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An overview of quality control, quality assurance and quality management in clinical biochemistry laboratory

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ABSTRACT

A clinical laboratory is engaged in sampling and testing of patient's samples. The quality of a clinical biochemistry laboratory can be described by its accuracy and reliability of analytical outcomes and time bound delivery of result report. The output of the delivery system in healthcare management rests on the success of quality control and standards of laboratory testing and reporting. The system of regular assessment and monitoring of quality had gradually enhanced clinical care over the time. Clinical biochemical laboratories have made considerable progress in addressing the needs of quality control, to make a difference in patient care by giving reliable results. Quality control (QC) of clinical laboratory is a control sample testing process that is statistically validated to scrutinize and assess analytical procedures applied to obtain the test values of a patient's specimen for clinical interpretation. A system of QC database, created by performing routine testing of quality control samples, enables to draw QC statistics for the tests conducted in the clinical laboratory. The QC of laboratories had travelled a long distance from "Shewhart cycle" to six sigma quality management system. The clinical biochemistry laboratory has grown from strength to strength in managing, conducting and reporting clinical diagnostic tests. QC ensures that the testing protocol is under control and the test results are reliable and meet the required quality standards as specified by the regulatory authority. The purity and truthfulness of control samples for QC are not only required for proficiency testing but also of prime importance for managing the overall quality. Though QC can be assessed by Westgard's quality-control selection grids but a chart akin to the method decision chart namely, Operating Specifications (OPSpecs chart) may be of more use and choice. Westgard's quality-control microcomputer program is amenable to automation. The quality assessment is further strengthened by devising a new graphical tool, the sigma quality assessment chart, for establishing the quality standards of recent testing procedures on a sigma scale. A relatively easy way of assessing the authenticity and imprecision is to compare the within and between laboratories means and standard deviations provided that different laboratories are employing the same instruments and procedures for analyses. The overall quality assessment of the clinical biochemistry laboratory has evolved, wherein internal quality control has been the core of QC that is reinforced by integral external quality assessment. The point of care testing, that is mostly fully automated, is not untouched of QC and require equally stringent QC measures to control the system of checks and balances without increasing much to the cost and affecting the system of maintenance of instruments.

Keywords: *Automation, Clinical Laboratory, External Quality Assessment, Internal Quality Control, Inter-Laboratory Quality Control, Laboratory Information Systems, Quality Control, Quality Assurance, External Quality Assessment Scheme, Quality Assurance System, Quality Management System, Westgard Sigma Rule.*

1. Introduction

A clinical biochemistry laboratory is engaged sampling and testing of patient's samples. The laboratory testing employs various testing procedures with varying degrees of complexity depending on the nature of test viz. histological, biochemical and microbiological among the ambit of clinical laboratory. The quality of a clinical biochemistry laboratory can be described by its accuracy and reliability of analytical outcomes and time bound delivery of result report and there should be checks and balances in all aspects of analyses and operation [75].

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In healthcare management, the output of the delivery system rests on the success of quality control and standards of laboratory testing and reporting [48]. The regulatory authorities at national level and international agencies keep a vigil on the QC of clinical laboratories and seek information on various aspects of QC assessment apart from regular QC data. It is mandatory on the part of laboratories to provide proof of QC measures and to establish the authenticity and usefulness of the analytical methods in the context of intended application [20]. Appropriate tools are required to validate the QC test statistically [26]. The International Organization for Standardization (ISO) 15189) [55] has been regarded as quality certifying agency.

The external quality assessment or the proficiency testing, available in many countries, verify the relative performance of a clinical laboratory in comparison to its contemporaries on the basis of pooled sample analyses. Proper implementation of good laboratory practices is hampered by the voluntary nature of accreditation of clinical laboratories [47].

