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Laboratory Medicine, 2025, **56**, 70–80
https://doi.org/10.1093/labmed/lmae069
Advance access publication 7 August 2024
Science

Laboratory Medicine

External quality assurance experience with Royal College of Pathologists of Australasia Program at an academic hospital in South Africa

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Abstract

Introduction: Laboratories use their performance in external quality assurance (EQA) to establish quality planning strategies and to assess whether testing processes require improvement.

Methods: The EQA performance of the hematology and coagulation test parameters on the Royal College of Pathologists of Australasia EQA program was evaluated over a 4-year cycle at an academic hospital in Johannesburg, South Africa. 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.

Results: The laboratory achieved a mean testing score of 98.7 ± 4.0%. There were 103 (10.7%) unacceptable results. On investigation, root causes included: presurvey issues (83%), transcription errors (9%), random errors (6%), and test performance errors (3%). All test parameters evaluated achieved an acceptable median APS during the study period. The mean *z*-scores, however, were >2 and unacceptable for mean cell hemoglobin concentration and hematocrit. On investigation, this was attributed to significant delay in transport and storage of full blood count samples. White cell count and d-dimer achieved a $\sigma \geq 6$.

Conclusion: EQA participation assisted the laboratory in maintaining a quality system. Close monitoring is necessary for international laboratories to avoid sample delays that can affect result quality.

Key words: external quality assurance; proficiency testing; hematology analytes; coagulation analytes; academic laboratory

Abbreviations: EQA, external quality assurance; APS, analytical quality specification; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; RCPA, Royal College of Pathologists of Australasia; TEa, allowable total error; EFLM; European Federation of Laboratory Medicine; IQC, internal quality control; FBC, full blood count; WCC, white cell count; RCC, red cell count; HB, hemoglobin; HCT, hematocrit; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; RDW, red cell distribution width; MPV, mean platelet volume; DIFF, differential; ESR, erythrocyte sedimentation rate; DRVVT, dilute Russell viper venom test; VWF, von Willebrand factor; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; CLIA, Clinical Laboratory Improvement Amendments

Introduction

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 program 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]

The main purpose of EQA is to monitor and document the quality of preanalytical, analytical, and postanalytical laboratory processes to improve laboratory performance.[1] EQA survey material is sent to participating laboratories at least twice per year. Laboratories analyze 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. The clinical significance of unacceptable EQA results is assessed and, if necessary, affected patient results are also reviewed. 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. Moreover, EQA provides the

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opportunity for monitoring of analytical accuracy with changes in testing platforms and identifies interlaboratory discrepancies. EQA samples can also be used for validation of new methods and instruments in the laboratory.[3]

In South Africa, participation in a recognized EQA scheme is a requirement of the South African National Accreditation System.[2] 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 program in over 80 countries worldwide.[4] The laboratory uses its performance in the RCPA EQA scheme to objectively establish quality planning strategies and to assess whether testing processes require improvement.[5] EQA test performance on the RCPA scheme is determined from analytical performance specification (APS), *z*-scores, and allowable total error (TEa) in accordance with European Federation of Laboratory Medicine (EFLM) specifications.[6,7] 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. The APS, which uses the median and the assigned APS, indicates whether the difference from the target value is acceptable. The APS can be determined in accordance with 1 of the 3 models established at the EFLM Strategic Conference in Milan in 2014.[6] The RCPA scheme recognizes that some models are more suitable for certain measurands. For example, in tests with clinical classifications or decision limits, such as hemoglobin A1c and diabetes mellitus, APS can be determined in accordance with clinical decision applications (Milan model 1). The APS, however, is frequently based on biological variation (Milan model 2), as this model can be applied to most measurands. Finally, the state-of-the-art criteria (Milan model 3) represent the highest APS that is technically achievable.[8] The RCPA scheme also assesses the laboratory performance with a *z*-score, whereby the performance of the laboratory is compared with the results obtained by the participants in the peer group.[4] 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 TEa. This is calculated from several measurements and presented in the end-of-cycle report. Sigma (σ) metric is a quality assurance tool that combines the TEa, bias, and imprecision.[9] The measured σ metric provides guidance for establishing acceptability levels and frequencies of internal quality control (IQC) runs in the clinical laboratory.[10,11]

To date, few studies have evaluated the influence of participation in EQA on ongoing improvement of the laboratory's quality system. The aim of this record review was to describe the EQA performance of hematology and coagulation test analytes at the CMJAH laboratory and the laboratory's response to unacceptable EQA results over the 4-year cycle.

