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Selecting a Risk-Based SQC Procedure for a HbA1c Total QC Plan

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Abstract

Background: Recent US practice guidelines and laboratory regulations for quality control (QC) emphasize the development of QC plans and the application of risk management principles. The US Clinical Laboratory Improvement Amendments (CLIA) now includes an option to comply with QC regulations by developing an individualized QC plan (IQCP) based on a risk assessment of the total testing process. The Clinical and Laboratory Standards Institute (CLSI) has provided new practice guidelines for application of risk management to QC plans and statistical QC (SQC).

Methods: We describe an alternative approach for developing a total QC plan (TQCP) that includes a risk-based SQC procedure. CLIA compliance is maintained by analyzing at least 2 levels of controls per day. A Sigma-Metric SQC Run Size nomogram provides a graphical tool to simplify the selection of risk-based SQC procedures.

Applications: Current HbA1c method performance, as demonstrated by published method validation studies, is estimated to be 4-Sigma quality at best. Optimal SQC strategies require more QC than the CLIA minimum requirement of 2 levels per day. More complex control algorithms, more control measurements, and a bracketed mode of operation are needed to assure the intended quality of results.

Conclusions: A total QC plan with a risk-based SQC procedure provides a simpler alternative to an individualized QC plan. A Sigma-Metric SQC Run Size nomogram provides a practical tool for selecting appropriate control rules, numbers of control measurements, and run size (or frequency of SQC). Applications demonstrate the need for continued improvement of analytical performance of HbA1c laboratory methods.

Keywords

QC plan, statistical quality control, Sigma-Metric, patient risk, run size, frequency of QC

Quality control (QC) practices are changing in medical laboratories today in response to new regulatory requirements and new practice guidelines. The Centers for Medicare & Medicaid Services (CMS) has adopted a new risk-based QC option called an individualized QC plan (IQCP)[1] for compliance with the US Clinical Laboratory Improvement Amendments (CLIA) regulations.[2,3] CMS, together with the Centers for Disease Control and Prevention (CDC), have issued specific guidance for implementation of IQCPs[4] to help laboratories comply with the new option. The Clinical and Laboratory Standards Institute (CLSI) began in 2011 advocating the use of risk management to provide more comprehensive QC plans for medical tests. Principles of risk management were described in CLSI EP23,[5] with emphasis on risk assessment of the total testing process that includes preanalytical, analytical, and postanalytical phases. New guidance for statistical QC (SQC), CLSI C24-Ed4,[6] was published in 2016 and describes a roadmap for the design and selection of risk-based SQC strategies for the analytical phase.

To implement risk-based QC, medical laboratories need to identify a practical approach that satisfies regulatory requirements and adheres to the basic principles of both quality management and risk management. We recommend the development of a total QC plan (TQCP) that includes a risk-based SQC procedure designed for the quality required by a test and the precision and bias observed for a measurement procedure.[7] We summarize the developmental approach here and describe a graphical tool to support the selection of control rules, the number of control measurements, and the run size (number of patients between QC events, or frequency of

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QC). Applications are illustrated for the Sigma quality expected with current HbA1c measurement procedures.

Methods

CLSI C24-Ed4[6] defines terms that are important in understanding the development of QC plans:

- **Quality control plan**—a document that describes the practices, resources, and sequences of specified activities to control the quality of a particular measuring system or measurement procedure to ensure requirements for its intended use are met.
- **Quality requirement**—specification of the characteristics necessary for a product or service to be fit for its intended use. Note: For a laboratory measurement procedure, the quality requirement is usually expressed in terms of an allowable total error (TEa, ATE). If the measurement error in a patient's result exceeds the TEa, the result fails to meet its quality requirement.
- **Quality control (QC) strategy**—the number of QC materials to measure, the number of QC results and the QC rule to use at each QC event, and the frequency of QC events. Note: May also be referred to as QC procedure.
- **Quality control (QC) event**—the occurrence of one or more QC measurements and a QC rule evaluation using the QC results.

According to Parvin,[8] the purpose of the CLSI document is to provide a "roadmap for designing, assessing, and implementing a statistical QC strategy that is consistent with the patient risk concepts introduced in CLSI EP23." We discuss the C24-Ed4 guidance in detail elsewhere[9] and the need for practical tools for selection of risk-based SQC procedures based on estimation of Parvin's MaxE(N_{uf}) patient risk parameter.[10] A practical issue for laboratories is the need for a SQC planning process that can be quickly and easily implemented by analysts. Calculation of Parvin's patient risk parameter is difficult and requires specialized informatics support, therefore graphical estimates from nomograms offer a practical alternative. Yago and Alcover[11] and Bayat[12] developed electronic spreadsheets to support the risk calculations and provided nomograms that relate the observed Sigma-Metric to Parvin's MaxE(N_{uf}) risk parameter.

