Brief Report

Ongoing improvements in laboratory performance of coagulation factors VIII and IX: recent experience from the RCPAQAP

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Abstract: Coagulation factors VIII and IX are the coagulation factors most regularly tested by haemostasis laboratories, in part because Haemophilia A (FVIII deficiency) and Haemophilia B (FIX deficiency) represent the most common bleeding disorders, and in part because of their known associations with bleeding risk. The Royal College of Pathologists Australasia Quality Assurance Programs (RCPAQAP) is an international QAP with over 100 laboratories enrolled in the Coagulation Factors VIII and IX Program. The aim of the work presented here is to evaluate the assessment criteria for FVIII and FIX over a six-year period (2013–2018) and identify areas of benefit and weakness, in part resulting from a recent (2016) change in criteria (from assessment against factor deficient plasma reagent to plasma calibrator, as this was felt to be more relevant for determination of factor level). We identified an ongoing improvement [reduction in numbers of laboratories outside the RCPAQAP Analytical Performance Specifications (APS)] for both FVIII and FIX over this period of change in assessment criteria. FVIII outliers almost halved from 43 to 23 laboratories, and FIX outliers reduced by over 60% from 36 to 14 laboratories. It is hypothesised that the change in assessment criteria contributed to this improvement in Coagulation Factors program performance by laboratories, although other elements may have also contributed.

Keywords: Coagulation factor VIII/FIX; quality assurance program; assessment

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Introduction

Coagulation factors VIII and IX are the coagulation factors most regularly tested by haemostasis laboratories, in part because Haemophilia A (FVIII deficiency) and Haemophilia B (FIX deficiency) represent the most common bleeding disorders, and in part because of their known associations with bleeding risk. One-stage assays are widely used to measure these coagulation factors (1) with chromogenic assays less widely used (2). There are several clinical reasons to determining FVIII and FIX levels, including to identify factor deficiencies (either due to haemophilia or other reasons such as trauma), as well as for monitoring factor replacement therapies at times of interventions or in response to bleeding events, and/or apparent resistance to factor replacement that may arise in inhibitor development (1-3). Assurance of the quality of laboratory testing is essential in ensuring the performance of the test and hence the results produced (4,5). Internal quality control processes can be readily applied by provision of commercial plasma controls and is primarily a measure of reproducibility (precision) (6). External quality assurance is a supplementary process, allowing for peer group comparison of each analyte with other laboratories, and thus is primarily a measure of accuracy (6).

The Royal College of Pathologists Australasia Quality Assurance Programs (RCPAQAP) is an international QAP with over 1000 worldwide participants, including 100 laboratories enrolled in the Coagulation Factors VIII and

IX Program (7). To assess the improvements in laboratory performance in the Coagulation factors program, survey data for FVIII and FIX testing over a six-year period (2013 to 2018) was analysed. Importantly, the assessment criteria during this period were changed from versus factor deficient plasma reagent to versus plasma calibrator. To ensure no adverse outcome of the change, a benefits and weaknesses analysis of this change was performed, and data was evaluated to determine whether the change had a positive impact on Coagulation Factors survey performance by laboratories.

Methods

Each of the RCPAQAP programs has an assessment criterion based upon which laboratories are assessed for their performance. For FVIII and FIX results submitted by participants from 2013 to 2015, the assessment criterion was 'factor deficient plasma reagent'. From the period 2016 to 2018, FVIII and FIX results were assessed in regards to the plasma 'Calibrator' used by the laboratory for that test, since upon review by the expert panel of RCPAQAP Haemostasis Advisory Committee, this comparison was considered more relevant for factor assays, given the calibration process involved.