Precision and accuracy of clinical test results can be assured through regular QC, which is of prime importance, as it makes a biochemical laboratory authentic and reliable. QC is a self-regulatory process that refines the testing procedures and validates the patient's results that are supposed to be accurate. QC is a dynamic process that is evolving and improving and, therefore, streamlining of QC process is essential for its improvement [45], which can be achieved through appropriate interventions at pre-analytical, analytical and post-analytical levels. Laboratories require adopting systems with appropriate support in terms of training and customization that form the basis of any external audit. Whitehead & co-worker delineated internal quality control (IQC) from external quality assessment (EQA) and explained IQC procedure that is restricted to a particular laboratory and detects the faulty results in real time for the release of patients results [8]. They defined EQA as a mechanism that checks the efficiency and performance of a laboratory retrospectively but it has no role in ameliorating the efficiency and performance of laboratory output per se immediately at the time of QC [74]. The interchangeable use of EQA & external quality control may be misleading for laboratory workers who may presume that IQC precludes the necessity for EQA. The IQC & EQA are complementary procedures, wherein IOC's primary objective is to keep checks and balances that is able to detect error and its sources on daily basis to enhance the reliability, repeatability and accuracy of test results; while EQA addresses issues that minimizes the inter-laboratory discrepancies in test results by highlighting the differential results between laboratories [49].

2. Brief historical account of Quality Control

Walter Andrew Shewhart, who introduced 'Shewhart cycle' is recognized as the father of modern quality control, contributed to the establishment and development 'process control' in 1924 [57]. A graphical chart, containing data points from QC result, was introduced by Levy- Jennings in the 1950s to visually represent the functionality of a laboratory working with biochemical test. The concept of serum pool was introduced by Rausch and Freier who coined the term “standards” that was ultimately known as “control samples” [17]. Roberts in 1959 described graphical method for calculating geometric moving averages for determining the working of a process [52]. The concept of patient result for determining the functioning of a laboratory QC was introduced by Kaoru Ishikawa and gradually gained importance during 1960–1970 of which the first beneficiaries were hematology and biochemistry laboratories that employed quality using control patients' tests [28,31]. Dennis Dorsay, in 1963, introduced erythrocyte indexes as a measure of QC and made it operational in many hematology analyzers [12]. A revolution was brought in QC process by bringing a new concept of dual blood sampling by taking samples twice on two consecutive days as advocated by Ductra, to replace the need of control samples in QC [13]. In the arena of biochemical analyses a new method called 'Average of normals' was introduced by Hoffmann & co-workers for detecting the systematic errors by calculating mean of the normal test results [24]. “Bull's algorithm” or “X_{-B}” was launched for quality control in hematology analyzers [5]. Jerome Nosanchuk and Arthur Gottmann tallied the current results of each patient with previous outcomes and devised a new technique for detecting errors due to analyzers which turned out to be a reliable and economic QC method [46].

Cembrowski & Westgard elucidated the utility of 'moving averages' in QC parameters. Westgard and his co-workers had published a series of papers for addressing the issues of QC, a landmark that described the use of multi-rule Shewhart Chart for QC in clinical biochemistry [68,65]. Ricos & co-workers devised a new parameter for generating information on QC specifications by recording the natural variance of observations for different biochemical parameters [49]. The QC process was made handy by Westgard through introduction of “OPSpecs charts” [71]. The issues of non-analytical errors were addressed extensively during the 1990s. Subsequently, to keep a check on post-analytical errors, a computerized configuration system was devised for proper flow of laboratory information that also prevented few types of pre-analytical errors [41].

3. Quality Control Protocols

QC ensures that the testing protocol is under control and the test results are reliable and meet the required quality standards as specified by the regulatory authority [66, 6]. A prospective QC describes the most recent analytical runs by statistical analysis of control samples, patient records and instrument-based electronic checks. The retrospective QC highlights past performances that includes independent quality assessment and proficiency check, summary of QC data provided by an authorized QC programme of the region or manufacturer, verification of calibration and follow-up clinician inquiries [77]. The purity and truthfulness of control samples for QC are not only required for proficiency testing but also of prime importance for managing the overall quality. The patient's results are vulnerable to a variety of errors, encompassing reagent matrix effects to instrument calibration as per the required testing function, that need to be addressed in QC for the proper identification of potential errors in test results [14]. Adequate checks and balances are essential for the maintenance of regular and accurate monitoring of laboratory sample test, wherein QC is essential for ensuring the correctness and accuracy of patient's result. QC of clinical laboratory is a control sample testing process that is statistically validated to scrutinize and assess analytical procedures applied to obtain the test values of patient's specimen for clinical interpretation [1]. The QC system should be well documented and thought out process with clear understanding of the events to provide stability to the system and reliability in the results. The systematic approach of QC system must be demonstrated by the laboratories to prove the coordinated activities that can be subjected to audit and evaluation by institutional as well as external team.