Those nomograms have been further adapted to provide the simple Sigma-Metric SQC Run Size nomogram included here.[9] Example conditions were chosen to represent an HbA1c examination procedure where ATE was 6.0%, CV was 1.0%, and bias was varied from 0.0% to 3.5% to change the Sigma-Metric from 6.0 to 2.5. MaxE(N_{uf}) was calculated from Excel spreadsheets. Run size was calculated as 100/MaxE(Nuf) in accordance with Parvin's model where QC events bracket 100 patient samples (ie, M = 100). Run length was plotted on a logarithmic y-axis vs the Sigma-Metric on a linear x-axis to prepare the nomogram.

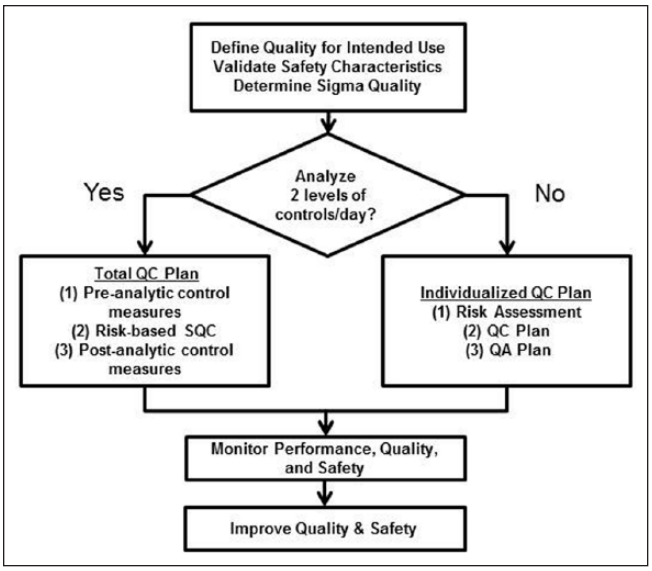

Figure 1. Approach for developing QC plans that conform to US CLIA requirements.

Development of QC Plans

The flowchart in Figure 1 outlines an approach for developing QC plans, either a TQCP that includes a risk-based SQC procedure, or an IQCP that requires a detailed risk assessment of the total testing process. The initial task is to validate the quality of the method, then consider whether or not the laboratory can analyze a minimum of 2 levels of controls/day. If the answer is yes to analyzing 2 levels of controls/day, the CLIA regulatory option for minimum daily QC is satisfied and the laboratory can develop a TQCP without a formal risk assessment. The laboratory should identify preanalytic control measures, select a risk-based SQC procedure, and add postanalytic control measures to formulate a total QC plan. If no, then the laboratory must satisfy the CLIA option for an IQCP, which requires a risk assessment, a QC plan, and a QA plan to monitor performance, quality and safety. We advise laboratories to satisfy the CLIA option for 2 levels of controls per day and implement risk-based SQC procedures whenever possible because it is simpler than performing a complicated risk assessment of the total testing process. In developing a total QC plan, the selection of preanalytic and postanalytic controls can be guided by manufacturer's instructions for use, as well as possible sources of error (or failure modes) identified in the laboratory, without the need to assess the probability of occurrence of failures, the severity of harm from such failures, and the detectability of such failures by available control mechanisms.

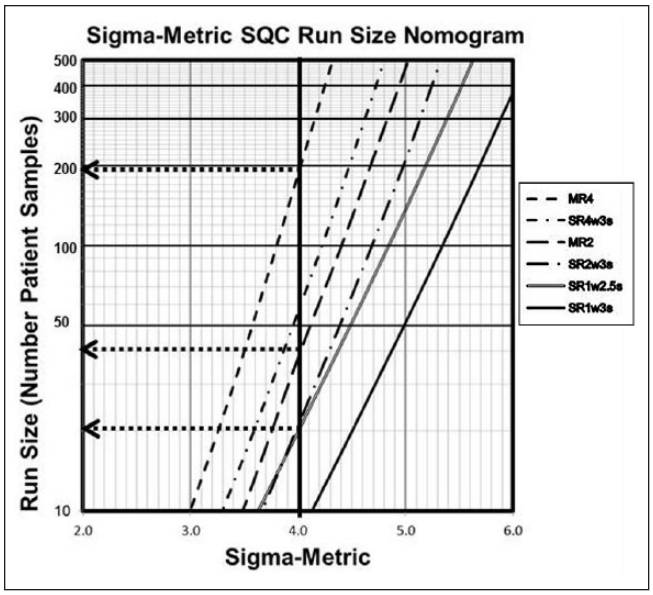

Figure 2. Nomogram for selection of risk-based SQC procedures. Run size is shown on the y-axis vs the Sigma-Metric on the x-axis. The vertical line represents a method with 4.0-Sigma quality. Run size is read on the y-axis for the intersections of the Sigma line with the lines representing different SQC procedures, as illustrated by the dashed horizontal lines.