The acceptable range of results for RCPAQAP participants is determined by the Analytical Performance Specifications (APS), which is also set by the same expert panel of RCPAQAP Haemostasis advisory committee members. The APS consists of lower and upper limits. For both FVIII and FIX, the lower limit is set at "+ or –3 U/dL" (absolute units) when the factor level is ≤10 U/dL, and the upper limit is set at "+ or –25%" (relative units) when the factor level is >10 U/dL. Results outside these lower and upper limits are therefore flagged as being outside the APS on participant survey reports. Such assessments permit laboratories to review their performance against other ('peer') laboratories using the same (or even different) methods. In addition to survey reports after each run of survey, an overall review of laboratory performance is also provided to participants at the end of each calendar year.

For this study, FVIII and FIX data on participant APS as collected between 2013 to 2018 was reviewed, with 2013–2015 reflecting assessment against 'factor deficient plasma reagent' and data from 2016–2018 reflecting assessment against plasma 'calibrator'. Six surveys were distributed in each year, with each comprising two samples, for a total of 12 samples/year. Samples reflect a full range of analyte concentrations (i.e., ranging from deficient to normal). Specific participant assessment based on reagent/calibrator is performed when there are ten or more users in a reagent/calibrator group. Here, the laboratory result is then compared against the median of all users of the same reagent/calibrator. For reagent/calibrator groups with less than ten users, assessment is based on the overall median.

The coefficients of variation (CVs) for each group were also compared to assess overall performance. To compare the CV's more succinctly, data for samples containing the same approximate level of factor, as distributed to participants in different surveys, have been grouped together. In each year, five different levels of plasma with different factor levels are distributed to participants. For the purpose of this evaluation, the groups have been identified as Level A, B, C, D and E. As each of these five levels have varying amounts of factors VIII and IX, it allows for comparison of performance in each of these level groups.

In brief, performance of laboratories over this six-year period has been analysed, in part to determine if the change in assessment criteria has had a positive impact for laboratories by comparing the number of outliers by each assessment criteria for each analyte, FVIII and FIX. In addition, performance of each reagent and calibrator group has been considered to provide evidence for or against the change in assessment criteria.

Results

There were a total 72 data sets for the six-year (2013–2018) period, which overall comprised 10006 participant-reported FVIII results and 8888 FIX results. As noted in methods, FVIII and FIX results were assessed based on the factor deficient plasma reagent used by the laboratory as the assessment criteria between 2013 and 2015, but against plasma calibrator between 2016 and 2018. *Figures 1-4* show the factor deficient plasma reagents and plasma calibrators used for each of FVIII and FIX, and the maximum number of users in each group for each year of assessment.

The data presented in *Figure 1* identifies that the number of users for each of the factor deficient reagents used has not shown significant variation through the years 2013 to 2015, with the exception of IL Factor VIII deficient plasma, which has had an increase in users. Similarly, *Figure 2* identifies that the number of users of FIX reagents has not shown significant variation, with the exception of IL Factor IX deficient plasma. *Figures 3* and *4* shows that SM Standard Human Plasma calibrator had an increase in the number of users for FVIII and FIX, DS Unicalibrator has a decrease in

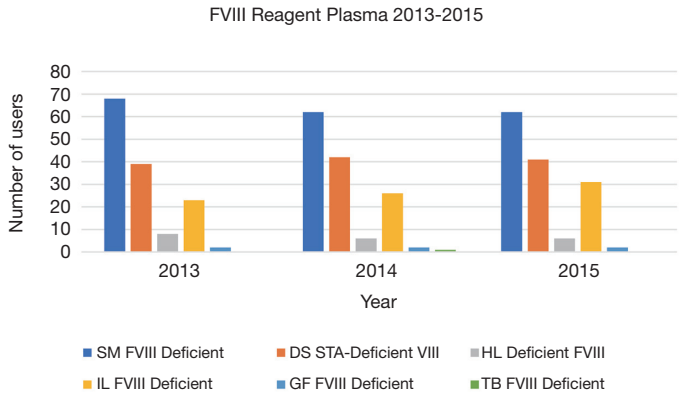

Figure 1 Factor VIII reagent plasma used by participants of the RCPAQAP Coagulation Factors program between 2013 and 2015. The number of users presented here are the maximum number of users across the survey runs in each of the reagent groups for each year. FVIII, Factor VIII; SM FVIII Deficient, Siemens Factor VIII Deficient plasma; DS STA-Deficient VIII, STA-Deficient VIII plasma; HL Deficient FVIII, Helena Deficient Factor VIII plasma; IL FVIII Deficient, Instrumentation Laboratory Factor VIII Deficient plasma; GF FVIII Deficient, Griffol Factor VIII Deficient plasma; TB FVIII Deficient, Trinity Biotech Factor VIII Deficient plasma.