Methods

Study Protocol

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M210713). Data were collected from the RCPA EQA reports for the hematology and coagulation test analytes at the CMJAH laboratory in Johannesburg, South Africa, between December 1, 2016, and December 31, 2020. The CMJAH laboratory receives 6 to 24 EQA samples per hematology and coagulation analyte per year. The EQA material matrix is noncommutable and as such does not behave like a patient sample. EQA sample matrix–related biases may therefore occur, owing to physical and chemical differences in noncommutable samples, as compared with patient samples. The following data according to the data collection sheet were entered from the cycle reports: APS values and *z*-scores per analyzer and analytical methodology. The assigned *z*-scores were available on RCPA reports from 2019. The APS values were calculated according to the equation laboratory result minus peer group mean (Supplemental Table 1). The *z*-score was 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 SD.[6] A *z* greater than or equal to –2.0 or $z \geq 2.0$ were regarded as unacceptable. In addition, the bias and imprecision were collected for available tests from the end-of-cycle report to calculate the TEa according to the equation TEa = bias +1.65 × SD. The calculated TEa was then used to assess the laboratory's performance according to the EFLM biological variation database.[7] The σ metric was subsequently calculated for these tests according to the equation: σ = (TEa—Bias) /CV.[9] The performance values for σ was considered at the following levels: $\sigma \geq 6$, σ 4-6, σ 3-4 and $\sigma < 3$.[9]

For nonconforming EQA results, the laboratory investigation into the root cause of the testing error was recorded. The testing errors were broadly classified as transcription error, presurvey issue, sample receipt/handling, test performance, data handling by EQA provider, and reporting and interpretation.[12] 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

Full blood count (FBC) parameters namely; white cell count (WCC), red cell count (RCC), hemoglobin (HB), hematocrit (HCT), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, and mean platelet volume (MPV); differential (DIFF) parameters, namely, percentage of neutrophils, percentage of lymphocytes, percentage of monocytes, percentage of basophils, and percentage of eosinophils. Automated reticulocyte parameters were measured using each of the laboratory's 3 Sysmex XN9000 hematology analyzers (Roche Diagnostics; referred to as XN10-1, XN10-2, and XN-20). The erythrocyte sedimentation rate (ESR) was measured on the StaRRsed (Mechatronics) analyzer. 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 normalized 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 2 STA-R/Max

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Evolution coagulation analyzer (Diagnostica Stago; referred to as STA-R/Max-1 and STA-R/Max-2). The reagents were supplied by the respective manufacturers and the analyzer were installed at the CMJAH laboratory in 2016.

Data Analysis

Data was captured on an Excel spreadsheet (Microsoft Office 2010) and analyzed using Statistica 13.2 software. Descriptive statistics was applied. Normally distributed continuous data (*z*-scores and APS values) were presented as mean ± SD and variables with non-Gaussian distribution as medians with IQRs. Categorical data were 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 χ^2test or 2-tailed Fisher's exact test where necessary. Subgroup analysis with multiple pairwise comparisons was subsequently performed applying the Bonferroni correction, with a *P* value <.0083 considered statistically significant.

Results

All 18 hematology and 20 coagulation test parameters evaluated achieved an acceptable median APS during the study period. The median *z*-scores for the hematology tests were within acceptable limits, with the exception of the MCHC and HCT (TABLE 1). The median *z*-scores for the HCT on all 3 Sysmex analyzer were, however, above 2 and unacceptable. The unacceptable HCT performance was attributed to a presurvey issue in 2020. The median *z*-scores for the coagulation tests (where available) were all within acceptable limits (TABLE 2).

All test parameters achieved a satisfactory mean testing score of 98.7 ± 4.0% during the study period. A significant decrease in the EQA performance in 2020 was noted for the following parameters: HB, HCT, and calculated parameters MCV, MCH, MCHC, RDW, percentage of monocytes, and automated reticulocyte count (%) on the Sysmex hematology analyzer (TABLE 3). For the coagulation parameters, a significant decrease in the EQA performance was observed in 2020 for coagulation factor IX, thrombin time, and VWF Ristocetin cofactor activity on Sta-R/Max-1 as well as coagulation factor IX on Sta-R/Max-2 (TABLE 4).

