0.33 [0.47]	acceptable	0.04 [0.14]	acceptable
	%basophil	-0.3 [0.56]	acceptable	0.15 [0.96]	acceptable
	automated reticulocyte count (%)	-0.1 [5.71]	acceptable	-0.04 [0.15]	acceptable
	automated reticulocyte count (absolute)	0.09 [0.26]	acceptable	0.03 [0.11]	acceptable

StaRRsed	Erythrocyte Sedimentation Rate	-0.23 [0.29]	acceptable	0.13 [1.09]	acceptable
Sta-R/Max-1	Coagulation Factor VIII	0.68 [1.85]	acceptable	0.05 [0.44]	acceptable
	Coagulation Factor IX	0.43 [0.55]	acceptable	0.17 [0.14]	acceptable
	Coagulation Factor II	-0.53 [0.28]	acceptable	-0.13 [0.09]	acceptable
	Coagulation Factor V	0.37 [0.71]	acceptable	0.00 [0.20]	acceptable
	Coagulation Factor VII	0.57 [0.28]	acceptable	0.14 [0.29]	acceptable
	Coagulation Factor X	0.75 [0.56]	acceptable	0.07 [0.27]	acceptable
	Coagulation Factor XI	-0.49 [0.49]	acceptable	-0.09 [0.22]	acceptable
	Coagulation Factor XII	-1.02 [0.44]	acceptable	-0.24 [0.18]	acceptable
	PT	-0.76 [0.16]	acceptable	-0.12 [0.05]	acceptable
	INR	-0.51 [0.30]	acceptable	-0.01 [0.11]	acceptable
	fibrinogen	-0.88 [0.21]	acceptable	-0.10 [0.12]	acceptable
	aPTT	-0.08 [0.75]	acceptable	-0.04 [0.07]	acceptable
	Thrombin time	0.14 [0.59]	acceptable	0.04 [0.04]	acceptable
	D-Dimer	0.48 [0.32]	acceptable	0.06 [0.05]	acceptable
	Lupus sensitive PTT screen*	-		-0.04 [0.11]	acceptable
	Lupus sensitive PTT screen ratio**	-		-0.16 [0.24]	acceptable
	DRVVT screen*	-		-0.03 [0.05]	acceptable
	DRVVT screen ratio*	-		-0.20 [0.22]	acceptable
	VWF antigen *	-		0.15 [0.20]	acceptable
	VWF Ristocetin cofactor *	-		0.32 [0.66]	acceptable
Sta-R/Max-2	Coagulation Factor VIII	0.45 [1.30]	acceptable	0.16 [0.36]	acceptable
	Coagulation Factor IX	-0.1 [0.55]	acceptable	-0.02 [0.15]	acceptable
	Coagulation Factor II	-0.47 [0.26]	acceptable	-0.12 [0.12]	acceptable
	Coagulation Factor V	0.88 [1.37]	acceptable	0.14 [0.15]	acceptable
	Coagulation Factor VII	0.64 [0.72]	acceptable	0.20 [0.39]	acceptable

	Coagulation Factor X	0.52 [0.22]	acceptable	0.13 [0.16]	acceptable
	Coagulation Factor XI	0.42 [0.42]	acceptable	0.3 [0.36]	acceptable
	Coagulation Factor XII	-0.32 [0.29]	acceptable	-0.07 [0.11]	acceptable
	PT	-0.83 [0.26]	acceptable	-0.16 [0.07]	acceptable
	INR	-0.42 [0.24]	acceptable	-0.08 [0.10]	acceptable
	fibrinogen	-0.48 [0.28]	acceptable	-0.13 [0.12]	acceptable
	aPTT	-0.30 [0.44]	acceptable	-0.04 [0.06]	acceptable
	Thrombin time	0.32 [0.47]	acceptable	0.03 [0.1]	acceptable
	D-Dimer	0.70 [0.25]	acceptable	0.08 [0.05]	acceptable
	Lupus sensitive PTT screen*	-		0.06 [0.10]	acceptable
	Lupus sensitive PTT screen ratio*	-		-0.08 [0.15]	acceptable
	DRVVT screen*	-		0.06 [0.15]	acceptable
	DRVVT screen ratio*	-		-0.04 [0.12]	acceptable
	VWF antigen *	-		0.06 [015]	acceptable
	VWF Ristocetin cofactor *	-		0.06 [0.20]	acceptable

Key: APS, analytical performance specification; IQR, interquartile range; aPTT, activated Partial Thromboplastin Time; VWF, von Willebrand Factor; PT, prothrombin time; DRVVT, dilute Russell's viper venom time; INR, International Normalised Ratio; -, not available.

*z scores not reported by the RCPA EQA scheme during the 4-year period.

The EQA performance for each of the tests between 1 December 2016 and 31 December 2020 are shown in Table 3.2. All the test parameters achieved a satisfactory mean testing score during the study period of > 80%. A significant decrease in the EQA performance (of < 80%) in 2020 was noted for the following parameters: HB, HCT and calculated parameters MCV, MCH, MCHC, RDW and %monocytes on the Sysmex® haematology analysers. For the coagulation parameters, a significant decrease in the EQA performance (of < 80%) was observed in 2020 for VWF Ristocetin cofactor activity on Sta-R/Max-1®.

Table 3.2 Comparison of overall performance on the Royal College of Pathologists of Australasia External Quality Assurance, 2016 to 2020

Analyser	Test parameter	No of cycles	EQA PERFORMANCE (%)				p value
Year			**2017**	**2018**	**2019**	**2020**	
Sysmex XN10-1	white cell count	48	100	100	100	100	>0.05
	red cell count	48	100	100	100	100	>0.05
	haemoglobin	48	100	100	100	81	0.001
	haematocrit	48	100	100	100	63	0.001
	mean cell volume	48	100	100	100	45	0.001
	mean corpuscular haemoglobin	48	100	100	100	77	0.001
	mean cell haemoglobin concentration	48	100	100	100	59	0.001
	red cell distribution width	48	100	100	100	63	0.001
	platelet count	48	100	100	100	100	>0.05
	mean platelet volume	48	100	100	100	100	>0.05
	%neutrophil	16	100	75	100	100	0.007
	%lymphocytes	16	100	75	100	100	0.007
	%monocytes	16	100	100	100	63	0.001
	%eosinophil	16	100	100	100	100	>0.05
	%basophil	16	100	100	100	100	>0.05
Sysmex XN10-2	white cell count	48	100	100	100	100	>0.05
	red cell count	48	100	100	100	100	>0.05
	haemoglobin	48	100	100	100	72	0.001

	haematocrit	48	100	100	100	63	0.001
	mean cell volume	48	100	100	100	45	0.001
	mean corpuscular haemoglobin	48	100	100	100	77	0.001
	mean cell haemoglobin concentration	48	100	100	100	59	0.001
	red cell distribution width	48	100	100	100	63	0.001
	platelet count	48	100	100	100	100	>0.05
	mean platelet volume	48	100	100	100	100	>0.05
	%neutrophil	16	100	75	100	100	0.007
	%lymphocytes	16	88	75	100	100	0.001
	%monocytes	16	88	100	100	63	0.001
	%eosinophil	16	100	100	100	100	>0.05
	%basophil	16	100	100	100	100	>0.05
	automated reticulocyte count (absolute)	16	100	100	100	88	0.001
	automated reticulocyte count (%)	16	100	100	100	100	>0.05
Sysmex XN20	white cell count	48	100	100	100	100	>0.05
	red cell count	48	100	100	100	100	>0.05
	haemoglobin	48	100	100	100	77	
	haematocrit	48	100	100	100	63	0.001
	mean cell volume	48	100	100	100	45	0.001
	mean corpuscular haemoglobin	48	100	100	100	77	0.001
	mean cell haemoglobin concentration	48	100	100	100	81	0.001
	red cell distribution width	48	100	100	100	63	0.001
	platelet count	48	100	100	100	91	0.001
	mean platelet volume	48	96	100	100	91	0.019
	%neutrophil	16	100	75	100	100	0.007
	%lymphocytes	16	88	75	100	100	0.001
	%monocytes	16	88	100	100	63	0.001