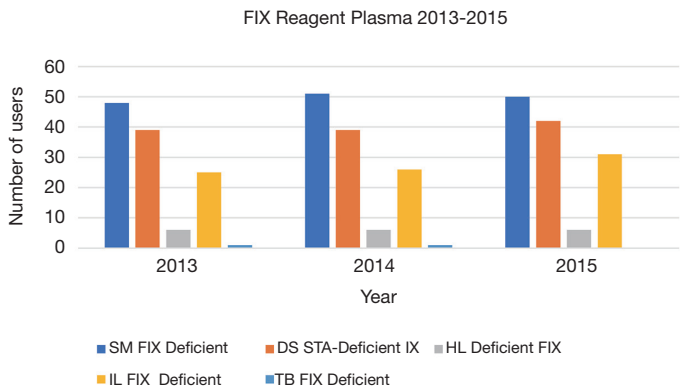

Figure 2 Factor IX reagents used by participants of the RCPAQAP Coagulation Factors program between 2013 and 2015. The number of users presented here are the maximum number of users across the survey runs in each of the reagent groups for each year. FIX, Factor IX; SM FIX Deficient, Siemens Factor IX Deficient plasma; DS STA-Deficient IX, STA – Deficient Factor IX plasma; HL Deficient FIX, Helena Deficient Factor IX plasma; IL FIX Deficient, Instrumentation Laboratory Factor IX Deficient plasma; TB FIX Deficient, Trinity Biotech Factor VIII Deficient plasma.

users for FVIII and FIX, while IL Calibration plasma users has remained reasonably consistent.

A summary of the number of responses received from participants is shown in *Figure 5* and *Table 1* for both assessment criteria with separation of factor deficient plasma reagent/plasma calibrator for where there are more than ten users. The numbers of outliers/acceptable results are also shown in *Figure 5* and *Table 1*.

Figure 6 shows the trends in the percentage of outliers in each FVIII reagent group between 2013 and 2015. The percentage of background outliers generally, when no filter was applied was <3% between 2013 to 2018. There were minor variations to percentage outliers in these years; however, no identifiable consistent trend was evident. In contrast, when the change to assessment criteria was made from reagent to calibrator, there was a more relevant identifiable trend. Percentage outliers (with reagent filter) between 2013 to 2015 was wider, ranging from 0.4–3.9%, whereas percentage outliers (calibrator filter) between 2016 to 2018 ranged from 0–2.5%.

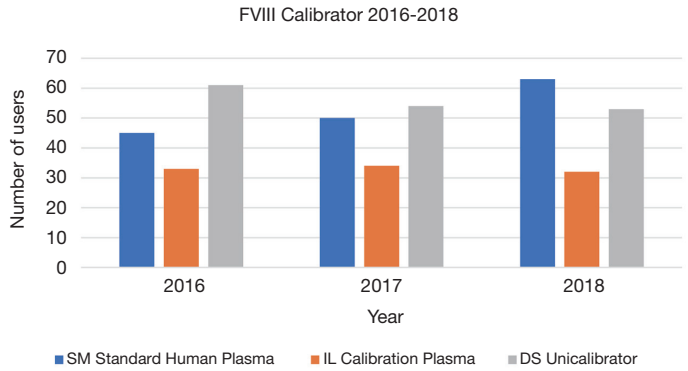

Figure 3 Factor VIII Calibrators used by participants of the RCPAQAP Coagulation Factors program between 2016 and 2018. The number of users presented here are the maximum number of users across the survey runs in each of the calibrator groups for each year. FVIII, Factor VIII; SM Standard Human Plasma, Siemens/Dade Standard Human Plasma; IL Calibration Plasma, Instrumentation Laboratory Calibration Plasma; DS Unicalibrator, Diagnostica STAGO Unicalibrator.