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. Presurvey issues accounted for most of the errors (n = 85, 83%) (TABLE 5). The major reason was insufficient sample stability owing to travel restrictions during the COVID-19 pandemic. This resulted in a delay in South African laboratories subscribing to RCPA receiving samples from Australia over 5 cycles in 2020 and was addressed by the EQA scheme with the appointment of a new courier company. The subsequent 4 cycles in 2020 showed an improvement in the red cell parameters with no unacceptable results. The results of the January-December 2021 EQA surveys, which confirmed this ongoing improvement, are presented in Supplemental Table 2. There were 9 (9%) transcription errors. There were also 6 (6%) errors where the source of deviation was unknown, and the root cause could not be determined with investigation. Moreover, none of the errors persisted with subsequent EQA surveys and were not present in preceding EQA submissions. There were 3 (3%) errors related to test performance. (1) The EQA for coagulation factor V was not processed prior to the submission deadline as a result of unavailability of coagulation factor V reagents. This was attributed to coagulation factor V being a low-volume test. On receipt of the reagents, the EQA sample was analyzed and results were within consensus. (2) ESR EQA failure was attributed to the elevated environmental temperature, which affected the instrument performance. Review of the temperature chart at the time of EQA analysis revealed a mean laboratory temperature of 26°C (reference for instrument performance 18°C-25°C) as a result of inconsistent power supply. The power supply issue was resolved with subsequent improved ESR performance. (3) Poor coagulation Factor XI performance was attributed to IQC performance. Review of the Levey Jennings (LJ) control chart at the time of EQA analysis revealed out of range IQC post calibration. The IQC reagent was changed by the supplier from Deficient XI (Diagnostica Stago) to Immunodef XI (Diagnostica Stago) with subsequent improved performance.

The TEa for the test parameters on the end-of-cycle reports was within the EFLM biological goals except for the following parameters: platelet count on all hematology analyzers, coagulation factors V and XII on Sta-R/Max-1 and coagulation factor XI on both coagulation analyzers (TABLE 6 and 7). For platelet counts, this was attributed to a high median %bias (Sysmex XN10-1 11.1 [4.4] and Sysmex XN-20 12.1 [9.9]), which exceeded the EFLM minimal acceptable bias (7.6%). Stabilized blood EQA samples result in a higher platelet count for hematology analyzers with a lower threshold to count platelets. In contrast, the TE for coagulation Factors V, XI, and XII was attributed to a high median imprecision (coagulation factor V on Sta-R/Max-1 SD of 7.4 [1.3]; coagulation factors XI on Sta-R/Max-1 SD of 6.8 [6.5] and Sta-R/Max-2 SD of 9.0 [1.9]; coagulation factor XII on Sta-R/Max-1 SD of 4.2 [1.6]). TABLE 8 shows median σ metric levels and proposed IQC algorithm for the CMJAH laboratory.[9,13] On comparison of the 3 hematology and 2 coagulation analyzers, the analyzer-to-analyzer variability was not significant (*P* >.05).

Discussion

EQA in clinical laboratories was introduced over 6 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 30 years 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 4-year study period, all the hematology and coagulation test parameters evaluated achieved an acceptable median APS. In the RCPA EQA scheme, goals are primarily based on biological variation (Milan model 2). It is, however, difficult to compare performance with other EQA schemes. Although significant measures have been taken to harmonize APS between EQA schemes, differences still exist. This is owing

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TABLE 1. Testing Scores for Hematology Tests on the Royal College of Pathologists of Australasia External Quality Assurance Scheme, 2016-2020

