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Technical Report

Application of SQC model to optimize an internal quality control schedule for Haemoglobin A_{1c} measurement on the Capillarys analyzer

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Abstract

Objectives: In the context of the accreditation of medical laboratories according to the ISO 15189:2012 standard, the optimisation of an internal quality control (IQC) schedule is an important element of analytical quality. The study focuses on an essential test for the follow-up of diabetic patients: Haemoglobin A_{1c} (HbA_{1c}).

Methods: The analysis was performed on three TERA® Capillarys (Sebia®) analyzers. Data were collected for 1 month calculating imprecision and analytical bias. A total error allowable (TEa) of 6% was used to calculate the Sigma metrics. A statistical quality control (SQC) procedure based on the Sigma metrics of the analytical procedure, the selected rules and numbers of control measurements were applied to determine the optimised run size and to guarantee the required quality of patient care.

Results: With a mean of 5-Sigma. "Normalised Chart" showed a good/excellent performance for the HbA_{1c} method. The SQC run size nomogram indicated a desirable event size of around 53 samples/capillary (for n=1 and 1_{3s}) and 170 samples/capillary (for n=2 and 1_{3s}).

Conclusion: Our study demonstrated the usefulness of the sigma metric SQC run size nomogram to determine the control strategy for HBA_{1c} and contributes to the quality of results rendered to patients.

Keywords: Haemoglobin A_{1c}, internal quality control, six Sigma, SQC strategy

Haemoglobin A_{1c} (HbA_{1c}) measurement is the essential test for monitoring diabetes. Our laboratory performed between 600 and 700 HbA_{1c} tests per day on 3 instruments Capillarys 3 TERA Flex Piercing from Sebia®. While analysers based on high-performance liquid chromatography (HPLC) use a single cation exchange column. Each Sebia Capillarys 3 Tera instrument includes 12 silica capillaries functioning in parallel. When the instrument has several analytical units. Internal quality control (IQC) planning is often thought of as a complex issue. The IQC run interval refers to the condition in which patient specimens are measured by a procedure that is characterised by a defined start and stop time. Today, two control monitoring planning processes can be put in place to control the quality of the results:

- In continuous mode also called "bracketed IQC" because the results at the beginning and end of a "bracket" are used to verify that patient results measured within the "bracket" are acceptable.
- In point mode also called "critical control point IQC", the performance of the analytical process can be verified after the measurement of patients. In this context, it is necessary to check the performance of the measurement procedure both before and after the event.

For high production continuous processes, both modes can be applied.

A common approach would be to employ the same control rules and number of control measurements regardless of the

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performance of the parameter being measured. Recently, statistical quality control (SQC) procedures have been proposed as an alternative method of planning the frequency of IQC more related to risk management concepts according to the Westgard rules used, the number of control levels and the Sigma metric observed for the analytical process. In 2008, mathematical models developed by Parvin [1] introduced the rejection characteristics of SQC procedures to predict the risk of erroneous patient results based on the calculation of the maximum expected increase in the number of unreliable final patient test results, termed Max E (Nuf). Martin Yago and Silvia Alcover translated the complex equations of Parvin's model into curves on a nomogram to be more practical and more accessible for laboratories [2] and Bayat et al. [3] proposed graphical tools converted into run size numbers. These run-size nomograms make it practical for laboratories to select appropriate control rules, the total number of control measurements/events, and the number of patient samples between quality control events. Several studies have shown that the optimisation of quality control (QC) schedule was an important element in maintaining the quality of analytical systems [4, 5]. In a French context where the mandatory accreditation of medical biology laboratories in accordance with ISO 15189:2012 [6] requirements encourages the development of real tools to justify and optimise the management of IQC. The aim of our study was the development of a total IQC plan risk-based SQC procedure that includes the number of patients between QC events. The number of control measurements. The selection of control rules. The quality HbA_{1c} requirement and robustness of Capillarys 3 TERA.

Materials and Methods

Three analysers Capillarys Tera Sebia® (Lisses. France) were evaluated according to the technical validation protocol in accordance with the requirements of ISO 15189:2012 [6]. Imprecisions were estimated using quality controls of the company SEBIA® and an external quality assessment provided by the Probioqual® program (Lyon. France).