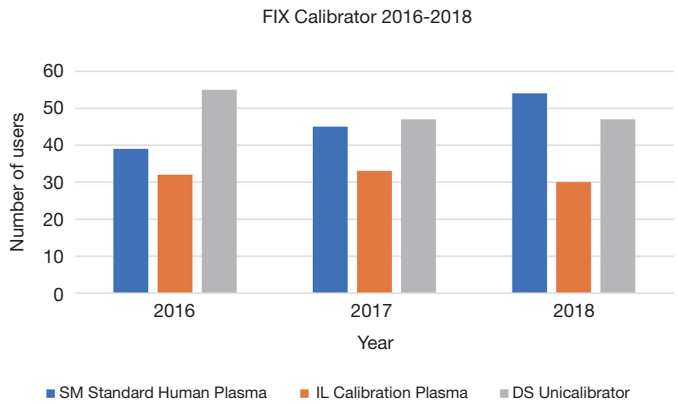

Figure 4 Factor IX Calibrators used by participants of the RCPAQAP Coagulation Factors program between 2016 and 2018. The number of users presented here are the maximum number of users across the survey runs in each of the calibrator groups for each year. Abbreviations: FIX, Factor IX; SM Standard Human Plasma, Siemens/Dade Standard Human Plasma; IL Calibration Plasma, Instrumentation Laboratory Calibration Plasma; DS Unicalibrator, Diagnostica STAGO Unicalibrator.

Figure 7 shows the trends in percentage of outliers in FIX results with assessment based on reagent and calibrator. Similar to FVIII, the percentage of background outliers generally, when no filter was applied was <3% between 2013 to 2018. When assessment was changed from reagent to calibrator there was a more applicable trend. Percentage outliers (with reagent filter) between 2013 to 2015 were wider, ranging from 0.9–3.0%, whereas percentage outliers (calibrator filter) between 2016 to 2018 ranged from 0.3–1.7%.

From *Figures 6* and 7, the overall reduction in the number of outliers for FVIII and FIX results reported by participants from 2013 to 2018 can also be seen. This seems may reflect a year by year improvement, but more importantly the percentage of outliers is higher for both FVIII and FIX (*Figures 6*,7) when assessment was against reagent, than when assessment was against calibrator. There were 43 laboratory results marked as outliers in 2013 when the assessment criteria was using reagent filter. By 2018, when assessment criteria were changed to using calibrator filter, the number of outliers had reduced by nearly 50% to 23. Similarly, for FIX, there were 36 laboratory results identified as outliers in 2013, which reduced by over 60% to 14 laboratories by 2018.