Instrument	Test parameter	*z*-score (median [IQR])	APS value (median [IQR])
Sysmex XN10-1	White cell count	−0.52 [0.39]	−0.01 [0.16]
	Red cell count	−0.07 [0.19]	−0.01 [0.10]
	Hemoglobin	0.55 [2.11]	−0.10 [0.21]
	Hematocrit	2.14 [6.10]*	−0.08 [0.22]
	Mean cell volume	0.51 [2.32]	−0.07 [2.57]
	Mean corpuscular hemoglobin	0.97 [1.16]	0.03 [0.16]
	Mean cell hemoglobin concentration	−1.65 [4.85]*	−0.08 [0.31]
	Red cell distribution width	1.39 [4.49]	−0.25 [0.25]
	Platelet count	−0.83 [0.39]	−0.13 [0.07]
	Mean platelet volume	−0.35 [0.58]	0.03 [0.08]
	%Neutrophil	0.50 [0.92]	0.07 [0.34]
	%Lymphocytes	0.46 [1.14]	−0.10 [0.22]
	%Monocytes	−0.95 [2.78]	0.11 [0.27]
	%Eosinophil	0.26 [0.44]	0.07 [0.04]
	%Basophil	0.03 [0.44]	0.01 [0.04]
Sysmex XN10-2	White cell count	−0.47 [0.27]	−0.06 [0.09]
	Red cell count	−0.15 [0.36]	0.02 [0.08]
	Hemoglobin	1.42 [1.53]	0.01 [0.30]
	Hematocrit	2.46 [5.23]*	−0.01 [0.26]
	Mean cell volume	0.53 [2.23]	−0.03 [2.87]
	Mean corpuscular hemoglobin	1.09 [1.91]	−0.03 [0.21]
	Mean cell hemoglobin concentration	−1.67 [4.18]*	−0.02 [0.34]
	Red cell distribution width	1.38 [4.78]	−0.25 [0.37]
	Platelet count	−0.09 [0.09]	−0.03 [0.07]
	Mean platelet volume	−0.28 [0.22]	−0.01 [0.12]
	%Neutrophil	0.50 [0.92]	0.07 [0.34]
	%Lymphocytes	0.28 [2.21]	0.13 [0.49]
	%Monocytes	−0.59 [2.80]	−0.01 [0.41]
	%Eosinophil	0.08 [0.56]	−0.19 [0.28]
	%Basophil	−0.29 [0.66]	−0.01 [0.05]
	Automated reticulocyte count (%)	0.25 [5.04]	0.10 [0.10]
	Automated reticulocyte count (absolute)	−0.06 [0.33]	0.32 [0.27]
Sysmex XN-20	White cell count	−0.11 [0.45]	0.03 [0.12]
	Red cell count	−0.16 [0.53]	−0.04 [0.08]
	Hemoglobin	0.64 [2.65]	−0.05 [0.18]
	Hematocrit	2.26 [5.04]*	−0.05 [0.20]
	Mean cell volume	0.53 [3.35]	−0.08 [2.86]
	Mean corpuscular hemoglobin	0.77 [2.75]	−0.04 [0.16]
	Mean cell hemoglobin concentration	−1.94 [3.50]*	0.04 [0.28]
	Red cell distribution width	1.25 [4.60]	−0.26 [0.46]
	Platelet count	−0.92 [0.38]	−0.15 [0.07]
	Mean platelet volume	−0.23 [0.21]	−0.03 [0.05]
	%Neutrophil	0.33 [0.98]	0.01 [0.19]
	%Lymphocytes	0.23 [0.15]	0.10 [0.24]
	%Monocytes	−0.91 [1.45]	−0.11 [0.27]
	%Eosinophil	0.33 [0.47]	0.04 [0.14]
	%Basophil	−0.3 [0.56]	0.15 [0.96]
	Automated reticulocyte count (%)	−0.1 [5.71]	−0.04 [0.15]
	Automated reticulocyte count (absolute)	0.09 [0.26]	0.03 [0.11]
StaRRsed	Erythrocyte sedimentation rate	−0.23 [0.29]	0.13 [1.09]

APS, analytical performance specification
*requires trouble shooting/unacceptable.

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TABLE 2. Testing Scores for Coagulation Tests on the Royal College of Pathologists of Australasia External Quality Assurance Scheme, 2016-2020

Instrument	Test parameter	*z*-score (median [IQR])	APS value (median [IQR])
Sta-R/Max-1	Coagulation Factor V	0.37 [0.71]	0.00 [0.20]
	Coagulation Factor VII	0.57 [0.28]	0.14 [0.29]
	Coagulation Factor VIII	0.68 [1.85]	0.05 [0.44]
	Coagulation Factor IX	0.43 [0.55]	0.17 [0.14]
	Coagulation Factor X	0.75 [0.56]	0.07 [0.27]
	Coagulation Factor XI	–0.49 [0.49]	–0.09 [0.22]
	Coagulation Factor XII	–1.02 [0.44]	–0.24 [0.18]
	Coagulation Factor II	–0.53 [0.28]	–0.13 [0.09]
	PT	–0.76 [0.16]	–0.12 [0.05]
	INR	–0.5 [0.30]	–0.01 [0.11]
	fibrinogen	–0.88 [0.21]	–0.10 [0.12]
	aPTT	–0.08 [0.75]	–0.04 [0.07]
	Thrombin time	0.14 [0.59]	0.04 [0.04]
	D-Dimer	0.48 [0.32]	0.06 [0.05]
	Lupus sensitive PTT screen	—	–0.04 [0.11]
	Lupus sensitive PTT screen ratio	—	–0.16 [0.24]
	DRVVT screen	—	–0.03 [0.05]
	DRVVT screen ratio	—	–0.20 [0.22]
	VWF antigen	—	0.15 [0.20]
	VWF Ristocetin cofactor	—	0.32 [0.66]
Sta-R/Max-2	Coagulation Factor V	0.88 [1.37]	0.14 [0.15]
	Coagulation Factor VII	0.64 [0.72]	0.20 [0.39]
	Coagulation Factor VIII	0.45 [1.30]	0.16 [0.36]
	Coagulation Factor IX	–0.1 [0.55]	–0.02 [0.15]
	Coagulation Factor X	0.52 [0.22]	0.13 [0.16]
	Coagulation Factor XI	0.42 [0.42]	0.3 [0.36]
	Coagulation Factor XII	–0.32 [0.29]	–0.07 [0.11]
	Coagulation Factor II	–0.47 [0.26]	–0.12 [0.12]
	PT	–0.83 [0.26]	–0.16 [0.07]
	INR	–0.42 [0.24]	–0.08 [0.10]
	fibrinogen	–0.48 [0.28]	–0.13 [0.12]
	aPTT	–0.30 [0.44]	–0.04 [0.06]
	Thrombin time	0.32 [0.47]	0.03 [0.1]
	D-dimer	0.70 [0.25]	0.08 [0.05]
	Lupus sensitive PTT screen	—	0.06 [0.10]
	Lupus sensitive PTT screen ratio	—	–0.08 [0.15]
	DRVVT screen	—	0.06 [0.15]
	DRVVT screen ratio	—	–0.04 [0.12]
	VWF antigen	—	0.06 [015]
	VWF Ristocetin cofactor	—	0.06 [0.20]