Howanitz & co-workers examined 500 US institutions through Q-probe survey and attributed the non-compliance of QC in US laboratories to the cost and complexity of the procedures [25]. Gross irregularities were observed by Ross & co-worker while reviewing 337 records of tertiary care hospital in 1987. A variety of errors were pointed out that included both pre-analytical viz. mistaken patient identity, improper briefing of patients regarding the requirements of pre-sampling requirements, wrong specimen instrumentation, improper handling of specimen and improper laboratory orders as well as post analytical errors namely, delayed, untraceable or incomplete, wherein twenty-nine mistakes were accounted to non-laboratory personnel [53]. Clinical laboratories were rapidly transformed into large diagnostic business hub armed with automated multi-tasking work stations with limited laboratory tests and miniaturized instrumentation for point-of-care applications under token supervision that has not only

created unemployment among the qualified laboratory technologist and laboratory scientist but also reduced the standard of services of the clinical laboratory and laboratory industry [77]. The standard of laboratory was compromised and quality deterioration was ascribed to a general drive to cut the cost. It was noticed that there was a general tendency to employ under-trained laboratory technicians in place of qualified medical technologists, overburdening employees and less reliance on general float.

Downgrading can be countered by motivation, inculcating positiveness and proper training of laboratory technocrats; resorting to standard operating procedures and good quality assays from the reputed laboratories; proper checks and balances to assure QC and its review by external agencies; unbiased administration, task force approach towards patients [77]. Youden's two-sample diagram is useful for collaborative laboratory quality testing wherein Youden plot is analyzed. This is particularly aimed at inter-laboratory comparisons [29, 78]. In the Youden approach, the untreated results are imported by the trial organizers from different participating laboratories and subjected to a statistical procedure *viz.* z-score marks for scaling of the results which forms the basis for pointing out inaccuracies in the result. The concerned laboratories are intimated about the inaccuracies as well as appropriate suggestions for the required corrections, thereof.

An effective quality control ensures authentic results by finding and eliminating shortcomings of the analyses process adopted by the laboratory beforehand so as to avoid delivery of inaccurate test results to the patients. A laboratory may fail in QC test due to faulty analytical methods and technical snags, typographical errors, reagent and PT materials instability, improper sampling and stochastic errors [27]. As a general rule, the QC samples are tested at the start of shift, after calibration and repair of equipment, change of analytical reagents and upon probable inaccuracies in patient's result [61]. Quality process includes analytical processes namely, assay validation, gross operating procedures of analyses, data interpretation, documentation and reporting [21].

The QC system should be optimized that reduces the multiple analytical runs without compromising the patient's results. It should be mandatory on the part of manufacturer to label and define the time period for getting best results in terms of accuracy and precision of the equipments and analytical chemicals. They should tell about the nature of QC samples and their placement protocol. The above information should be utilized by the individual laboratories to fix their QC run length depending on their stability of samples, periodicity of result reporting, work flow pattern, human resource capability and cost of retesting [62]. The QC sampling interval should not exceed the maximum duration as defined by the manufacturer and in any case it should be less than 24 hours. As per CLSIC-24 guidelines of USA, QC samples must be tested at least once after an analytical testing [76]. Randomized run of quality check samples should be preferred over the nonrandom placement of QC sample for a genuine estimate of error in patient result. Quality planning, quality laboratory procedure, quality control in laboratory, quality assessment and quality improvement, the 5 Qs, forms the basis of Total Quality Management (TQM) in a clinical laboratory, whereas good laboratory practices (GLP) that includes all the activities aimed at providing accurate and timely reports. The GLP activities were categorized under structure, process and outcome [16].

Weykamp & co-workers inducted six sigma model for examining the QC targets and explained the QC of current procedures by utilizing PT/EQA data and presented the interpretation in a graph akin to method decision chart [73]. Westgard Sigma Rules offers a modest and fast method for picking desired control rules and the number of QC tests required to identify clinically significant errors and advocated the 6-sigma quality management system (QMS) to help QC personnel of the clinical laboratory to give immaculate guidance for achieving the desired quality for the proposed use of the results generated by QC evaluation protocols [67].

4. Quality Control Test in Biochemical Laboratory

A 'result' is the outcome of a diagnostic test that is conducted in the clinical laboratory for diagnosis of health condition. Two categories of results, qualitative or quantitative are important in QC that are outcomes of testing from patient and control samples [9].