Comparative CVs for data returned for different years is

2013—FVIII	No filter	Reagent filter	SM factor VIII deficient plasma	DS STA-deficient VIII	IL FVIII deficient plasma
Total results received	1,672	1,519	796	447	276
Accepted results	1,629	1,494	780	440	274
Outliers	43	25	16	7	2
2013—FIX	**No filter**	**Reagent filter**	**SM factor IX deficient plasma**	**DS STA-deficient IX**	**IL factor IX deficient plasma**
Total results received	1,430	1,320	576	448	296
Accepted results	1,394	1,295	568	440	287
Outliers	36	25	8	8	9
2014—FVIII	**No filter**	**Reagent filter**	**SM factor VIII deficient plasma**	**DS STA-deficient VIII**	**IL FVIII deficient plasma**
Total results received	1,652	1,541	746	484	311
Accepted results	1,621	1,506	725	482	299
Outliers	31	35	21	2	12
2014—FIX	**No filter**	**Reagent filter**	**SM factor IX deficient plasma**	**DS STA-deficient IX**	**IL factor IX deficient plasma**
Total results received	1,447	1,363	592	467	304
Accepted results	1,421	1,343	582	461	300
Outliers	26	20	10	6	4
2015—FVIII	**No filter**	**Reagent filter**	**SM factor VIII deficient plasma**	**DS STA-deficient VIII**	**IL FVIII deficient plasma**
Total results received	1,649	1,553	724	491	338
Accepted results	1,619	1,524	715	475	334
Outliers	30	29	9	16	4
2015—FIX	**No filter**	**Reagent filter**	**SM factor IX deficient plasma**	**DS STA-deficient IX**	**IL factor IX deficient plasma**
Total results received	1,467	1,393	574	483	336
Accepted results	1,443	1,371	568	470	333
Outliers	24	22	6	13	3

Figure 5 Summary of results from 2013 to 2015 for FVIII and FIX reagent groups with more than 10 users. 'No filter' indicates all results reported to RCPAQAP. 'Reagent filter' indicates all results reported to RCPAQAP as ascribable to a particular reagent. 'Accepted results' indicates those results within the Analytical Performance Specifications (APS). 'Outliers' indicates results outside the APS. Abbreviations: FVIII, Factor FVIII; FIX, Factor IX; SM FVIII Deficient, Siemens Factor VIII Deficient plasma; DS STA-Deficient VIII, STA – Deficient VIII plasma; IL FVIII Deficient, Instrumentation Laboratory Factor VIII Deficient plasma; SM FIX Deficient, Siemens Factor IX Deficient plasma; DS STA-Deficient IX, STA-Deficient Factor IX plasma; IL FIX Deficient, Instrumentation Laboratory Factor IX Deficient plasma.

shown in *Tables 2* and *3*. This data shows a clear reduction in the periods representing comparison against 'reagent' to against 'calibrator'.

These findings indicate that the performance of participants in the RCPAQAP coagulation factors programs has improved over the years as well providing support to the hypothesis that the change in assessment criteria from reagent to calibrator was at least partially responsible for some of this improvement. Reduction in the number of participants flagged as outliers may also be an indication of improvements in participating laboratories assay performance.

Discussion

Measurement of coagulation Factors VIII and IX is important to assess bleeding and also potentially thrombosis risk (1-3,8). The RCPAQAP coagulation Factors VIII and IX program is designed to provide an opportunity to

Table 1 Summary of results from 2016 to 2018 for FVIII and FIX calibrator groups with more than 10 users

Year and factor	No filter	Calibrator filter	SM standard human plasma	IL calibration plasma	DS Unicalibrator
2016—FVIII					
Total results received	1,646	1,620	528	378	714
Accepted results	1,620	1,599	525	378	696
Outliers	26	21	3	0	18
2016—FIX					
Total results received	1,500	1,474	458	366	650
Accepted results	1,483	1,458	454	365	639
Outliers	17	16	4	1	11
2017—FVIII					
Total results received	1,622	1,602	584	384	634
Accepted results	1,599	1,584	576	382	626
Outliers	23	18	8	2	8
2017—FIX					
Total results received	1,466	1,446	520	372	554
Accepted results	1,452	1,435	515	371	549
Outliers	14	11	5	1	5
2018—FVIII					
Total results received	1,765	1,745	731	378	636
Accepted results	1,742	1,722	724	373	625
Outliers	23	23	7	5	11
2018—FIX					
Total results received	1,578	1,554	632	366	556
Accepted results	1,564	1,541	628	362	551
Outliers	14	13	4	4	5

'No filter' indicates all results reported to RCPAQAP. 'Calibrator filter' indicates all results reported to RCPAQAP as ascribable to a particular Calibrator. 'Accepted results' indicates those results within the Analytical Performance Specifications (APS). 'Outliers' indicates results outside the APS. FVIII, Factor VIII; FIX, Factor IX; SM Standard Human Plasma, Siemens/Dade Standard Human Plasma; IL Calibration Plasma, Instrumentation Laboratory Calibration Plasma; DS Unicalibrator, Diagnostica STAGO Unicalibrator.