	%eosinophil	16	100	100	100	100	>0.05
	%basophil	16	100	75	100	100	0.007
	automated reticulocyte count (absolute)	16	100	100	88	100	0.001
	automated reticulocyte count (%)	16	100	100	100	88	0.001
StaRRsed	Erythrocyte sedimentation rate	8	100	100	75	88	0.480
Sta-R/Max-1	Coagulation Factor VIII	24	100	100	83	100	0.001
	Coagulation Factor IX	24	100	100	100	83	0.001
	Coagulation Factor II	12	100	100	100	100	>0.05
	Coagulation Factor V	12	100	100	92	83	0.001
	Coagulation Factor VII	12	100	100	100	100	>0.05
	Coagulation Factor X	12	100	100	100	100	>0.05
	Coagulation Factor XI	12	100	100	100	100	>0.05
	Coagulation Factor XII	12	100	100	100	100	>0.05
	PT	32	100	100	100	100	>0.05
	INR	32	100	100	100	100	>0.05
	fibrinogen	32	100	100	100	100	>0.05
	aPTT	32	100	100	100	100	>0.05
	Thrombin time	32	100	100	100	88	0.001
	D-Dimer	16	100	100	100	100	>0.05
	Lupus sensitive PTT screen	12	100	100	100	100	>0.05
	Lupus sensitive PTT screen ratio	12	100	100	100	100	>0.05
	DRVVT screen	12	100	100	100	100	>0.05
	DRVVT screen ratio	12	100	100	100	100	>0.05
	VWF antigen	8	100	100	100	100	>0.05
	VWF Ristocetin cofactor activity	8	-	75	100	75	0.028

Sta-R/Max-2	Coagulation Factor VIII	24	100	100	83	100	0.001
	Coagulation Factor IX	24	83	100	100	83.3	0.001
	Coagulation Factor II	12	100	100	100	100	>0.05
	Coagulation Factor V	12	100	100	92	100	0.001
	Coagulation Factor VII	12	92	83	100	100	0.001
	Coagulation Factor X	12	100	100	100	100	>0.05
	Coagulation Factor XI	12	83	100	100	100	0.001
	Coagulation Factor XII	12	100	100	100	100	>0.05
	PT	32	100	100	100	100	>0.05
	INR	32	100	100	100	100	>0.05
	fibrinogen	32	100	100	100	100	>0.05
	aPTT	32	100	100	100	100	>0.05
	Thrombin time	32	88	100	94	88	>0.05
	D-Dimer	16	100	100	100	100	>0.05
	Lupus sensitive PTT screen	12	100	100	100	100	>0.05
	Lupus sensitive PTT screen ratio	12	100	88	100	100	0.001
	DRVVT screen	12	100	100	100	100	>0.05
	DRVVT screen ratio	12	100	100	100	100	>0.05
	VWF antigen	8	100	100	100	100	>0.05
	VWF Ristocetin cofactor activity	8	-	75	100	100	0.028

Key: EQA, External Quality Assurance; aPTT, Activated partial thromboplastin time; VWF, Von Willebrand Factor; PT, prothrombin time; DRVVT, dilute Russell's viper venom time; INR, International Normalised Ratio

There were 103 unacceptable results, which accounted for 10.7% of all the tests (n=960) submitted to the EQA scheme during the study period (Figure 3.1). Pre-survey issues accounted for most of the errors (n=85, 83%). The major reason was loss of sample stability owing to travel restrictions during the COVID-19

pandemic. This was followed by transcription errors (n=9, 9%). There were also 6 (6%) errors where the source of deviation was unknown and the root cause could not be determined with investigation and troubleshooting. Moreover, none of the errors persisted with subsequent EQA surveys and were not present in preceding EQA submissions (Figures 3.2 to 3.4) and were therefore random errors. There were 3 (3%) errors related to test performance which were attributed to poor performance of reagents for coagulation Factor V, problems with the environmental temperature for the ESR analysis and poor performance of IQC reagents for coagulation Factor XI. The preventative and corrective actions are described in Table 3.3 and Table 5S Appendix 1.

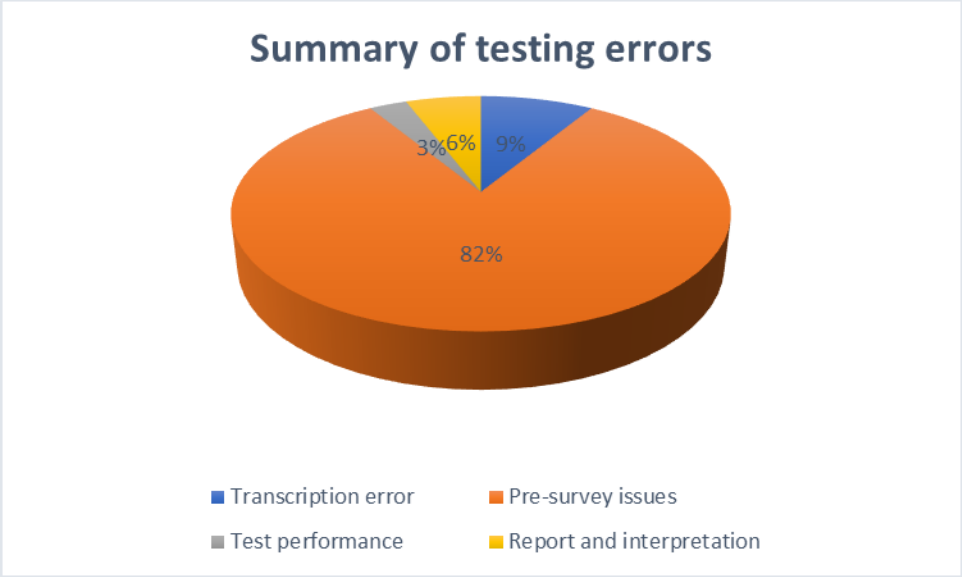

Figure 3.1 Reasons for unacceptable external quality assurance results between 2016 and 2020

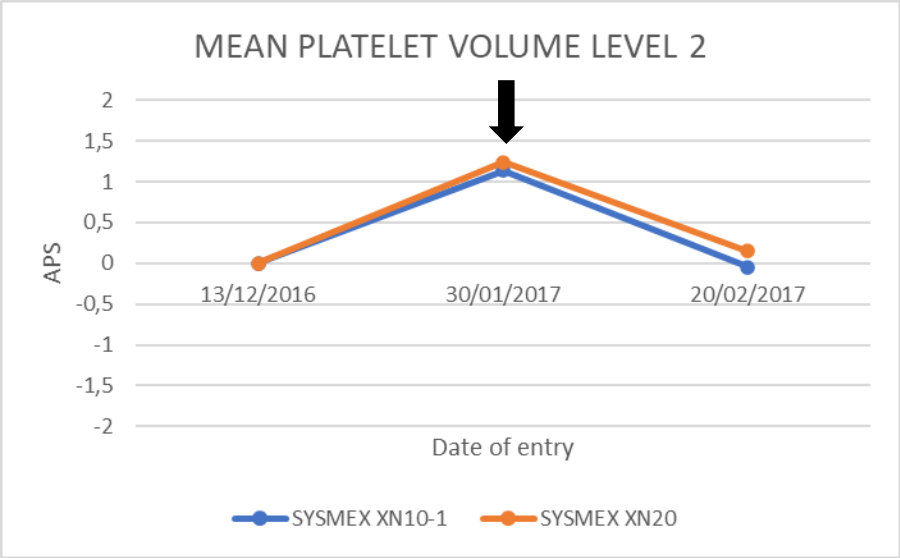

Figure 3.2 Analytical performance specification scores before and after the random error of mean platelet volume on the Sysmex XN10-1 and XN-20