QC results are the outcome of test performed on predetermined standard control samples with known values so as to validate the analytical process and functioning of equipments within a desired range of provisions thereby authenticating the reliability of patient test results.

Validation of testing process is the first step towards the use of patient's results for clinical purpose. The standard control samples comprise a normal control and an abnormal control. The normal comprised of physiological standard that falls in the normal range of distribution, whereas the values of a particular analyte control product lies outside the normal physiologic range of concentration, low or high, in case of an abnormal control. Accurate and precise results can be ensured by resorting to regular QC that uses both normal and abnormal controls to check the analytical process as a part of good laboratory practices [7]. Controls are required to be run at increased frequency if the stability of the test is less than one day or suspected to be less due to some changes that occurred inadvertently. Systematic and periodic testing of QC control samples is important to create the QC database for the effective validation of testing system. Validation of a testing process is achieved by comparing the QC result with that of pre-defined values obtained from QC database. Quality Assurance Program (QAP) of the Clinical Biochemistry Laboratory was evaluated and Quality Indicators (QI) were assessed in terms of pre-analytical, analytical and post-analytical phases and concluded that assessing the performance of QI provides an insight into the efficacy of the QAP assist in identifying the gaps in the QAP opens up new avenues for continuous quality improvement [58].

5. Optimization of Reference/Control Sample Quality

The International Federation of Clinical Chemistry and Laboratory Medicine had defined the control solution as “specimen or solution which is analyzed solely for quality control purposes, not for calibration". The terms control solution, control material and control sample or control specimen are used interchangeably in the biochemical clinical laboratories to designate a well-defined product that is specifically made for QC test with known concentration and available in different packages and forms. The control samples should be easy to handle and use without much complicated reconstitution process that enhances error. It should reflect the properties of the patient's samples in composition, viscosity and other biochemical properties.

The ready to use solutions are preferred over lyophilized products as and when possible. The variations between the sample lots should be minimized to avoid misinterpretation in terms of systematic errors. Changing the sample lots frequently increases workload in verifying the product range; therefore, samples with long expiry date and a bulk of control samples are preferred over small quantities. The control samples should represent the target values close to medical decision points involving reference intervals from healthy as well as sick patients. A negative and a weak positive control are recommended for a qualitative test whereas; the controls may be graded for semi-quantitative tests. A control may be assayed or unassayed and the latter being less expensive. FDA, USA has notified the classification of assayed QC products for clinical microbiology [15]. Assayed control products are not generally used for routine assays and are recommended for high value research purpose. Assayed control samples are marketed with labeled target values as per reference method calculation.

The unassyed control products are analyzed by the laboratories to know the target value and acceptable variation. If the control product lots are from the same manufacturer, the lot to lot variations in QC results are worked out by taking mean of 5 samples without rejecting any data point unless due to operational error for establishing the mean and accepting the fresh lot of control product [60]. However, SD of previous lot is taken until sufficient data is generated from the new lot.

6. Statistical Parameters in Quality Control Test

Quality control (QC) of clinical laboratory is a control sample testing process that is statistically validated to scrutinize and assess analytical procedures applied to obtain the test values of patient's specimen for clinical interpretation. QC database, generated by testing the control samples, forms the basis for QC statistics for every test that is conducted in a laboratory [63]. The QC data is specifically generated for different level of controls, and therefore, the statistical parameters derived from normal and abnormal levels of control apply to that level and portray the variation in tests specific to levels of concentration. Mean and standard deviation are the two frequently used basic statistics for decision making in a clinical laboratory for QC. However, coefficient of variation (CV) is also used under specific conditions. CV is the fraction of standard deviation that is attributed to mean of the observations and expressed as percentage. CV permits the laboratories to make easy assessment about the test's general precision. In some European laboratories, random variation in biological parameters in humans has been recognized as a measure of efficiency and accuracy of laboratory analyses [51]. The coefficient of variation arising out of biological diversity have been delineated into between and within individual variations whereas, the variations emanating from an analysis process can be partitioned in two subcategories namely, within-day and between-day analytical variations [30]. Standard deviation is the prime statistic to judge the accuracy but while comparing efficacy of two different methods of estimation of a biochemical product, say blood glucose concentration, CV is often more reliable and SD alone may provide misleading information as it increases as the analyte concentration increases. In QC, trend refers to a progressive loss of delivering accurate results and precision of an evaluation system. Several factors may be responsible for the loss of reliability viz. non-maintenance and improper calibration of equipments, expired chemicals and control samples and improper storage of reagents.