Statistical analysis

To plan the SQC procedures; several steps were executed:

First step

The imprecision evaluation was calculated from the internal controls manufactured by Sebia®. On each capillary, one level of quality control was measured, alternating a normal control at the beginning of the run and a pathology control at the end of the run. The 1_{3s} single rule was used at each QC event. For each analyser, QC data were collected for 1 month with around three hundred results per level (Table 1). Imprecision (expressed as coefficient of variation, CV) was calculated according to the following formula:

$$CV\% = \frac{SD}{mean} \times 100$$

Analytical bias was estimated using externalised internal quality control against the peer group (Table 1). The mean value of the instrument group (excluding data more than two standard deviations away from the mean) was used to determine the target value of the peer group. Bias% was determined as:

$$Bias\% = \frac{\text{Our mean-Peer group mean}}{\text{Peer group mean}} \times 100$$

Second step

To calculate a Sigma metric, the missing piece for many laboratories was the good choice for the tolerance limits of total error allowable (TEa). Sandberg et al. [7] defined a consensus statement for the total error (TEa) choice.

Model 1. Based on the effect of analytical performance on clinical outcomes.

Model 2. Based on components of biological variation of the measurand.

Model 3. Based on state-of-the-art.

In this study, we decided to use the state-of-the-art and a total error allowable of 6% was also used for the College of American Pathologists (CAP) [8].

The sigma-metric index was calculated as follows and presented in Table 1:

$$\text{Sigma metrics } (\delta) = \frac{(TEa\% - Bias\%)}{(CV\%)}$$

The quality performance of HbA_{1c} method was estimated using the Sigma method decision chart (Fig. 1) as described by James O Westgard [9].

Third step

Based on electronic spreadsheets have been developed by Yago and Alcover for single-rule SQC procedures [2] to determine the maximum expected increase in the number of unacceptable patient results reported during the presence of an undetected out-of-control error condition MaxE(NUF) and from the sigma-metrics value that characterises the analytical process. According to the recommendations of Bayat et al. [3], the MaxE (NUF) results have been converted into run size numbers following the formula:

$$\text{Run size} = \frac{100}{(\text{MaxE(NUF)})}$$

For 1 level of IQC and a 1_{3s} blocking rule, the following run sizes were determined:

- Run size=1 for 3 Sigma-Metrics.
- Run size=7 for 4 Sigma-Metrics.
- Run size=53 for 5.0 Sigma-Metrics.
- Run size=373 for 6 Sigma-Metrics.

For 2 level of IQC and a 1_{3s} blocking rule, the following run sizes were determined:

Table 1. Measurement of HbA_{1c} Sigma at two concentration levels for three Capillarys Tera Sebia®

Group	Test/ unit	TEa (CAP)	Level 1							Level 2						
			Mean	SD	CV (%)	Number of results	BIAS (%)	BIAS (% TEa)	CV (% TEa)	Sigma metrics	Mean	SD	CV (%)	Number of results	Bias (%)	BIAS (% TEa)	CV (%TEa)	Sigma metrics
Peer group	Haemoglobin A_{1c} (%)	6%	5.35	0.08	1.43	4714		8.30	0.10	1.22	4659							
Capillarys N°1	Haemoglobin A_{1c} (%)	6%	5.32	0.06	1.13	300	-0.57	9.5	18.8	4.8	8.25	0.09	1.10	276	-0.57	9.5	18.3	4.9
Capillarys N°2	Haemoglobin A_{1c} (%)	6%	5.31	0.05	1.01	312	-0.70	11.7	16.8	5.2	8.21	0.07	0.90	312	-1.10	18.3	15.0	5.4
Capillarys N°3	Haemoglobin A_{1c} (%)	6%	5.3	0.06	1.08	326	-0.74	12.3	18.0	4.9	8.22	0.09	1.05	312	-1.02	17.0	17.5	4.7

HbA_{1c}: Haemoglobin A_{1c}; TEa: Allowable Total Error.