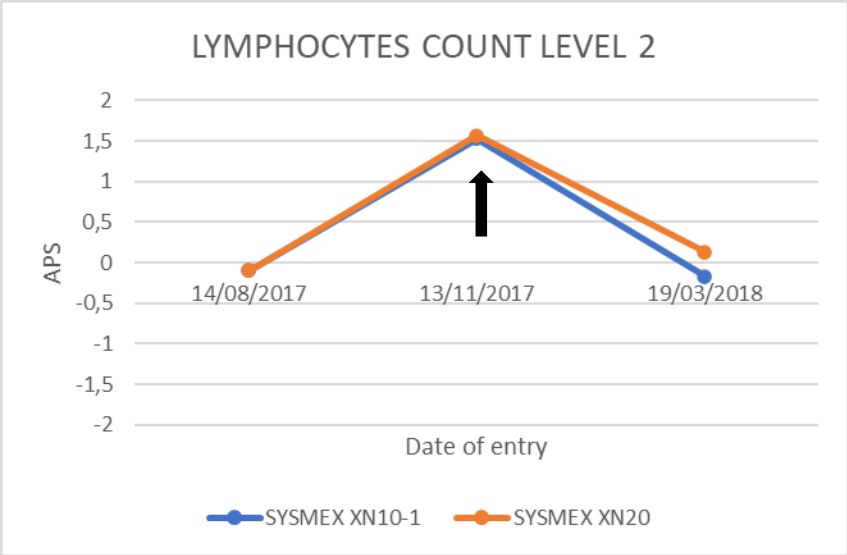

Figure 3.3 Analytical performance specification scores before and after the random error on lymphocyte count on the Sysmex XN10-1 and XN-20

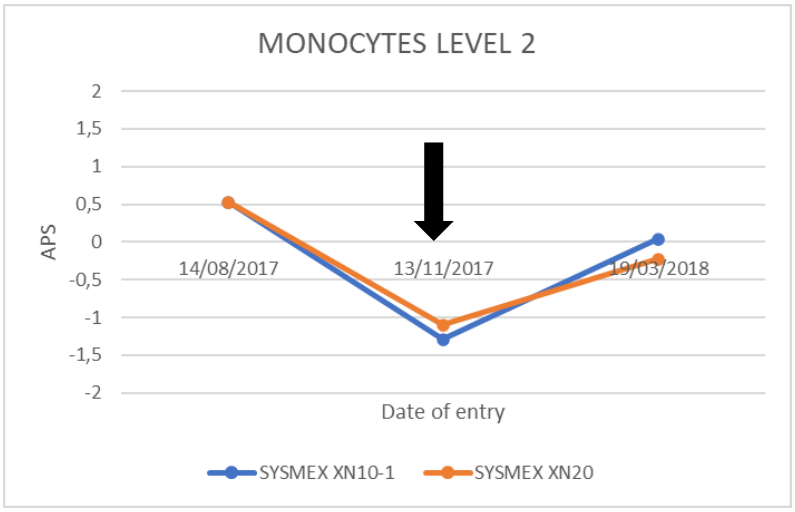

Figure 3.4 Analytical performance specification scores before and after the random error on monocyte count on the Sysmex XN10-1 and XN-20

Table 3.3 Reasons for unacceptable External Quality Assurance results, 2016 to 2020			
Testing Error	**Number of occurrences**	**Reasons**	**Preventative and corrective action**
Transcription error	9	-Results incorrectly transcribed -Incorrect units of reporting	-Review process of result recording / reporting
Pre-survey issues	85	-Sample instability	-Review use of transportation with the EQA provider during COVID-19 lockdown. -New courier company established
Test performance	3	-Reagent problems -Problems with environmental temperature control -Problems with Internal quality control	-Order reagents in time and review the operation status of the analysers -Review IQC and temperature charts
Report and interpretation	6	-Unknown root cause	-The random error did not persist with future EQA surveys
Key: EQA, External Quality Assurance; COVID-19, Coronavirus Disease of 2019.			

The sigma metric values for haematology and coagulation test parameters between 2016 and 2020 which were provided by the RCPA EQA scheme are listed on Table 3.4. For WCC, RCC, HB and platelet parameters, the %CVs used to calculate the sigma metric score were within acceptable limits with acceptable %bias (Table 6S Appendix 1). All the parameters, except platelet count and coagulation Factor XI, were within minimum acceptable total allowable error limits. Table 3.5 shows average sigma metric levels and proposed IQC algorithm for the CMJAH laboratory. The following parameters: WCC, HB, aPTT, thrombin time, fibrinogen, and d-dimers achieved a $\sigma \geq 6$. The PT, INR, platelet count and automated reticulocyte count (absolute and %) showed a poor performance of $\sigma < 3$. On comparison of the three haematology and two coagulation analysers, the analyser-to-analyser variability was not significant ($p>0.05$).

Table 3.4 The six sigma metric values for haematology and coagulation test parameters, 2016 to 2020									
Analyser	**Test parameter**	**2017**		**2018**		**2019**		**2020**	
		σ	**Interpretation**	**σ**	**Interpretation**	**σ**	**Interpretation**	**σ**	**Interpretation**
Sysmex XN10-1	**FIRST CYCLE FOR THE YEAR**								
	white cell count	18.62	World class	22.92	World class	8.95	World class	6.79	World class
	red cell count	5.23	Good	5.77	Good	3.84	Moderate	7.23	World class
	haemoglobin	6.14	World class	5.67	Good	3.79	Moderate	1.28	Poor
	platelet count	6.69	World class	3.55	Moderate	1.44	Poor	1.44	Poor
	SECOND CYCLE FOR THE YEAR								
	white cell count	10.33	World class	13.75	World class	15.84	World class	13.63	World class
	red cell count	4.45	Good	2.88	Poor	7.23	World class	7.23	World class
	haemoglobin	3.79	Moderate	4.50	Good	7.71	World class	1.41	Poor
	platelet count	1.09	Poor	2.90	Poor	0.37	Poor	-0.08	Poor
Sysmex XN10-2	**FIRST CYCLE FOR THE YEAR**								
	white cell count	11.42	World class	12.14	World class	34.43	World class	15.77	World class
	red cell count	7.20	World class	4.82	Good	6.42	World class	5.77	Good
	haemoglobin	5.88	Good	5.56	Good	5.78	Good	1.03	Poor
	platelet count	4.71	Good	3.91	Moderate	1.91	Poor	2.61	Poor
	SECOND CYCLE FOR THE YEAR								
	white cell count	20.63	World class	15.85	World class	14.63	World class	10.78	World class
	red cell count	5.24	Good	4.12	Good	5.74	Good	4.41	Good
	haemoglobin	6.00	World class	2.61	Poor	5.00	Good	0.95	Poor
	platelet count	3.57	Moderate	4.74	Good	3.46	Moderate	0.09	Poor
	Automated reticulocyte count %	4.72	Good	4.44	Good	0.31	Poor	3.10	Moderate
	Automated reticulocyte count (Absolute)	4.18	Good	3.14	Moderate	3.70	Moderate	3.03	Moderate