Any drastic change in the mean, positive or negative, of control sample is termed as shift in QC performance test. A shift may result from major failure of maintenance of laboratory equipments, reagents, ambient temperature and humidity etc. A change in the mean of control samples indicate systematic error whereas, the deviation of mean from the expected value of QC result is termed as random error which can be quantified through working out the SD of the random error. A random error may be acceptable or unacceptable depending on the SD value as defined by the laboratory.

7. Statistical Limits for comparison of Quality Control Results

Standard deviation is a statistic that measures the amount of variation of a set of values in relation to the mean of data set. In a QC, it is a measure to quantify the deviations arising out of randomness in the observed values of the test results in relation to a control value within in the limits of acceptable variation. Precision of the test may be judged from standard deviation by observing the deviation of individual values from the population mean. This provides an idea of imprecision. Mean and standard deviation (SD) are worked out from the results obtained from same lot of control within the data set and it offers an estimate of the reliability of a test at definite concentrations. Repeatability of a test result is considered to be consistent if the SD is on lower side, whereas high SD is indicative of inconsistency and high error. Both laboratory reagents and faulty equipment can lead to inconsistency in repeatability of QC or patient's result. Malfunctioning of equipment, if any, should be corrected immediately to address the QC problem. The test results of control specimens should lie close upon multiple measurements. Patient's test result should be high on accuracy and precision in situations that demand regular repeated tests to track the prognosis. Coefficient of variation is also used under specific conditions as it allows easy judgment on general precision of the tests by comparing the various results.

Levey-Jennings Chart

It is a graphical representation, named after Stanley Levey and Elmer R. Jennings who pioneered the use of this chart, of QC data points for visual analyses functionality of a particular clinical laboratory. The L-J chart is an extension of Shewart X-bar [57] chart that possessed single set of data for the estimation of sigma on the basis of standard deviation. Usually, in L-J chart, the X-axis is represented by days of months against the QC data on the Y-axis and separate charts are created for each test and control level. The QC results are entered into the QC log at regular interval. After the QC log is prepared, QC values are plotted on the L-J chart for assessment of quality of the analysis. The objective of L-J chart is to look for systematic error and random error.

The first step in the process of decision making is to fix a decision limit on the basis of the clinical need of stringency of the result in question. The QC observations will be randomly distributed around the mean value and about 68% of the observations will fall within 1±SD whereas, approximately 95.5% of all QC values will lie within the limits of ±2SD and only about 4.5 % of all QC observations fall outside 2±SD provided that analytical process is functioning well. Likewise, 99.7 % of the observed QC values will lie within ±3SD. Therefore, only about 3 observations out of 1000 tests are likely to fall outside ±3SD by chance factor.

In general, any QC value that exceeds 3 SD are rejected and attributed to errors associated with testing process and patient result is withheld for repetition. Straight lines are drawn at mean value and at mean ± 1, 2 and 3 SD marks for the ease of interpretation of data. Once the QC data is plotted in the form of L-J chart, it is easy to analyze the data and draw inferences regarding the validity and accuracy of a QC result and to decide upon the acceptability of the analytical run. The sigma and SD are estimated on the basis larger population mean in case of L-J chart whereas, these statistics are estimated on the basis of small rational sub-groups in the preparation of Shewhart individual control chart.

The out of control run was defined [23] for accepting a quality control result based on standard deviation wherein QC results were rejected when either a single QC value surpasses ±3SD from mean or two successive QC values crosses ±2SD limit. The QC parameters were further investigated on the basis of the efficacy and suitability of different laboratory QC rules as defined and refined by Westgard and his co-workers [68, 65, 71, 67, 70, 72]. Early detection of trends and shifts is possible by examining the results of two simultaneous control runs. Westgard rules, which utilize Shewhart control charts for data interpretation, provide the general guidelines whether or not the patient results can be released on the basis of QC runs. Initially, Westgard defined the criteria for detecting the type 1 and type 2 errors that result from rejection of a correct result and acceptance of an incorrect result, respectively [70, 69]. These were modified later to identify random as well as systematic errors by defining a specific error limits for a particular test [68]. Westgard and co-workers had devised a set of six rules, used individually or in combination, to decide on the acceptance of patient result by tracking the rows of variables that are out of control on the basis of a QC run. When any of these rules is violated, the process behind the numbers is 'out-of-control' and should be stopped and investigated.