APS, analytical performance specification; aPTT, activated partial thromboplastin time; DRVVT, dilute Russell viper venom time; INR, international normalized ratio; PT, prothrombin time; VWF, von Willebrand factor; —, not available.

to the wide variability in the different Milan models used for establishing APS as well as factors such as the procedures used to establish target value, data set, assessment of total error, and rationale for the selection of the APS.[8,14]

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 standardized 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 4-year study period, the mean *z*-scores were >2 and unacceptable for the FBC parameters MCHC and HCT. On investigation, this

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TABLE 3. Comparison of Overall Performance of Hematology Tests on the Royal College of Pathologists of Australasia External Quality Assurance, 2016 to 2020

Analyser	Test parameter	No. of cycles	EQA performance (%)				
			2017	2018	2019	2020	Median [IQR]
Sysmex XN10-1	White cell count	48	100	100	100	100	100 [0]
	Red cell count	48	100	100	100	100	100 [0]
	Hemoglobin	48	100	100	100	81[a]	100 [10]
	Hematocrit	48	100	100	100	63[a]	100 [19]
	Mean cell volume	48	100	100	100	45[a]	100 [28]
	Mean corpuscular hemoglobin	48	100	100	100	77[a]	100 [12]
	Mean cell hemoglobin concentration	48	100	100	100	59[a]	100 [21]
	Red cell distribution width	48	100	100	100	63[a]	100 [19]
	Platelet count	48	100	100	100	100	100 [0]
	Mean platelet volume	48	100	100	100	100	100 [0]
	%Neutrophil	16	100	75[a]	100	100	100 [13]
	%Lymphocytes	16	100	75[a]	100	100	100 [13]
	%Monocytes	16	100	100	100	63[a]	100 [19]
	%Eosinophil	16	100	100	100	100	100 [0]
	%Basophil	16	100	100	100	100	100 [0]
Sysmex XN10-2	White cell count	48	100	100	100	100	100 [0]
	Red cell count	48	100	100	100	100	100 [0]
	Hemoglobin	48	100	100	100	72[a]	100 [14]
	Hematocrit	48	100	100	100	63[a]	100 [19]
	Mean cell volume	48	100	100	100	45[a]	100 [28]
	Mean corpuscular hemoglobin	48	100	100	100	77[a]	100 [12]
	Mean cell hemoglobin concentration	48	100	100	100	59[a]	100 [21]
	Red cell distribution width	48	100	100	100	63[a]	100 [19]
	Platelet count	48	100	100	100	100	100 [0]
	Mean platelet volume	48	100	100	100	100	100 [0]
	%Neutrophil	16	100	75[a]	100	100	100 [13]
	%Lymphocytes	16	88	75[a]	100	100	88 [13]
	%Monocytes	16	88[a]	100	100	63[a]	88 [19]
	%Eosinophil	16	100	100	100	100	100 [0]
	%Basophil	16	100	100	100	100	100 [0]
	Automated reticulocyte count (absolute)	16	100	100	100	88[a]	100 [6]
	Automated reticulocyte count (%)	16	100	100	100	100	100 [0]
Sysmex XN-20	White cell count	48	100	100	100	100	100 [0]
	Red cell count	48	100	100	100	100	100 [0]
	Hemoglobin	48	100	100	100	77[a]	100 [12]
	Hematocrit	48	100	100	100	63[a]	100 [19]
	Mean cell volume	48	100	100	100	45[a]	100 [28]
	Mean corpuscular hemoglobin	48	100	100	100	77[a]	100 [12]
	Mean cell hemoglobin concentration	48	100	100	100	81[a]	100 [10]
	Red cell distribution width	48	100	100	100	63[a]	100 [19]
	Platelet count	48	100	100	100	91[a]	100 [5]
	Mean platelet volume	48	96	100	100	91[a]	96 [5]
	%Neutrophil	16	100	75[a]	100	100	100 [13]
	%Lymphocytes	16	88	75[a]	100	100	88 [13]
	%Monocytes	16	88[a]	100	100	63[a]	88 [19]
	%Eosinophil	16	100	100	100	100	100 [0]
	%Basophil	16	100	75[a]	100	100	100 [13]
	Automated reticulocyte count (absolute)	16	100	100	88[a]	100	100 [6]
	Automated reticulocyte count (%)	16	100	100	100	88[a]	100 [6]
StaRRsed	Erythrocyte sedimentation rate	8	100	100	75[a]	88	88 [13]