Analyser	Test parameter	2017		2018		2019		2020	
		σ	Interpretation	σ	Interpretation	σ	Interpretation	σ	Interpretation
Sysmex XN20	**FIRST CYCLE FOR THE YEAR**								
	white cell count	14.60	World class	20.56	World class	25.81	World class	15.78	World class
	red cell count	11.59	World class	5.79	Good	5.26	Good	7.22	World class
	haemoglobin	9.00	World class	6.00	World class	5.67	Good	1.00	Poor
	platelet count	3.35	Moderate	2.49	Poor	0.86	Poor	0.72	Poor
	SECOND CYCLE FOR THE YEAR								
	white cell count	13.67	World class	10.87	World class	12.09	World class	12.91	World class
	red cell count	4.44	Good	4.13	Good	5.78	Good	4.46	Good
	haemoglobin	11.20	World class	2.78	Poor	6.13	World class	1.00	Poor
	platelet count	5.83	Good	6.50	World class	0.34	Poor	0.38	Poor
	Automated reticulocyte count %	3.35	Moderate	4.73	Good	0.28	Poor	2.26	Poor
	Automated reticulocyte count (Absolute)	2.05	Poor	3.47	Moderate	2.27	Poor	0.55	Poor
Sta-R/Max-1	Coagulation Factor VIII	0.09	Poor	0.34	Poor	-0.31	Poor	0.45	Poor
	Coagulation Factor IX	1.06	Poor	1.27	Poor	1.66	Poor	2.98	Poor
	Coagulation Factor II	1.28	Poor	0.49	Poor	1.05	Poor	1.56	Poor
	Coagulation Factor V	1.82	Poor	0.76	Poor	0.97	Poor	<0	Poor
	Coagulation Factor VII	2.50	Poor	1.17	Poor	2.85	Poor	1.95	Poor
	Coagulation Factor X	2.81	Poor	0.95	Poor	2.58	Poor	2.83	Poor
	Coagulation Factor XI	1.43	Poor	0.69	Poor	0.86	Poor	0.35	Poor
	Coagulation Factor XII	0.34	Poor	-0.49	Poor	-0.08	Poor	0.44	Poor
	PT	1.14	Poor	0.99	Poor	1.49	Poor	1.13	Poor
	INR	1.95	Poor	1.44	Poor	1.48	Poor	1.49	Poor
Analyser	**Test parameter**	**2017**		**2018**		**2019**		**2020**	

		σ	Interpretation	σ	Interpretation	σ	Interpretation	σ	Interpretation
Sta-R/Max-1	fibrinogen	3.65	Moderate	3.46	Moderate	3.18	Moderate	6.26	World class
	aPTT	1.82	Poor	2.19	Poor	3.12	Moderate	1.46	Poor
	d-dimer	6.59	World class	9.13	World class	7.54	World class	6.01	World class
Sta-R/Max-2	Coagulation Factor VIII	0.86	Poor	0.00	Poor	0.21	Poor	Poor	Good
	Coagulation Factor IX	0.67	Poor	2.15	Poor	1.07	Poor	3.92	Moderate
	Coagulation Factor II	2.91	Poor	1.96	Poor	0.52	Poor	1.67	Poor
	Coagulation Factor V	1.41	Poor	1.86	Poor	1.04	Poor	<0	Poor
	Coagulation Factor VII	1.12	Poor	0.99	Poor	3.77	Moderate	1.93	Poor
	Coagulation Factor X	7.13	World class	1.77	Poor	2.67	Poor	4.40	Good
	Coagulation Factor XI	-0.18	Poor	0.12	Poor	0.51	Poor	0.79	Poor
	Coagulation Factor XII	1.36	Poor	0.42	Poor	0.46	Poor	0.95	Poor
	PT	0.73	Poor	2.16	Poor	1.42	Poor	1.56	Poor
	INR	1.54	Poor	1.64	Poor	1.33	Poor	1.26	Poor
	fibrinogen	3.23	Moderate	3.14	Moderate	5.13	Good	4.90	Good
	aPTT	1.92	Poor	2.16	Poor	2.34	Poor	2.57	Poor
	d-dimer	5.79	Good	9.13	World class	6.41	World class	8.48	World class

Key: aPTT, Activated partial thromboplastin time; PT, prothrombin time; INR, International Normalised Ratio; no EFLM biological data available for thrombin time

Table 3.4 Proposed Sigma metric algorithm

Median Sigma value	Parameter	Number of IQC per analytical run	Westgard IQC rule	Comment
≥6 (World class)	White cell count d-dimer	1-normal alternating with low	1_{3s} single control rule	This implies a good quality testing process and therefore simple IQC rules are effective
4-6 (Good)	Red cell count Haemoglobin	2-normal and low	Multirule: $1_{3s}/2_{2s}/R_{4S}$	
3-4 (Moderate)	Automated reticulocyte count % Fibrinogen	≥2-normal, low and high	Multirule: $1_{3s}/2_{2s}/R_{4S}$ / 4_{1S}	More IQC samples and more stringent rules are required.
<3 (Poor)	Platelet count Coagulation Factor II Coagulation Factor V Coagulation Factor IX Coagulation Factor X Coagulation Factor XI Coagulation Factor XII aPTT PT INR	-	-	Stop and investigate

Key: aPTT, Activated partial thromboplastin time; PT, prothrombin time; INR, International Normalised Ratio;

4. DISCUSSION

EQA in clinical laboratories was introduced over six decades ago as a tool to assess the quality of the laboratory's overall performance. The laboratory at CMJAH has participated in the RCPA EQA scheme for more than a decade to monitor the quality of its testing processes. In conjunction with IQC as a quality monitoring tool, EQA has contributed to improvements in the laboratory quality system through identification and correction of systematic errors.

The RCPA scheme uses the APS as an analytical performance goal to assess the quality of the participating laboratories' performance. During the four-year study period, all the haematology and coagulation test parameters evaluated achieved an acceptable APS. In the RCPA EQA scheme, goals are based on biological variation and the highest level of analytical performance, namely the state-of-the-art criteria (Milan model 2 and 3). It is, however, difficult to compare performance with other EQA schemes. While significant measures have been taken to harmonize APS between EQA schemes, differences still exist. This is owing to the wide variability in the different Milan models employed for establishing APS as well as factors such as the procedures used to establish the target value, the data set, assessment of total error, and the rationale for the selection of the APS (19).

More recently the RCPA scheme also measures the participants' observed performance based on z-scores among peer groups, which is calculated as the difference between the individual laboratory test results and the mean result of the peer group divided by the peer group SD. An advantage of the z-score is that it is a standardised value for all test parameters. Nonetheless, a disadvantage is that this statistical method depends on the SD of the peer group. Thus, although RCPA has introduced the z-score as a measure of performance, this should be interpreted in conjunction with the APS. During the four-year study period, the mean z-scores were >2 and unacceptable for the FBC parameters namely MCV and HCT. On investigation, this was attributed to a pre-survey issue. EQA results may be influenced by the deterioration of specimens during transportation and storage before testing. Many specimens need to be transported as refrigerated or frozen specimens. As such it is necessary to deliver the specimens within a specified time frame.