Validation of Safety Characteristics

A critical part of risk management is the validation of method performance, or "safety characteristics" in the industrial risk management guidelines. Manufacturers must establish safety characteristics for precision and bias (and others) and laboratories must verify that the observed performance is acceptable for the intended use of the test. The required steps are to (1) define the quality for intended use, (2) obtain experimental data to validate safety characteristics such as precision and bias, and (3) determine quality on the Sigma-scale. These steps are part of the standard procedures for the validation of analytical methods.[13] With respect to HbA1c, the quality for intended use has been defined by the College of American Pathologists (CAP) and the National Glycohemoglobin Standardization Program (NGSP) as an ATE, (or TEa) of 6.0%. Precision is typically estimated from a replication experiment over a minimum of 20 days, or a minimum of one month's QC data, and presented as a standard deviation (SD) or coefficient of variation (CV). Bias can be estimated from a comparison of methods experiment (preferably vs a recognized reference method) or from a proficiency testing (PT) survey having Target Values assigned by a reference method, such as provided by CAP and published on the NGSP website. A Sigma-Metric can be calculated as (ATE-Bias)/SD using concentration units or as (%ATE-%Bias)/%CV using percentage units. Alternatively, a graphic estimate can be made by constructing a Method Decision Chart and plotting an "operating point" that represents the observed bias and observed precision.[13]

Analytical Controls

Statistical QC provides the simplest control mechanism for monitoring many factors that affect analytical performance. Selection of an appropriate SQC procedure is therefore a critical part of a TQCP. For this purpose, we propose a simple Sigma-Metric SQC Run Size nomogram (Figure 2) that relates the observed Sigma-Metric to the control rules, number of control measurements, and run size. Run size, defined as the number of patient samples between QC events, is shown on the y-axis vs the Sigma-Metric on the x-axis. The slanted lines from left to right represent different SQC procedures, as identified in the key at the right and the figure legend:

- **MR4** represents a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule with 4 control measurements per QC event and a probability of false rejection of 0.03 or 3% ($P_{fr} = 0.03$);
- **SR4w3s** is a 1_{3s} single rule procedure with 4 control measurements per QC event, $P_{fr} = 0.01$;
- **MR2** is a $1_{3s}/2_{2s}/R_{4s}$ multirule procedure with 2 control measurement per QC event, $P_{fr} = 0.01$;
- **SR2w3s** is a 1_{3s} single rule with 2 control measurements per QC event, $P_{fr} = 0.00$;
- **SR1w2.5s** is a $1_{2.5s}$ single rule with 1 control per QC event, $P_{fr} = 0.01$; and
- **SR1w3s** is a 1_{3s} single rule with 1 control measurement/ QC event, $P_{fr} = 0.00$.

The nomogram shows that a high Sigma method needs only a low amount of QC and supports large run sizes (or a low frequency of SQC), whereas a low-Sigma method requires a large amount of QC and short run sizes (or a high frequency of SQC). To apply the nomogram, (1) locate the Sigma-Metric value on the x-axis, (2) draw a vertical line to intersect the various lines that represent different SQC procedures, (3) for the point of intersection with an SQC line identify the run size from the value on the y-axis, then (4) identify the control rules and the number of control measurements for that line.

Applications

Assessment of the quality of 7 point-of-care (POC) HbA1c methods has been documented by Lenters-Westra and Slingerland.[14] Precision was estimated from a replication experiment that followed the CLSI EP-5 guideline.[15] Bias was estimated from a comparison of methods experiment that followed the CLSI EP-9 guideline[16] and each test method was compared to three IFCC Secondary Reference Measurement Procedures. One of the POC methods showed about 4-Sigma quality, another 3.5-Sigma, another 3-Sigma, 2 other methods are between 3-Sigma and 2-Sigma, and 2 methods worse than 2-Sigma.