EQA, external quality assurance.
[a]$P < .0083$.

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TABLE 4. Comparison of Overall Performance of Coagulation Tests on the Royal College of Pathologists of Australasia External Quality Assurance, 2016 to 2020

Analyzer	Test parameter	No. of cycles	EQA performance (%)				
			2017	2018	2019	2020	Median [IQR]
Sta-R/Max-1	Coagulation Factor V	12	100	100	92[a]	83	92 [9]
	Coagulation Factor VII	12	100	100	100	100	100 [0]
	Coagulation Factor VIII	24	100	100	83[a]	100	100 [9]
	Coagulation Factor IX	24	100	100	100	83[a]	100 [9]
	Coagulation Factor X	12	100	100	100	100	100 [0]
	Coagulation Factor XI	12	100	100	100	100	100 [0]
	Coagulation Factor XII	12	100	100	100	100	100 [0]
	Coagulation Factor II	12	100	100	100	100	100 [0]
	PT	32	100	100	100	100	100 [0]
	INR	32	100	100	100	100	100 [0]
	fibrinogen	32	100	100	100	100	100 [0]
	aPTT	32	100	100	100	100	100 [0]
	Thrombin time	32	100	100	100	88[a]	100 [6]
	D-dimer	16	100	100	100	100	100 [0]
	Lupus sensitive PTT screen	12	100	100	100	100	100 [0]
	Lupus sensitive PTT screen ratio	12	100	100	100	100	100 [0]
	DRVVT screen	12	100	100	100	100	100 [0]
	DRVVT screen ratio	12	100	100	100	100	100 [0]
	VWF antigen	8	100	100	100	100	100 [0]
	VWF Ristocetin cofactor activity	8	-	75[a]	100	75[a]	75 [13]
Sta-R/Max-2	Coagulation Factor V	12	100	100	92[a]	100	100 [2]
	Coagulation Factor VII	12	92	83[a]	100	100	96 [2]
	Coagulation Factor VIII	24	100	100	83[a]	100	100 [9]
	Coagulation Factor IX	24	83[a]	100	100	83[a]	92 [17]
	Coagulation Factor X	12	100	100	100	100	100 [0]
	Coagulation Factor XI	12	83[a]	100	100	100	100 [4]
	Coagulation Factor XII	12	100	100	100	100	100 [0]
	Coagulation Factor II	12	100	100	100	100	100 [0]
	PT	32	100	100	100	100	100 [0]
	INR	32	100	100	100	100	100 [0]
	fibrinogen	32	100	100	100	100	100 [0]
	aPTT	32	100	100	100	100	100 [0]
	Thrombin time	32	88[a]	100	94	88	91 [8]
	D-Dimer	16	100	100	100	100	100 [0]
	Lupus sensitive PTT screen	12	100	100	100	100	100 [0]
	Lupus sensitive PTT screen ratio	12	100	88[a]	100	100	100 [3]
	DRVVT screen	12	100	100	100	100	100 [0]
	DRVVT screen ratio	12	100	100	100	100	100 [0]
	VWF antigen	8	100	100	100	100	100 [0]
	VWF Ristocetin cofactor activity	8	-	75[a]	100	100	100 [13]

aPTT, activated partial thromboplastin time; DRVVT, dilute Russell viper venom time; EQA, external quality assurance; INR, international normalized ratio; PT, prothrombin time; VWF, von Willebrand factor
[a]$P < .0083$.

was attributed to a presurvey issue. EQA results may be influenced by the deterioration of specimens during transportation and storage before testing.