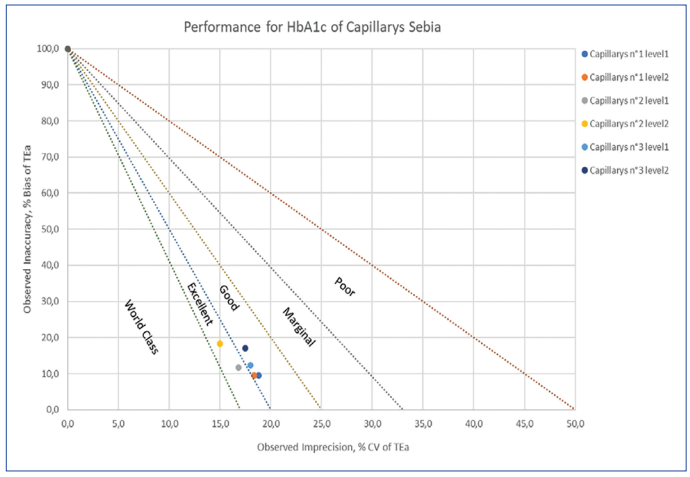

Figure 1. Normalized method decision chart of HbA_{1c} measured with three Capillarys Tera. Inaccuracy (bias. trueness) is the y-axis. Imprecision (CV) is the x-axis.

HbA1c: Haemoglobin A_{1c}.

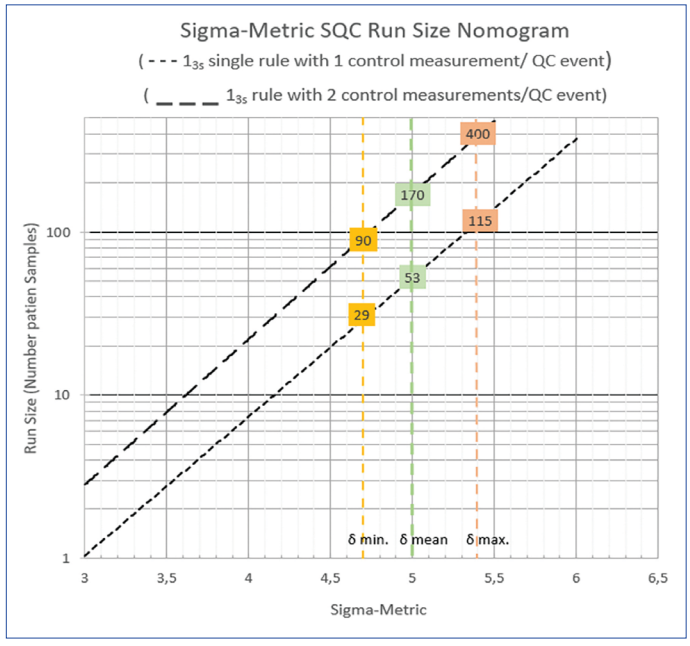

Figure 2. Sigma-metric SQC run size nomogram for estimating the number of patient samples between QC events for bracketed operation of a continuous production process for HbA_{1c} Capillarys Tera Sebia.

SQC: Statistical quality control; HbA_{1c}: Haemoglobin A_{1c}; QC: Quality control.

- Run size=3 for 3 Sigma-Metrics.
- Run size=20 for 4 Sigma-Metrics.
- Run size=50 for 4.4 Sigma-Metrics.
- Run size=500 for 5.5 Sigma-Metrics.

We have drawn a Sigma-metric run size nomogram using "1 control measurement associated with the 1_{3s} blocking rule" and "2 control measurements associated with the 1_{3s} blocking rule", in which run size was plotted on the y axis versus the observed Sigma-metric on the x-axis (Fig. 2).

Table 2. Determination run sizes appropriate for HbA_{1c} for each capillary in continuous mode also called "bracketed IQC"

Test/unit	Mean Sigma (min-max)	Run sizes/Capillary (min- max)
Haemoglobin A_{1c} (%)	5.0	53
(Using a 1_{3s} single rule with 1 control measurement/QC event)	(4.7-5.4)	(29-115)
Haemoglobin A_{1c} (%)	5.0	170
(Using a 1_{3s} single rule with 2 control measurement/QC event)	(4.7-5.4)	(90-400)