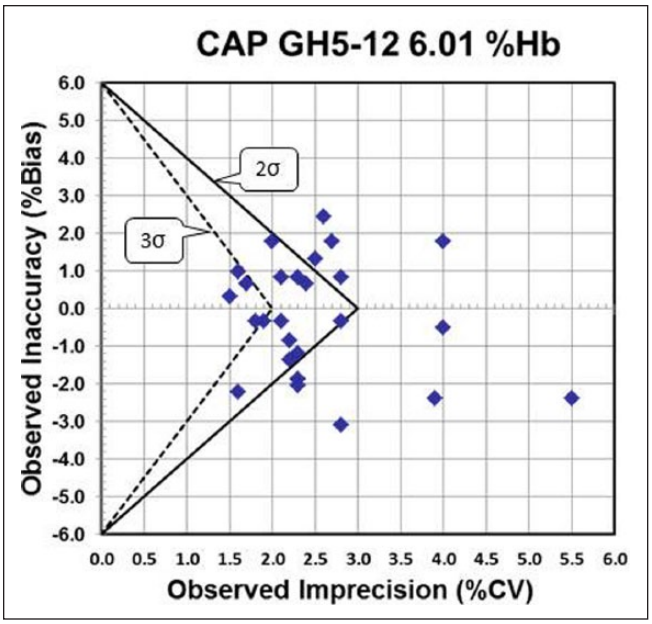

Figure 3. Sigma proficiency assessment chart for 2016 College of American Pathologists (CAP) survey results for HbA1c GH5-12 sample with concentration of 6.01%Hb. ATE = 6.0%. Observed %Bias is shown on y-axis vs observed %CV for each of 26 method groups.

Woodworth et al[17] studied 6 HbA1c methods (5 laboratory, 1 POC) used in 4 academic medical laboratories. Method precision and bias were again determined according to the CLSI EP5 and EP9 protocols. For the 40 samples in the comparison of methods experiment, results were obtained from an NGSP Secondary Reference Measurement Procedure. When ATE was defined as 6.0%, the calculated "patient-weighted Sigmas" were 0.36, 1.43, 1.57, 2.29, 2.84, and 3.90. In addition, the authors calculated Parvin's MaxE(N_{uf}) risk parameter,[13] which gave results of 71.48, 49.92, 34.27, 11.00, 6.30 and 0.60 for bracketed SQC operation using a 1_{2s} control rule and N = 2. This risk parameter is related to the frequency of SQC or the number of patient samples between QC events. Run size can be calculated as100/MaxE(N_{uf}), which gives values of 1, 2, 3, 9, 16, and 167 patient samples, respectively

Given that the best method performance from each of these studies is about 4-Sigma, the SQC procedures that are needed can be determined as shown in Figure 2. The vertical line represents 4-Sigma quality. The intersections with the slanted lines provide information about the controls rules, number of control measurements, and run size. For POC methods where short run sizes would be practical, selection of a 1_{3s} single rule with N = 2 or a $1_{2.5s}$ rule with N = 1 would be appropriate for run sizes up to 20 patient samples (see lowest horizontal arrow). An assumption of the risk model is that patient samples be bracketed with a QC event in front and a QC event at the end. Bracketed SQC is also a recommended practice in the new CLSI C24-Ed4 guideline. That would mean 2 controls at the beginning and end of the run if using a 1_{3s} control rule, whereas only 1 control is required at the beginning and end if using a $1_{2.5s}$ rule. For a 4-Sigma automated method employed in a central laboratory, a larger run size would likely be of interest. One appropriate SQC strategy would be to implement a multirule procedure such as $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ with N = 4 (MR4 in Figure 2) and a run size of about 180 to 190 patient samples (see highest horizontal arrow). To provide shorter run size and quicker reporting intervals, an appropriate strategy would be to use a $1_{3s}/2_{2s}/R_{4s}$ multirule with N = 2 and 40 patient samples (see middle horizontal arrow).

For many of the other methods from these studies,[14,17] the observed Sigma-Metrics are 3 or less, which means it is impossible to achieve optimal QC with minimal patient risk unless using multirule procedures with even larger Ns. Such methods are not economically feasible in most laboratories, thus it is critical to select high quality methods to provide reliable patient test results.