A set of multiple rules have been devised by Westgard and co-workers to assess the paired control runs [68]. The error can rise from the analyte or from the instrumentation. Upon precise analyses, these rules are sensitive enough to detect the small errors that may be insignificant. In order to delineate the insignificant errors, Westgard & coworkers [65] devised power operated quality control choice grid which allowed to pick the appropriate QC rule as per the desired level of error tolerance and frequency of error. Computer program is available that can enhance the accuracy of analyte imprecision [72]. The efficiency of new testing procedure can be validated by the use of 'Sigma-Metric' devised by Westgard for total QC based on statistical parameters and supervising the QC on the sigma Scale [67].

Westgard QC rules

Westgard's QC rules are expressed as numeric-alphabet notations, where numeric denotes the number of QC runs and the alphabet defines the statistical limit for examining the QC observations *viz.* 12s rule is not complied where only one QC is run and observed value fall outside 3 times of standard deviation on either side of the mean value [64].

12s rule: It applies when one QC test value is greater than two SD from the mean. This error may result from random error and does not necessarily reflect an analytical error. Random error can be confirmed through second test run as about 4.5% of first run will fall between 2 SD and 3 SD.

There is need to examine the relationship between the SD value and the control result and source of error should be examined. If no faults are detected, then a single QC value outside 2 SD should be acceptable.

13s rule: It applies when one QC test value is greater than three SD from the mean which may be due to random error [11].

22s rule: It applies when two successive QC values fall outside 2 SD, both times either greater or smaller than the mean and applicable to single level of control in two successive runs or both levels of control in a single run when one QC test value is greater than three SD from the mean. This error results from systematic error. It has application for both within and across the runs where the former affects all QC results derived from current analysis. Noncompliance of across QC run is indicative of error in one portion of the analytical curve, whereas non-adherence to within QC run is indicative of systematic error that may influence the entire curve [44].

R4s rule: This rule is violated if in a single run, the difference between the normal and abnormal control result is at least 4SD. It applies between control levels when two successive QC values of the same control level reach at least 4 SD from the mean or when one control value fall on mean plus 2SD side and the other is beyond the -2 SD limit. It is applicable for the current run and detects exclusively random errors.

Noncompliance to any of the above rules may not always lead to non-acceptance of the analytical run as these rules can detect noncompliance due to small non-random error or analytical bias which may not be significant enough to affect the clinical interpretations. These small biases can be removed through proper calibrations and maintenance of equipments.

3-1s: It applies when three successive QC test values that are greater than one SD fall on the same side of mean either greater or smaller.

41s rule: Non-compliance of this rule indicates systematic error wherein one or both control levels may be associated with its manifestation. It applies when four successive QC test values within 1 SD fall on the same side of mean.

10x rule: It applies when ten successive QC test values lie on the same side, left or right, of the mean regardless of the magnitude either within a control level or between control levels. Non-compliance of this rule is an indicative of a shift and systematic error.

The rules 3-1s and 4-1s have two-fold applications *viz.* within products at level 1 control results and between control products at levels I, II and III in paired combinations. The breach of results that occur within control products, point to a systematic error over a wide range of concentrations. Software programmes have been developed for automation to decide on the rejection of an analytical run. Judicial applications of these rules are warranted to minimize false rejections. False rejections have been reduced in high volume chemistry and hematology equipments by proper application of Westgard rules [68]. The control run must be optimized for the stringency and frequency as per the need of the accuracy and extent of error associated with the test. For error prone tests, frequency of control run is increased and rejection rate is enhanced by using stringent rules that narrows the acceptance limit. Koch & co-workers had advocated for two control runs for every 18 patients in place of 13s, 22s, and the R3.6s rules.

The optimized QC procedures that reduce the frequency of required QC tend to be favoured against those that optimized QC procedures that increase the frequency of QC run.