The Coronavirus Disease of 2019 pandemic resulted in a widespread lockdown and caused a significant delay in transport and storage of FBC samples during this period. While storage of samples at 4°C – 8°C for seven days has been associated with increased stability of most FBC parameters in clinical specimens, the same does not apply to EQA samples (24, 25). The RCPA EQA scheme distributes stabilised whole blood samples that are partially fixated with aldehydes to increase the stability of the FBC parameters as per the WHO guideline recommendations for EQA (6, 26). This affords EQA samples an increased stability of several weeks at temperatures between 25 ºC and 37 ºC (27, 28). The temperature during transport of EQA samples is, however, not monitored or controlled. Therefore, sample integrity may be compromised. The delay in sample transport affected the EQA sample stability and was evidenced by the reporting of abnormal MCV, MCH, MCHC, HB, HCT, RDW and platelet parameters to the EQA scheme. Furthermore, the subsequent entries were also out of consensus as the transport delay could not be resolved owing to lockdown constraints. Problems with EQA survey material stability are more common with participation in international EQA schemes (20). It is therefore necessary for international laboratories to monitor the shipping dates in order to be alerted to delays of samples which can affect the quality of results.

It is encouraging to note that with long-term EQA participation, the laboratory achieved a satisfactory mean testing score of least 80% over the four-year study period. Similarly, other studies have demonstrated that EQA performance is related to the length of laboratory participation in an EQA scheme (21, 22). In these studies, experience in particular with sample handling/receipt of EQA samples as well as reporting of interpretive EQA results contributed to the decline in the rate of unacceptable results. Nonetheless, despite the experience gained with the RCPA EQA scheme's procedures at the CMJAH laboratory, pre-survey issues followed by transcription errors accounted for the majority of the unacceptable results. The laboratory responded to the unacceptable EQA results by conducting an investigation into the root cause of the testing error. There were 6 (6%) errors classified as random where no explanation for the EQA error could be determined. The follow-up EQA results were within consensus. Transcription errors were related to errors in reporting of results to the EQA scheme, mixing up test results and reporting results with wrong units. This was corrected with laboratory staff re-training and ongoing monitoring.

In this study, problems with analytical test performance accounted for 3 (3%) of the unacceptable results. This was related to an IQC failure and laboratory environmental conditions which affected the instrument

performance as well as out-of-stock reagents for a low volume coagulation test. Identification of the root cause of the testing error assisted the laboratory in resolving these EQA failures and there were no subsequent entries which were out with consensus. These results compare favourably with laboratories from developed countries with well-established quality control systems. In 2012, the College of American Pathologists surveyed its participating laboratories in Africa. In this survey, methodological errors related to IQC, reagents and instruments were identified as the major cause for testing errors. Following good clinical laboratory practice training and ongoing monitoring of EQA performance, the number of methodological errors decreased by 35%. EQA participation therefore contributes to improvement in test performance.

More recently, six sigma metrics, a gold standard quality management system tool, has been extended to laboratory medicine in order to assess the quality of the overall testing processes. Laboratories which monitor IQC with six sigma metrics have reported a reduction in the error rate (16). However, experience with sigma metric in Haematology laboratories is limited (16,19). Surveys indicate that the majority of laboratories continue to apply traditional '2SD' warning rules and '3SD' rejection rules (19). Routine use of these IQC limits is associated with a false rejection rate of >5 % (4). This results in unnecessary and wasteful investigations such as repeating controls, troubleshooting and/or changing control limits. It is currently recommended that clinical laboratories implement six sigma metrics as the preferred quality management tool to control the errors in the total testing process. In this study, sigma metric was applied to assess the performance of the individual laboratory tests per analyser. The median σ value was ≥ 6 for WCC and d-dimer. This indicates a good quality testing process and therefore fewer QC samples, and less stringent rules are required to monitor IQC daily. The median σ value was < 3 for platelet count, aPTT, PT, INR and coagulation Factors II, V, IX, X, and XII. Similarly, Shaikh et al. (16), reported a sigma metric value of less < 3 for the platelet count and PT parameter. A TEa of 13.4% and 5.4% respectively were applied to calculate the sigma metric value. In contrast, El-Neaneay et al. (19), reported a mean sigma metric of ≥ 6 for the PT parameter on the Siemens® coagulation analyser (Siemens Healthineers, Marburg, Germany). This was achieved using the wider Clinical laboratory improvement Amendments (CLIA) TEa of 15% for the calculation of sigma metric value. The biologic goals from the EFLM database which were applied in this study are known to be more stringent as compared to the Ricos and CLIA criteria. These narrow TEa goals make it a challenge to achieve an acceptable sigma score. Bias and imprecision may be the preferred monitoring method for these parameters in haematology laboratories. This study also illustrated the measured sigma metric as an efficient tool to compare IQC across multiple analysers. The three haematology analysers

showed comparable sigma performances for FBC, DIFF and Retic, although not all parameters met the minimum performance goal of 3.0 Sigma. Similarly, comparable sigma performances between the two coagulations analysers were observed.

Several limitations of this study warrant consideration. Firstly, RCPA started reporting z-scores from March 2019. Therefore, this parameter could not be analysed and reliably assessed over the 4-year study period. Secondly, biological variation data for coagulation parameters is still limited. Further, the available data is based on small studies of a short duration and includes only specific parameters (12, 23). A future longitudinal study is required to determine the biological variation of coagulation parameters.

In conclusion, CMJAH laboratory's participation in the RCPA EQA scheme has facilitated continuous monitoring of all aspects of the testing process and improvement in laboratory performance. During the study period, approximately 81% of the unacceptable results were as a result of pre-survey issues related to sample instability. Errors related to sample receipt/handling, test performance, data handling by EQA provider and reporting and interpretation were not increased. Ageing of the analytical platforms with a decline in test performance was not observed over the four-year period. EQA participation assisted the laboratory in maintaining a quality system during the four-year study period. Moreover, six sigma metrics may be a beneficial quality management system tool for haematology laboratories with multiple analyzers.

5. APPENDICES

Appendix 1: Supplementary Tables

Table 1S. Biological variation data

Parameters	EFLM biological variation data Minimum specifications %bias	%CVa	%Total allowable error
White cell count	7.4	8.1	20.7
Red cell count	2.6	2.0	5.8
Haemoglobin	2.4	2.0	5.8
Platelet count	7.6	5.7	17.0
Automated reticulocyte count	10.8	7.3	22.8
Coagulation Factor VIII	9.0	6.5	19.8
Coagulation Factor IX	6.6	5.2	15.2
Coagulation Factor II	4.2	4.3	11.4
Coagulation Factor V	7.3	4.0	13.8
Coagulation Factor VII	7.3	6.1	17.5
Coagulation Factor X	4.8	4.4	12.1
Coagulation Factor XI	4.7	3.8	11.0
Coagulation Factor XII	4.7	3.8	11.0
PT	2.1	2.0	5.4
INR	2.0	1.9	5.1
Fibrinogen	7.5	7.6	20.1
aPTT	2.9	2.1	6.4
Thrombin time	No data		
Fibrinogen	16.3	6.4	47.5

Key: EFLM, European Federation of Clinical Chemistry and laboratory medicine; %CV. percentage coefficient of variation, aPTT, activated Partial Thromboplastin Time; PT, prothrombin time; INR, International Normalised Ratio.