participating laboratories to gauge their performance when compared to other laboratories using similar or different assay principles and identify areas of improvement. A change to this program's assessment criterion from reagent to calibrator was made from 2016 to enable the assessment criteria to be more relevant. The aim of this study was to determine if this change in assessment criteria has had a positive impact on the assessment of participants. In these six years of the coagulation factors QAP program, no changes have been made to the source of the material sent out to participating laboratories or the actual APS lower and upper limits as mentioned earlier. Hence, allowing this review to be reflective of what the assessment criteria change has had on the QAP program.

Looking at the CV's of both reagent and calibrator (*Tables 2,3*) allows for evaluating the performance of both assessment criteria. The FVIII and FIX survey results' CV's for reagent assessment indicates more variation than that of calibrator assessment, and it is also noted that higher CV's are seen more frequently with reagents than calibrators.

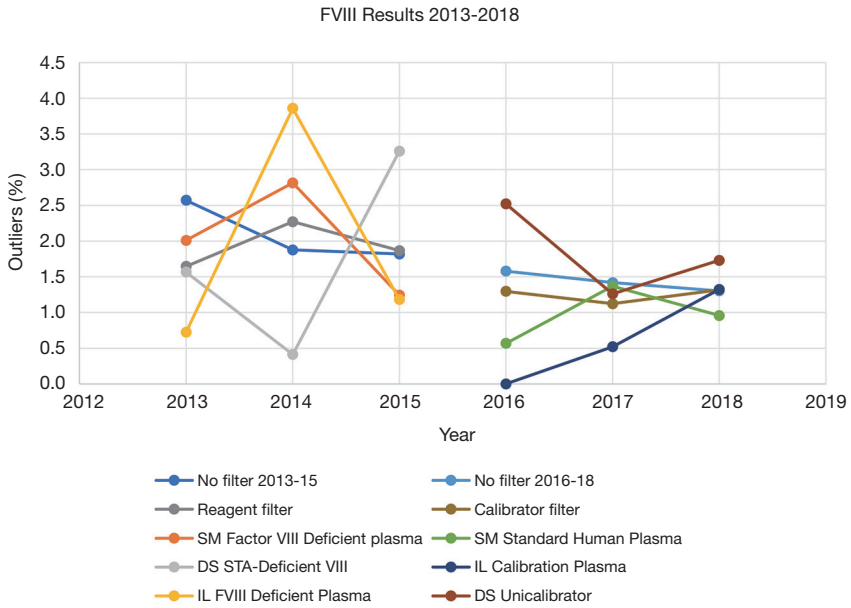

Figure 6 Trend of participants flagged as outliers for the two assessment methods, reagents and calibrators (with more than 10 users in each group), for Factor VIII based on the RCPAQAP Analytical Performance Specifications (APS). FVIII, Factor VIII; SM FVIII Deficient, Siemens Factor VIII Deficient plasma; DS STA-Deficient VIII, STA-Deficient VIII plasma; IL FVIII Deficient, Instrumentation Laboratory Factor VIII Deficient plasma; SM Standard Human Plasma, Siemens/Dade Standard Human Plasma; IL Calibration Plasma, Instrumentation Laboratory Calibration Plasma; DS Unicalibrator, Diagnostica STAGO Unicalibrator.