Results

At normal and high HbA_{1c} levels, imprecisions were less than 1.4% (NGSP units) and bias was less than 1.2% for all analysers tested (Table 1). The imprecision observed in our experiment was in the corresponding goals for imprecision (<2%) and the systematic bias observed was slightly outside of the target bias set by biological variation (1.1%) [10]. For HbA_{1c} the sigma metrics value was 5.0 (4.7-5.4) for both the levels of quality control in our study (Table 2). To apply the normalised chart, it is necessary to express the observed bias and CV as percentages of the TEa. Normalised chart (Fig. 1) showed a good/excellent performance for the HbA_{1c} method. In Figure 2, run size was plotted on the y-axis versus the observed Sigma metric on the x-axis. The results in Table 2 and Figure 1 described the optimised size of the event for HbA_{1c} Capillarys TERA considering the "sigma" index, the number of internal quality control levels in each event (n=1) and the blocking rule applied (1_{3s}). Based on these results, we could distinguish the desirable event size around 53 (29-115) samples for each capillary. Considering that we tested up to 700 HbA_{1c} per day on our three Capillarys TERA, this represented a run size of around 20 samples per capillary. Based on a scheme with three analysers, our QC strategy was consistent. The IQC strategy was evaluated in case of failure of one or two analysers. If we should use only two instruments, with 29 samples per capillary, our quality control schedule could be maintained. With a single analyser and 58 samples per capillary, our IQC strategy should be changed by doubling the levels and keeping a 1_{3s} blocking rule (Fig. 2).

Discussion

Each laboratory should define a control frequency specific to the context monitored. There was no opposable recommendation for this frequency, but the laboratory should prove it based on its risk analysis considering the number of tests, the robustness of the methods and the consequences of a drift of one of the systems. Risk analysis is the essential first step in the implementation of an IQC strategy. It consists of a summary of analytical issues that could lead to a potentially erroneous result. In the second step, it is necessary to determine the robustness of the method. The Six Sigma approach is a tool for assessing the robustness of the method [11]. The difficulty lies in the choice of the TEa, which can considerably modify the result of the Sigma level [5]. There are two schools of thought on how to design Statistical quality control (SQC) procedures. The traditional approach has been based on the total error model as described in the CLSI C24-Ed4 guideline for SQC [12] and the second approach fixed limits based on an "acceptability range" calculated as 2*APSMU (95% limit based on the Analytical Performance Specification for Standard Measurement Uncertainty) [13]. If it is unclear what TEa to use, different quality specifications can be tested before implementation to assess the impact on patient risk. In 2020, Ilardo et al. [5] proposed to use the Varela and Pacheco [14] tool to verify that the selected TEa was the most appropriate for the performance of the analytical test. In our study, we have chosen a total error of 6%. This selection corresponded to both a total error allowable used for the College of American Pathologists (CAP) [8] and analytical performance specifications for standard measurement uncertainty (APSMU) proposed by Braga and Panteghini [13].

The method decision chart, which takes all the information in the equation and renders it into a graphic format method decision chart, showed quality ranges from good to excellent for HbA_{1c} measured with Capillarys TERA analyzer. The sigma-metrics values obtained in our study were between 4.7 and 5.4, which was comparable with previous studies [4].

Intuitively, the best methods should be the most reliable and therefore require less effort to monitor and control. Conversely, the worse methods will need the most rules, more controls, and need to have that QC run more often. Quality planning and control strategy will be dependent on analyser complexity. In contrast to HPLC analysers which used a single cation exchange column, the control strategy for haemoglobin A_{1c} measurement on the Capillarys TERA analyzer may raise several points of concern. For example, should the Capillarys TERA be treated as a single measuring instrument, or should each individual capillary be viewed as an instrument? How frequently should the quality control be monitored? The frequency of IQC samples should be according to the manufacturer's recommendations but very often they have no clear strategy and transfer responsibility within the laboratory.

This study has demonstrated that using two or three analysers, the Sigma-Metric SQC run size nomogram has shown that the selected rules (a 1_{3s} single), the numbers of control measurements (1 control per capillary) and run size were appropriate. When using a single analyser, this strategy should be changed by switching to 2 control measurements per capillary event and keeping a 1_{3s} single rule.

Our study has shown for a 5-Sigma mean, an appropriate control strategy could employ a 1_{3s} single rule with 1 control measurement at the beginning and another (different level) at the

end of a run having around 50 patient samples, which was a similar finding to the study done by Westgard et al. [4].

Conclusion

Our study demonstrated a good sigma value for HbA_{1c} measured with Capillarys TERA. The development of a total IQC plan risk-based SQC procedures may improvise on decision making the quality control strategy and thus can contribute optimally to results quality. It was confirmed that the SQC model can be used as an important quality management tool to promote strategy development and optimising production costs.

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