Table 2S. Analytical performance specification criteria		
Parameters	**APS value**	
	lower limit	**upper limit**
White cell count	+ or - 0.5 ≤ 5.0 x10 ^9/L	+ or - 10% > 5.0 x10^9/L
Red cell count	+ or - 0.2 ≤ 2.0 x10^12/L	+ or - 10% > 2.0 x10^12/L
Haemoglobin	+ or - 5 ≤ 100 g/L	+ or - 5% > 100 g/L
Haematocrit	+ or - 0.04 ≤ 0.20	+ or - 20% > 0.20
Mean corpuscular haemoglobin	+ or - 2 ≤ 20 pg	+ or - 10% > 20 pg
Mean corpuscular volume	+ or - 5 ≤ 50 fL	+ or - 10% > 50 fL
Mean cell haemoglobin concentration	+ or -30 ≤ 300 g/L	+ or - 10% > 300 g/L
Red cell distribution width	+ or - 2 ≤ 10%	+ or - 20% > 10%
Platelet count	+ or - 25 ≤ 100 x10^9/L	+ or - 25% > 100 x10^9/L
Mean platelet volume	+ or - 2 ≤ 10 fL	+ or - 20% > 10 fL
Automated reticulocyte count	+ or - 10 ≤ 100	+ or - 10% > 100 x10^9/L
Erythrocyte Sedimentation Rate	+ or - 3.0 ≤ 10.0 mm/hr	+ or - 30% > 10.0 mm/hr
%Neutrophil	+ or - 1.0 ≤ 10.0%	+ or - 10% > 10.0%
%lymphocytes	+ or - 2.0 ≤ 10.0%	+ or - 20% > 10.0%
%monocytes	+ or - 3.0 ≤ 10.0%	+ or - 30% > 10.0%
%eosinophil	+ or - 3.0 ≤ 10.0%	+ or - 30% > 10.0%
%basophil	+ or - 3.0 ≤ 10.0%	+ or - 30% > 10.0%
Coagulation Factor VIII	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
Coagulation Factor IX	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
Coagulation Factor II	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
Coagulation Factor V	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
Coagulation Factor VII	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
Coagulation Factor X	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
Coagulation Factor XI	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
Coagulation Factor XII	+ or - 3 ≤ 10 IU/dL	+ or - 30% > 10 IU/dL
PT	+ or -2.0 ≤ 10.0 sec	+ or - 20% > 10.0 sec
INR	+ or - 0.3 ≤ 2.0 ratio	+ or - 15% > 2.0 ratio
Fibrinogen	+ or - 0.20 ≤ 1.0 g/L	+ or - 25% > 1.0 g/L
aPTT	+ or - 10 ≤ 40 sec	+ or - 25% > 40 sec
Thrombin time	+ or - 3 ≤ 12 sec	+ or - 25% > 12 sec
D-dimer	+ or - 0.25 ≤ 0.50 DD mg/L	+ or - 50% > 0.50 DD mg/L
aPTT screen	+ or - 9.0 ≤ 30 sec	+ or - 30% >30 sec
aPTT screen ratio	+ or - 0.3 ≤ 0.9 ratio	+ or - 30% > 0.9 ratio
DRVVT screen	+ or - 9.0 ≤ 30 sec	+ or - 30% > 30 sec
DRVVT screen ratio	+ or - 0.3 ≤ 0.9 ratio	+ or - 30% > 0.9 ratio
vWF antigen	+ or - 3 ≤ 10%	+ or - 30% > 10%
vWF Ristocetin cofactor activity	+ or - 4 ≤ 10%	+ or - 40% > 10%

Key: APS, analytical performance specification; aPTT, activated Partial Thromboplastin Time; vWF, von Willebrand Factor; PT, prothrombin time; DRVVT, dilute Russell's viper venom time; INR, International Normalised Ratio

Table 3S. The external quality assurance schedule	
Parameters	**Number of EQA entries a year**
White cell count	12
Red cell count	12
Haemoglobin	12
Haematocrit	12
Mean cell volume	12
Mean corpuscular haemoglobin	12
Mean cell haemoglobin concentration	12
Red cell distribution width	12
Platelet count	12
Mean platelet volume	12
White cell count	4
%Neutrophil	4
%Lymphocytes	4
%Monocytes	4
%Eosinophil	4
%Basophil	4
Erythrocyte sedimentation rate	2
Automated reticulocyte count	4
PT	8
INR	8
Fibrinogen	8
aPTT	8
Thrombin time	8
d-dimer	4
Coagulation Factor VIII	7
Coagulation Factor IX	7
Coagulation Factor II	3
Coagulation Factor V	3
Coagulation Factor VII	3
Coagulation Factor X	3
Coagulation Factor XI	3
Coagulation Factor XII	3
APTT screen	3
APTT screen ratio	3
DRVVT screen	3
DRVVT screen ratio	3
APTT mix	3
DRVVT mix	3
VWF antigen	2

VWF Ristocetin cofactor activity	2
Key: aPTT, activated Partial Thromboplastin Time; PT, prothrombin time; INR, International Normalised Ratio; DRVVT, dilute Russell's viper venom time; VWF, von Willebrand Factor.	

Table 4S. Analytical methods for haematology and coagulation analytes

Parameters	Analytical method	Instrument
White cell count	Flow cytometry with semi-conductor laser	Sysmex XN series
Red cell count	Impedance method	Sysmex XN series
Haemoglobin	cyanide-free sodium lauryl sulphate method	Sysmex XN series
Haematocrit	RBC cumulative pulse height detection	Sysmex XN series
Mean cell volume	Calculated method	Sysmex XN series
Mean corpuscular haemoglobin	Calculated method	Sysmex XN series
Mean cell haemoglobin concentration	Calculated method	Sysmex XN series
Red cell distribution width	Calculated method	Sysmex XN series
Platelet count	Impedance method	Sysmex XN series
Mean platelet volume	Calculated method	Sysmex XN series
%Neutrophil	Flow cytometry with semi-conductor laser	Sysmex XN series
%Lymphocytes	Flow cytometry with semi-conductor laser	Sysmex XN series
%Monocytes	Flow cytometry with semi-conductor laser	Sysmex XN series
%Eosinophil	Flow cytometry with semi-conductor laser	Sysmex XN series
%Basophil	Flow cytometry with semi-conductor laser	Sysmex XN series
Erythrocyte sedimentation rate	Westergren method	ELITech StaRRsed series
Automated reticulocyte count	Flow cytometry with semiconductor laser	Sysmex XN series
PT	Mechanical clot detection	STA-R/MAX
INR	Mechanical clot detection	STA-R/MAX
Fibrinogen	Von clauss	STA-R/MAX
aPTT	Mechanical clot detection	STA-R/MAX
Thrombin time	Mechanical clot detection	STA-R/MAX
D-dimer	Latex immunoassay	STA-R/MAX
Coagulation Factor VIII	Mechanical clot detection	STA-R/MAX
Coagulation Factor IX	Mechanical clot detection	STA-R/MAX
Coagulation Factor II	Mechanical clot detection	STA-R/MAX
Coagulation Factor V	Mechanical clot detection	STA-R/MAX
Coagulation Factor VII	Mechanical clot detection	STA-R/MAX
Coagulation Factor X	Mechanical clot detection	STA-R/MAX
Coagulation Factor XI	Mechanical clot detection	STA-R/MAX
Coagulation Factor XII	Mechanical clot detection	STA-R/MAX
PTT screen	Mechanical clot detection	STA-R/MAX
PTT screen ratio	Mechanical clot detection	STA-R/MAX
DRVVT screen	Mechanical clot detection	STA-R/MAX
DRVVT screen ratio	Mechanical clot detection	STA-R/MAX
aPTT mix	Mechanical clot detection	STA-R/MAX
DRVVT mix	Mechanical clot detection	STA-R/MAX
VWF antigen	Latex immunoassay	STA-R/MAX
VWF Ristocetin cofactor activity	Platelet aggregation/agglutination	STA-R/MAX

Key: RBC, Red blood cell; aPTT, activated Partial Thromboplastin Time; PT, prothrombin time; INR, International Normalised Ratio; DRVVT, dilute Russell's viper venom time; VWF, von Willebrand Factor.