Discussion

HbA1c is a critical test that demands high quality performance by laboratory methods. The quality required for intended use has been defined as an ATE of 6.0% by CAP and NGSP. While methods have improved considerably in the past few years, the use of the test has also become more critical for diagnosis as well as monitoring applications and ATE has been tightened from 15% a few years ago to 6% today. The quality expected for current HbA1c methods is documented by the 2016 CAP survey results shown in Figure 3. This "Sigma Proficiency Assessment Chart"[18] shows results for 26 method groups from 3307 laboratories for sample 12 from the 2016 GH5 survey that had an assigned value of 6.01 %Hb. The exact numbers of laboratories in each method group can be found in the data on the NGSP website. On this chart, the observed method group bias is plotted on the y-axis and the observed group CV on the x-axis. The solid > shaped line identifies 2-Sigma quality and the dashed line 3-Sigma quality. The average bias for the entire group of laboratories is only -0.19%, but individual method group biases range from -3.09% to 2.44%. Group CVs average 2.53% and range from 1.6% to 5.5%. Only 5 method groups show better than 3.0-Sigma quality, 10 are between 3.0 and 2.0-Sigma, and 11 show quality worse than 2.0-Sigma. Each point represents between laboratory performance which is expected to be worse than within laboratory performance. Nonetheless, they represent the quality that is expected when patients are tested by multiple methods employed in a health care system, or when patients are monitored by different laboratories over a geographic region.

In reviewing the quality of the HbA1c methods studied by Lenters-Westra and Slingerland[14] and Woolworth et al,[17] Little emphasized the need for careful selection of measurement procedures, implementation of optimal QC practices,

and the importance of monitoring bias by participating in PT surveys.[19] Laboratories should make use of the CAP survey results when selecting new measurement procedures, prioritizing those methods that have small biases, small CVs, and a Sigma-Metric of ≥3, preferably 4 or higher. Unfortunately, POC methods are not as well represented in the survey results as methods more suitable to central laboratories. According to the CLIA regulations, laboratories that implement "waived" methods are not required to participate in PT. Unfortunately, most POC methods are CLIA-waived, so the performance of those methods will not be as well documented nor will laboratories employing those methods have ongoing information about the biases of their methods.

For laboratories to implement the CLIA minimum QC requirement of 2 levels per day, the nomogram shows that methods need to achieve 5-Sigma quality. For a 5-Sigma method, an appropriate SQC 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 a maximum of 50 patient samples (visualize a vertical line at 5-Sigma on the x-axis of the nomogram and look at the y-value corresponding to the intersection with solid black line). That would provide optimal SQC for the workload of many small to medium laboratories. For higher volume laboratories, that same practice might be practical for continuous reporting at intervals of 50 patient results. For a larger reporting interval, a $1_{2.5s}$ control rule with 1 control measurement per QC event would support a run size of about 140 patient samples (intersection of 5-Sigma vertical line and double line).

The newest generation methods show promise for achieving high Sigma quality, as described recently by Lenters-Westra and English.[20] They documented that 2 highly automated methods achieve Sigma-metrics of ≥ 6.0 based on rigorous validation studies performed in a HbA1c reference laboratory. Such methods could be optimally controlled with a 1_{3s} control rule, one control level per QC event, and a run size of ≥ 370 patient samples. Until such method performance becomes commonplace, it will still require significant efforts to implement optimal SQC strategies that will guarantee the quality required for intended use and minimize the risk of patient harm. Laboratories should be very conservative in their QC practices, meaning short runs and more QC than the CLIA minimum requirement of 1 measurement on each of 2 levels per day. According to CAP guidelines, one control material should be in the normal range, up to 5.7 %Hb. Another could be selected in the range from 6.0 to 7.0%HbA1c to monitor the critical diagnostic level and another control material in the elevated range from 8.0 to 9.0 %HbA1c. The CLSI C24-Ed4 document provides good laboratory practices for establishing the mean and SD for control materials, as well as interpreting control results, and responding to out-of-control conditions. Careful implementation of SQC procedures and proper daily QC practices are still critical for HbA1c measurements today.

Conclusions

A total QC plan with a risk-based SQC procedure provides a simpler alternative to an individualized QC plan. A Sigma-Metric SQC Run Size nomogram provides a practical tool for selecting appropriate control rules, numbers of control measurements, and run size (or frequency of SQC). Applications demonstrate the need for continued improvement of analytical performance of HbA1c laboratory methods.

Abbreviations

ATE, allowable total error; CAP, College of American Pathologists; CDC, Centers for Disease Control and Prevention; CLIA, US Clinical Laboratory Improvement Amendments; CLSI, Clinical and Laboratory Standards Institute; CMS, Centers for Medicare & Medicaid Services; CV, coefficient of variation; IQCP, individualized quality control plan; NGSP, National Glycohemoglobin Standardization Program; POC, point of care; PT, proficiency testing; QC, quality control; SD, standard deviation; SQC statistical quality control; TEa, allowable total error; TQCP, total quality control plan.

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