The COVID-19 pandemic resulted in a widespread lockdown and caused a significant delay in transport and storage of FBC samples during this period. It is recommended that traditional FBC parameters in clinical specimens are analyzed 24 hours after sample collection when stored at room temperature. Although FBC parameters WCC, HCT, MCV, MCHC, and platelet count have a stability of 7 days when stored at 4°C to 8°C, the same does not apply to EQA samples.[15,16] The RCPA EQA scheme distributes stabilized whole blood samples that are partially fixated

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TABLE 5. Reasons for Unacceptable EQA Results, 2016 to 2020

Testing error	Number of occurrences	Observation	Comment
Transcription error	9	Mixing-up test results Report results with wrong units	Review process of test result recording / reporting
Presurvey issues	85	Sample instability	Review transportation mode with the EQA provider during COVID-19 lockdown resulting in insufficient sample stability. New courier company established
Test performance	3	Reagent shortage Poor performance of environmental temperature control Poor performance of internal quality control	Review reagent usage and orders Review internal quality control and temperature charts at the time EQA was measured
Report and interpretation	6	Source for the deviation is unknown	The random error did not persist with future EQA surveys

EQA, external quality assurance

TABLE 6. Calculated Allowable Total Error for Hematology Tests on the Royal College of Pathologists of Australasia External Quality Assurance, 2016 to 2020

Parameter	Sysmex XN10-1 median TEa	Sysmex XN10-2 median TEa	Sysmex XN-20 median TEa	EFLM TEa
White cell count	0.5 [0.2]	0.4 [0.2]	0.4 [0.1]	20.7
Red cell count	0.1 [0.1]	0.1 [0.0]	0.1 [0.0]	5.8
Hemoglobin	3.0 [2.2]	3.0 [4.1]	2.4 [4.6]	5.8
Platelet count	26.0 [6.7]	19.0 [7.2]	32.3 [15.6]	17.0
Automated reticulocyte count (%)	-	0.3 [1.0]	0.4 [1.2]	22.8
Automated reticulocyte count (absolute)	-	9.9 [0.6]	13.5 [8.2]	22.8

EFLM, European Federation of Clinical Chemistry and laboratory medicine, TEa, allowable total error.

TABLE 7. Calculated Allowable Total Error for Coagulation Tests on the Royal College of Pathologists of Australasia External Quality Assurance, 2016 to 2020

Parameter	Sta-R/Max-1 median TEa	Sta-R/Max-2 median TEa	EFLM TEa
Coagulation Factor V	15.2 [17.5]	11.7 [31.1]	13.8
Coagulation Factor VII	8.8 [2.7]	13.3 [8.2]	17.5
Coagulation Factor VIII	16.9 [3.6]	12.3 [5.4]	19.8
Coagulation Factor IX	11.5 [3.0]	11.8 [9.4]	15.2
Coagulation Factor X	5.3 [2.7]	3.7 [1.6]	12.1
Coagulation Factor XI	14.2 [8.3]	23.4 [11.7]	11.0
Coagulation Factor XII	13.7 [7.4]	9.1 [6.4]	11.0
Coagulation Factor II	8.8 [3.8]	6.3 [2.5]	11.4
PT	2.6 [0.3]	2.3 [0.6]	5.4
INR	0.2 [0.0]	0.1 [0.1]	5.1
Fibrinogen	0.2 [0.0]	0.2 [0.0]	20.1
aPTT	3.4 [1.2]	3.0 [0.5]	6.4
d-dimer	0.1 [0.0]	0.1 [0.0]	47.5

aPTT, activated partial thromboplastin time; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine, INR, international normalized ratio; PT, prothrombin time; TEa, allowable total error

with aldehydes to increase the stability of the FBC parameters as per the World Health Organization guideline recommendations for EQA.[17] This affords EQA samples an increased stability of several weeks at temperatures between 25°C and 37°C. 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.[18,19] It is therefore necessary for international laboratories to monitor shipping dates to be alerted to delays of samples that 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 ~99% over the 4-year study period. Similarly, other studies have demonstrated that EQA performance is related to the length of laboratory participation in an EQA scheme.[20,21] In these studies, experience with sample handling/receipt of EQA samples and reporting of interpretive EQA results in particular contributed to the decline in the rate of unacceptable results. Nonetheless,