Table 5S. Reasons for external quality assurance failures during the study period

Test parameter	Date	Testing Error	Root cause	Analyser	APS value	z-score	APS value on the subsequent EQA	z-score on the subsequent EQA
2017								
1. Mean platelet volume	30/01	6	Source for the deviation unknown	SYSMEX XN10-2 and XN20	1.14 and 1.24	-	-0.05 and 0.15	-
2. Lymphocytes	13/11	6	Source for the deviation unknown	SYSMEX XN10-2 AND XN20	1.53 and 1.57	-	0.13	-
3.Monocytes	13/11	6	Source for the deviation unknown	SYSMEX XN10-2 AND XN20	-1.29 and -1.10	-	-0.23	-
4.Coagulation Factor XI	30/01	4	Test performance Problem with the internal quality control performance	STAMAX2 Both levels	1.27 and 1.06	-	0.00	-
2018								
5. Neutrophil	11/07	1	Transcription error	SYSMEX XN10-1. XN10-2 AND XN20	1.88. 2.13 and 2.13	-	-0.07. -0.05. and 0.18	-

Test parameter	Date	Testing Error	Root cause	Analyser	APS value	z-score	APS value on the subsequent EQA	z-score on the subsequent EQA
6. Lymphocytes	11/07	1	Transcription error	SYSMEX XN10-1. XN10-2 AND XN20	-1.63. -1.45 and -1.48	-	-0.21. 0.33 and 0.09	-
2019								
7. Erythrocyte sedimentation rate	25/02	4	Test performance Problem with the environmental control	StaRRsed Interliner	1.3	2.9	0.1	0.2
8. Automated reticulocyte count	16/9	1	Transcription error	XN10-2 and XN-20	5.9. 6.6	74 and 82.9	0.1. 0.1	0.6 and 0.6
2020								
9. von Willebrand antigen	30/03	6	Source for the deviation unknown	STAMAX1	1		-0.15	
10. Automated reticulocyte count	16/06	1	Transcription error	SYSMEX XN20	1.2	2.2	0.7	2.8
11. Monocytes %	16/06 entry 2	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1.8. 1.4. and -1.2	-6.6. -5.1. and -4.2	-1. -1.8. -1.4	-3.3. -5.6. and -4.6
12. Monocytes %	24/08 entry 3	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1. -1.8. -and 1.4	-3.3. and 5.6. -4.6	-0.1. -0.6. 0	-0.1. -2.4 and 0

Test parameter	Date	Testing Error	Root cause	Analyser	APS value	z-score	APS value on the subsequent EQA	z-score on the subsequent EQA
13. Coagulation Factor V	14/09	4	Test performance Unavailability of the reagent	No entry on STAMax1			- End of cycle	-
14. Haematocrit	22/04 entry 4	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.3. 1.5. 1.25	6.54. 8.01. 6.54	1.3. 1.3. 1.25	16.6. 16. 17.3
	25/05	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.3. 1.3. 1.25	16.6. 16. 17.3	1.1. 1.1. 1.4	5.5. 5.5. 6.7
	16/06	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.1. 1.1. 1.4	5.5. 5.5. 6.7	1.4. 1.4. 1.4	12.15 for all
	20/07	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.4. 1.4. 1.4	12.15 for all	1. 0.8. 0.89	10.24. 8. 9.12
	17/08	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.3. 1.3. 1.25	9.7. 9.. 9.7	0.4. 0.3. 0.38	3.79. 2.53. 3.79
15. Haemoglobin	25/05	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1	1.2	6.10	1.1	5.5
	16/06	2	Pre-survey issues. Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.1. 1.1. 1.4	5.5. 5.5. 6.7	0.8. 1.4. 1.2	3.8. 6.4. 5.5

	Date	Testing Error	Root cause	Analyser	APS value	z-score	APS value on the subsequent EQA	z-score on the subsequent EQA
	20/07	2	Pre-survey issues Problem with sample stability	SYSMEX X10-2 AND XN20	1.4. 1.2	6.4. 5.5	1. 1. 1.3	4.5. 4.5. 5.6
	17/08	2	Pre-survey issues. Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1. 1. 1.3	4.5. 4.5. 5.6	0. 0.2. 0.2	0.2. 1.3. 1.3
16. Mean cell volume	28/01 entry 1	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	2.0. 3.0. 1.0	0.9. 0.9. 0.91	0.2. 0.2. 0.1	1.5. 1.5. 0.8
	23/03	2	Pre-survey issues Problem with sample stability	All	92. 91. 94	510. 502. 513	2.3 for all	7.1 for all
	22/04	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	2.3 for all	7.1 for all	2.8. 2.7. 2.9	16.6. 16. 17.3
	25/05	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	2.8. 2.7. 2.9	16.6. 16. 17.3	2.6. 2.5. 2.8	17.2. 16.4. 18
	16/06	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	2.6. 2.5. 2.8	17.2. 16.4. 18	2.7. 2.6. 2.8	19.1. 18.3. 19.9
	20/07	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	2.7. 2.6. 2.8	19.1. 18.3. 19.9	2. 1.9. 1	11.9. 11.1. 11.9
	17/08	2	Pre-survey issues. Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	2. 1.9. 1	11.9. 11.1. 11.9	0.9. 0.9. 0.9	4. 5. 5.

Test parameter	**Date**	**Testing Error**	**Root cause**	**Analyser**	**APS value**	**z-score**	**APS value on the subsequent EQA**	**z-score on the subsequent EQA**
17. Mean corpuscular haemoglobin	16/06	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.1. 1.5. 1.5	6.7. 9.3. 9.5	0.4. 0.7. 0.7	2.7. 4.8. 5
18. Mean cell haemoglobin concentration	22/04	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1.4. -1.5. -1.3	-5.10. -5.70 -4.90	-1.7. -1.6. -1.6	-8.50. -7.70. -8.00
	25/05	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1.7. -1.6. -1.6	-8.50. -7.70 -8.00	-1.6. -1.4. -1.6	-9.20. -7.90. -8.70
	16/06	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1.6. -1.4. -1.6	-9.20. -7.90. -8.70	-1.8. -1.5. -1.6	-9.80. -8.10. -8.80
	20/07	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1.8. -1.5. -1.6	-9.80. -8.10. -8.80	-1.2. -1.0. -1.1	-6.80 -5.40 -5.80
	17/08	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1.2. -1.0. -1.1	-6.80. -5.40. -5.80	-0.8. -0.8. -0.6	-3.40. -3.30. -2.40
19. Red cell distribution width	22/04	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.5. 1.4. 1.4	4.10. 4.00.3.90	-1.7. -1.6. -1.6	-8.50. -7.70. -8.00

	Date	Testing Error	Root cause	Analyser	APS value	z-score	APS value on the subsequent EQA	z-score on the subsequent EQA
	25/05	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	-1.7. -1.6. -1.6	-8.50. -7.70. -8.00	2.1. 2.2. 2	12.50. 12.90. 11.90
	16/06	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	2.1. 2.2. 2	12.50. 12.90. 11.90	1.4. 1.4. 1.4	8.50. 8.50. 8.30
	20/07	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.4. 1.4. 1.4	8.50. 8.50. 8.30	1.0. 1.0. 1	6.00. 5.80. 6.00
	17/08	2	Pre-survey issues Problem with sample stability	SYSMEX XN10-1. XN10-2 AND XN20	1.0. 1.0. 1	6.00. 5.80. 6.00	0.7. 0.9. 0.8	3.70. 4.40. 4.00
20. Platelet count	25/05	2	Pre-survey issues Problem with sample stability	SYSMEX XN20	-1	-5.40	0	0
Key: 1 Transcription error; 2 Pre-survey issues; 3 Sample receipt or handling; 4 Test performance; 5 Data handling EQA provider; 6 Report and interpretation; EQA, External Quality Assurance; APS, analytical performance specification.								