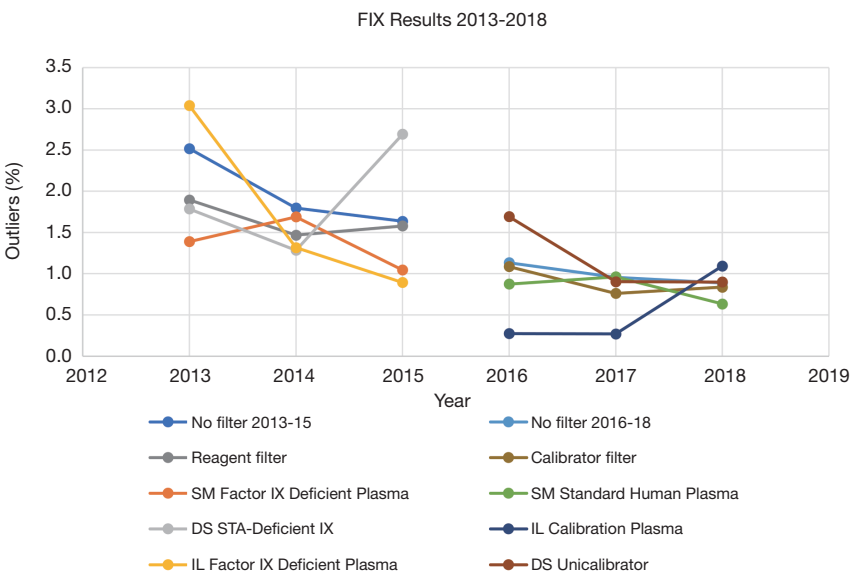

Figure 7 Trend of participants flagged as outliers for the two assessment methods, reagents and calibrators (with more than 10 users in each group), for Factor IX based on the RCPAQAP Analytical Performance Specifications (APS). FIX, Factor IX; SM FIX Deficient, Siemens Factor IX Deficient plasma; DS STA-Deficient IX, STA-Deficient Factor IX plasma; IL FIX Deficient, Instrumentation Laboratory Factor IX Deficient plasma; SM Standard Human Plasma, Siemens/Dade Standard Human Plasma; IL Calibration Plasma, Instrumentation Laboratory Calibration Plasma; DS Unicalibrator, Diagnostica STAGO Unicalibrator.

Table 2 Comparison of FVIII reagent and calibrator coefficient of variation (CV)

Factor FVIII level (%)	A	B	C	D	E
	70–125	30–60	20–50	30–90	30–90
SM factor VIII deficient plasma					
2013	8.8	11.6	14.5	8.9	11.2
2014	9.1	9.9	11.0	9.4	7.8
2015	8.3	9.6	11.2	9.4	8.8
IL FVIII deficient plasma					
2013	10.3	10.1	12.3	10.8	9.7
2014	9.8	12.5	9.9	8.9	11.0
2015	8.7	9.6	11.9	8.9	7.4
DS STA-deficient VIII					
2013	12.5	11.7	13.3	19.4	13.3
2014	13.2	14.7	14.4	12.4	11.4
2015	12.1	10.0	10.9	10.2	11.5
SM standard human plasma					
2016	9.0	9.0	9.9	9.0	7.3
2017	7.9	8.1	8.0	7.6	7.2
2018	7.3	7.5	6.7	7.6	6.7
IL calibration plasma					
2016	8.1	10.3	10	8.4	11.2
2017	8.9	10.7	12.6	9.3	7.3
2018	7.8	10.7	15.3	11.5	11.5
DS unicalibrator					
2016	7.6	11.1	10.4	9.3	8.4
2017	10.9	11.3	10.7	10.3	9.6
2018	10.3	8.8	11.0	9.3	9.0

The CV's of Factor VIII Deficient reagent plasmas and calibration plasmas used by participants of the RCPAQAP program between 2013 and 2015 for the five different levels, A, B, C, D and E, of FVIII that were distributed to RCPAQAP participants. FVIII, Factor VIII; SM FVIII Deficient, Siemens Factor VIII Deficient plasma; IL FVIII Deficient, Instrumentation Laboratory Factor VIII Deficient plasma; DS STA-Deficient VIII, STA-Deficient VIII plasma; SM Standard Human Plasma, Siemens/Dade Standard Human Plasma; IL Calibration Plasma, Instrumentation Laboratory Calibration Plasma; DS Unicalibrator, Diagnostica STAGO Unicalibrator.