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TABLE 8. Proposed Sigma Metric Algorithm[9,13]

Median σ 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 Hemoglobin	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 V Coagulation Factor VII Coagulation Factor VIII Coagulation Factor IX Coagulation Factor X Coagulation Factor XI Coagulation Factor XII Coagulation Factor II PT INR aPTT	-	-	Stop and investigate

aPTT, activated partial thromboplastin time; INR, international normalized ratio; IQC, internal quality control; PT, prothrombin time

despite the experience gained with the RCPA EQA scheme's procedures at the CMJAH laboratory, presurvey 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 retraining and ongoing monitoring. Although EQA contributed to improvements in the laboratory quality system, the limitations of EQA prevent EQA monitoring from being regarded as a primary tool for laboratory improvement. This can be attributed to factors such as the inability of EQA to monitor all aspects of the testing process; the differences between noncommutable EQA samples and clinical specimens, the use of mean participant results to set target values, and the variability in EQA assessment criteria

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 that 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 that were out with consensus. These results compare favorably with laboratories from developed countries with well-established quality control systems.[22,23] In 2012, the College of American Pathologists surveyed its participating laboratories in Africa.[19] 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.[21]

More recently, Six Sigma metrics, a gold standard quality management system tool, has been extended to laboratory medicine to assess the quality of the overall testing processes. Although laboratories that monitor IQC with Six Sigma metrics have reported a reduction in the error rate, experience with Six Sigma metrics in hematology laboratories is limited.[11,24] The majority of laboratories apply traditional "2SD" warning rules and "3SD" rejection rules. Routine use of these IQC limits is associated with a false rejection rate of >5%.[13] 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.[9] In this study, σ metric was applied to assess the performance of the individual laboratory tests per analyzer. The mean σ value was ≥6 for only 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 mean σ value was <3 for platelet count, aPTT, PT, INR, and coagulation factors. Similarly, Shaikh et al[11] reported a σ metric value of <3 for the platelet count and PT parameter. A TEa of 13.4% and 5.4%, respectively, was applied to calculate the σ metric value. In contrast, El-Neaney et al[24] reported a mean σ metric of ≥ 6 for the PT parameter on the Siemens coagulation analyzer (Siemens Healthineers). This was achieved using the wider Clinical Laboratory Improvement Amendments (CLIA) TEa of 15% for the calculation of σ metric value. The biologic goals from the EFLM database that were applied in this study are known to be more stringent than the Ricos and CLIA criteria.[7] These narrow TEa goals make it a challenge to achieve an acceptable σ score. Bias and imprecision may be the preferred monitoring method for these parameters in hematology laboratories.

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This study also illustrated the measured σ metric as an efficient tool to compare IQC across multiple analyzers. The 3 hematology analyzers showed comparable sigma performances for FBC, DIFF, and reticulocytes, although not all parameters met the minimum performance goal of $\sigma > 3$. Similarly, comparable σ performances between the 2 coagulation analyzers were observed.

Several limitations of this study warrant consideration. First, RCPA started reporting *z*-scores from 2019. Therefore, this parameter could not be analyzed and assessed over the 4-year study period. *Z*-scores were also not provided for the following parameters: lupus sensitive partial thromboplastin time screen and screen ratio, DRVVT screen and screen ratio, VWF antigen, and ristocetin cofactor activity. Second, biological variation data for ESR as well as coagulation thrombin time, lupus sensitive partial thromboplastin time screen and screen ratio, and DRVVT screen and screen ratio are not available on EFLM. The published data for the other coagulation parameters is also based on small studies of a short duration and should be interpreted with caution.[25,26] A future longitudinal study is required to determine reliable biological variation data for coagulation parameters.

In conclusion, CMJAH laboratory's participation in the RCPA EQA scheme facilitated continuous monitoring of the testing process. During the study period, the majority of the unacceptable results were as a result of presurvey issues related to sample instability. Errors related to sample receipt/handling, test performance, data handling by the EQA provider, and reporting and interpretation were not increased. EQA participation assisted the laboratory in maintaining a quality system during the 4-year study period. Moreover, Six Sigma metrics may be a beneficial quality management system tool for hematology laboratories with multiple analyzers.

Acknowledgments

Author contributions: N.S.M.: study design, manuscript writing, data entry; and data analysis; E.S.: study design, data analysis, critical review; S.L: study design, data analysis, critical review

Conflict of Interest Disclosure

The authors have nothing to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Laboratory Medicine* online.

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