Table 6S. The %CV and %Bias for haematology and coagulation test parameters. 2016 to 2020

Instrument	Test parameter	2017		2018		2019		2020	
		%Bias	%CV	%Bias	%CV	%Bias	%CV	%Bias	%CV
Sysmex XN10-1	FIRST CYCLE FOR THE YEAR								
	white cell count	0.22	1.1	0.07	0.9	0.12	2.3	0.33	3.0
	red cell count	0.04	1.1	0.01	1.0	0.04	1.5	0.02	0.8
	haemoglobin	1.5	0.7	0.7	0.9	0.5	1.4	2.1	2.9
	platelet count	8.3	1.3	6.7	2.9	11.1	4.1	10.5	4.5
	SECOND CYCLE FOR THE YEAR								
	white cell count	0.04	2	0.07	1.5	0.11	1.3	0.26	1.5
	red cell count	0.01	1.3	0.049	2	0.02	0.8	0.015	0.8
	haemoglobin	0.5	1.4	1.3	1	0.4	0.7	2	2.7
	platelet count	14.5	2.3	10.9	2.1	15.6	3.8	17.5	6.2
Sysmex XN10-2	FIRST CYCLE FOR THE YEAR								
	white cell count	0.14	1.8	0.07	1.7	0.04	0.6	0.2	1.3
	red cell count	0.04	0.8	0.022	1.2	0.019	0.9	0.027	1
	haemoglobin	1.1	0.8	0.8	0.9	0.6	0.9	2.4	3.3
	platelet count	1	3.4	4.5	3.2	8.4	4.5	2.4	5.6
	SECOND CYCLE FOR THE YEAR								
	white cell count	0.07	1	0.1	1.3	0.22	1.4	0.21	1.9
	red cell count	0.041	1.1	0.03	1.4	0.058	1	0.063	1.3
	Haemoglobin	0.4	0.9	1.1	1.8	1.3	0.9	2.3	3.7
	Test parameter	**2017**		**2018**		**2019**		**2020**	

		%Bias	**%CV**	**%Bias**	**%CV**	**%Bias**	**%CV**	**%Bias**	**%CV**
	platelet count	4.5	3.5	0.9	3.4	3.5	3.9	16.5	5.4
	Automated reticulocyte count (Absolute)	4.32	2.6	4.22	3.5	3.74	3.1	1.89	4.4
Sysmex XN20	FIRST CYCLE FOR THE YEAR								
	white cell count	0.26	1.4	0.14	1	0.05	0.8	0.19	1.3
	red cell count	0.00	0.5	0.01	1	0.02	1.1	0.03	0.8
	haemoglobin	0.40	0.6	0.40	0.9	0.70	0.9	2.50	3.3
	platelet count	3.60	4	7.30	3.9	12.10	5.7	13.20	5.3
	SECOND CYCLE FOR THE YEAR								
	white cell count	0.20	1.5	0.04	1.9	0.14	1.7	0.04	1.6
	red cell count	0.03	1.3	0.03	1.4	0.02	1	0.01	1.3
	haemoglobin	0.20	0.5	0.80	1.8	0.90	0.8	2.20	3.6
	platelet count	3.60	2.3	5.30	1.8	15.40	4.7	18.80	4.7
	Automated reticulocyte count %	0.13	4.5	0.08	3.2	0.99	51	0.05	6.7
	Automated reticulocyte count (Absolute)	5.77	4.6	0.98	4.1	0.7	6.4	7.46	14.2
Sta-R/Max-1	Coagulation Factor VIII	7.8	6.5	5.1	9.6	10.4	6.4	2.8	12.4
	Coagulation Factor IX	1.2	13.2	3.3	9.4	4.9	6.2	0.6	4.9
	Test parameter	**2017**		**2018**		**2019**		**2020**	

		%Bias	%CV	%Bias	%CV	%Bias	%CV	%Bias	%CV
	Coagulation Factor II	1.8	7.5	4.1	14.8	4.5	6.6	1.9	6.1
	Coagulation Factor V	1.8	6.6	3.3	13.9	2.6	11.6	61.4	7.3
	Coagulation Factor VII	2.5	6	2	13.3	2.4	5.3	2.5	7.7
	Coagulation Factor XI	1	7	1.4	13.9	5	7	1.4	27.4
	Coagulation Factor XII	3.9	7.3	9.7	6.7	7.2	10.4	5.7	1.6
	PT	0.62	4.2	1.03	4.4	0.79	3.1	0.77	4.1
	INR	0.02	2.6	0.06	3.5	0.07	3.4	0.04	3.4
	fibrinogen	0.03	5.5	0.01	5.8	0.09	6.3	0.08	3.2
	aPTT	1.67	2.6	0.26	2.8	1.09	1.7	1.13	3.6
	thrombin time	0.07	1.1	0.14	2.9	0.44	3.2	4.03	27.3
	d-dimer	0.043	7.2	0.021	5.2	0.014	6.3	0.019	7.9
Sta-R/Max-2	Coagulation Factor VIII	0.9	8.7	8.4	5	6.6	8.5	2.2	6.1
	Coagulation Factor IX	7.5	11.5	2.3	6	1.7	12.6	1.1	3.6
	Coagulation Factor II	1.8	3.3	2	4.8	5.6	11.1	1.7	5.8
	Coagulation Factor V	2.2	8.2	1.9	6.4	1.6	11.7	91.8	11.4
	Coagulation Factor VII	6.2	10.1	5	12.6	0.9	4.4	3.4	7.3
	Coagulation Factor X	1.4	1.5	0.8	6.4	0.6	4.3	1.1	2.5
	Test parameter	**2017**		**2018**		**2019**		**2020**	
		%Bias	**%CV**	**%Bias**	**%CV**	**%Bias**	**%CV**	**%Bias**	**%CV**
	Coagulation Factor XI	13.2	11.9	8.6	19.9	4	13.6	1.1	12.5
	Coagulation Factor XII	1.9	3.3	1.2	12.5	2.8	7.8	2.4	4.2
	PT	1.01	6	0.86	2.1	0.87	3.2	1.02	2.8

	INR	0.01	3.3	0.02	3.1	0.06	3.8	0.05	4
	fibrinogen	0.05	6.2	0.01	6.4	0.08	3.9	0.02	4.1
	aPTT	1.61	2.5	0.15	2.9	1.02	2.3	0.75	2.2
	thrombin time	0.53	3.2	0.67	4.7	0.1	3	2.13	2.1
	d-dimer	8.2	0.066	5.2	0.046	7.4	0.073	5.6	0.053
Key: aPTT. Activated partial thromboplastin time; PT, prothrombin time; INR, International Normalised Ratio; %CV, percentage coefficient of variation.									

Appendix 2: Ethics

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Dr NS Mokoka School of Pathology Department of Molecular Medicine and Haematology Medical School University
	E-mail: sophie.mokoka@gmail.com
CC:	Supervisor: Professor E Schapkaitz and Dr S Louw <Elise.Schapkaitz@nhls.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252
	E-mail: Iain.Burns@wits.ac.za
DATE:	2021/09/29
REF:	R14/49
PROTOCOL NO:	**M210713** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*A longitudinal assessment of external quality assurance performance of haematology and coagulation analytes at an academic laboratory*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

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Appendix 3: Plagiarism/turn-it-in report cover page

Turnitin Originality Report

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