Therefore, this further supports the change to calibrator assessment being more relevant.

From this investigation it is observed that performance of FVIII and FIX testing in the participating laboratories has improved over the past six years. Assessments based against calibrator rather than reagent showed reduction in the numbers of outliers in each peer group and provided improved comparability of results with reduced CVs. The decreasing trend in outliers supports the retention of the assessment criteria being based on calibrator. Based on the period of assessment (2013–2018) it can be concluded that the change in assessment criteria to reagent calibrator had no adverse bearing and in fact had a positive impact on the RCPAQAP Coagulation Factors survey performance.

In addition, this review provided an observation of the number of users of each reagent and calibrator type as

Table 3 FIX reagent and calibrator coefficient of variation (CV) from the RCPAQAP program (2013–2018)

Factor FIX level (%)	A	B	C	D	E
	70–125	30–60	≤30	30–90	≤30
SM factor IX deficient plasma					
2013	8.8	10.1	16.6	9.7	17.2
2014	10.0	10.6	15.4	11.4	16.0
2015	8.2	9.6	13.9	12.3	15.8
IL factor IX def plasma					
2013	10.5	13.1	10.2	10.0	13.9
2014	6.8	8.1	13.1	7.9	15.1
2015	10.0	10.4	16.1	9.8	12.2
DS STA-deficient IX					
2013	9.2	10.9	21.4	15	12.7
2014	12.5	12.8	18.8	12.4	14.4
2015	17.0	8.9	13.2	11.0	13.5
SM standard human plasma					
2016	6.0	7.9	15.7	7.4	11.6
2017	8.3	8.2	12.0	7.7	10.2
2018	7.8	7.8	12.4	7.2	11.2
IL calibration plasma					
2016	11.5	7.3	11.5	8.2	13.3
2017	8.9	11.0	13.6	12.8	12.3
2018	8.2	10.2	14.8	10.3	12.9
DS Unicalibrator					
2016	8.3	12.4	14.3	9.8	13.0
2017	9.5	10.7	17.8	10.1	14.6
2018	9.0	9.5	11.8	9.4	12.3

The CV's of Factor IX Deficient reagent plasmas and calibration plasmas used by participants of the RCPAQAP program between 2013 and 2015 for the five different levels, A, B, C, D and E, of FIX that were distributed to RCPAQAP participants. FIX, Factor IX; SM FIX Deficient, Siemens Factor IX Deficient plasma; IL FIX Deficient, Instrumentation Laboratory Factor IX Deficient plasma; DS STA-Deficient IX, STA-Deficient Factor IX plasma; SM Standard Human Plasma, Siemens/Dade Standard Human Plasma; IL Calibration Plasma, Instrumentation Laboratory Calibration Plasma; DS Unicalibrator, Diagnostica STAGO Unicalibrator.

shown in *Figures 1* to *4*. Although this information may not be as significant as the finding of improved performance due to change in assessment criteria, this data shows the trends of users of each reagent/calibrator manufacturer, which may be of interest if further data analysis on the performance of these reagents and calibrators is ever carried out.

There is agreement amongst EQA providers in the fact that EQA programs have an important role in the performance of a laboratory (6,9-11). Looking at other publications in this area of EQA, and based on the findings from this review, the need to standardise assessment criteria is evident (10). To be able to compare performance across various EQA's, standardisation in reporting is essential. It is the responsibility of EQA providers to deliver reports that are of significance to the participating laboratory as well as having some form of global standardisation in the

assessment criteria (12). The findings from this review support the requisite for harmonisation among EQA's to enable consistent peer comparisons across EQA's. Identifying clinically relevant assessment criteria for each laboratory test that has an EQA program will take time and will certainly be ongoing. However, the importance of creating global harmonisation amongst EQA providers and assessment criteria will be beneficial to the clinical laboratories as well as the scientific community.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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