Optimized analyte specific QC protocol reduced the frequency of type 1 error as well as expenses and lead to falsification of higher efficiency of their high-volume chemistry analyzer [37]. Koch and co-workers have advised to reorient the Library of Information Science QC programme and appropriate training of the operator and analysts for analyte specific QC procedures. The QC measures based on averages of patient clinical chemistry data were in place long time ago [24]. However, later investigations revealed that the averages of patient clinical data technique was inadequate for detecting error of control samples in QC test [77]. Smaller standard deviation of analytical technique as compared to the SD of the patient samples enhances the error detection capability of patient averages as it is one of the most important determinants of error detection [72]. QC can be managed in variety of ways including monthly review of peer laboratory QC trends. Laboratory proficiency testing is another way to authenticate laboratory protocols and training of operators and analyzers through the aid of professional QC providers such as College of American Pathologists [27]. Its proficiency program uses specimens similar to patient sample and authenticates testing proficiency of individual laboratory as well as uses the comparative data from competing laboratories to develop more precise values for proficiency samples. Though the proficiency testing programmes are designed to authenticate the QC performance it has added advantage to decipher the quality issues with reagents when instruments are working flawless without any problem of calibration. One of the added advantages of L-J chart is to use the patient results as control to monitor the faulty tests [43]. A laboratory technologist can detect the drift or problems associated with functioning of analyzer, that are generally unnoticed in QC testing, by observing the mean of patient's results over time.

Biological analytes show variation within the individual, small or large, specific to a particular analyte [2]. Those biological variations which show less variation need to be analysed more accurately, therefore, the testing accuracy in is a function natural variation. Inaccuracy can be measured through CV % and as a general rule; the variability arising out of process of analyses should be 50 % of the variability observed in the natural biological variation. Corrective measures can be taken to avoid imprecision as explained by Cooper [10]. Regular checking of expiry dates of chemicals and control samples, proper reconstitution of reagents. Retesting of control if the first test is out of range for ruling out random error but if the retesting result is within the acceptable limit; go for the patient sample analysis. If retesting is out of range, change the control sample lot and repeat the process to check the sample deterioration. If problem is not resolved with new control sample, then instrumentation needs to be checked for error sources.

The control samples must be routinely tested and all values should be recorded properly and entered in the chart regardless of being out of range. It is erroneous to keep only those values that fall within ±2SD, by routine re-running of control, as it will create a bias in favour of median values and it will be increasingly difficult to get a value in the normal accepted range as the SD will approach to zero in long run. If a patient's result is rejected due to failure of QC test, it is desirable to repeat the previous patient's result to clear the doubt retrospectively. An inaccuracy of 5% many not affect most of the patient whereas, a 25% bias will not be acceptable for almost all patients, thereby easy to take decisions on rejection.

The inaccuracies that fall in between these values need case by case attention. A blind follow of ±2SD rule for accepting a QC test may lead to false rejection of patient result. To exemplify, a 9th analytical run should not be disqualified if a single run fall outside 2SD but within 3SD in QC test limits as due to random error about 4.5% QC run will fall within ±2-3SD.

8. External Quality Assessment

Clinical governance is based on laying down protocols and fixing accountability for QC in the healthcare system by the devising a process of accreditation of clinical laboratories involved in testing and delivering patients result. The laboratories should follow the guidelines and adhere to the rationale and aims of statute clinical governance. External Quality Assessment (EQA) is a system of external audit that is integral to the QC process to ensure that proper check and balances are in place to assure the quality of test results. The main objective of EQA is to improve laboratory performance by tutoring, technical suggestions and standardization as per the clinical requirement and quality standards. EQA assures the competency of laboratories and may include inter-laboratory comparisons [74]. Alongside EQA procedures, there is a need to educate, train and monitor the technical personnel involved in pre and post analytical processes *viz.* patient sample collection, carriage, handling and reporting results. The quality assurance programme encompasses all IQC and EQA practices that ensure a systematic effort toward achieving a high standard and delivering best performance in diagnostic investigation though not perfect all the time and foolproof all through [19]. The low performance of a laboratory may be due to faulty equipments or regent issues or fault of technician or a combination thereof. Therefore, the information generated through EQA is often helpful in resolving the equipment and regent issues by providing feedback to the company for rectification.

Clinical governance operates either through cooperation between Government agencies (heath departments, drug control department, industry and commerce department) and the professionals involved in clinical testing or managed by statute academy as in Federal Republic of Germany. The EQA implementing countries have relied on experienced and qualified professional for designing adequate survey programmes. Many countries have made EQA mandatory by imposing penalty or legal binding and thereby assuring submission of external proficiency assessment (EPA) whereas, UK promotes EQA by bearing the cost of EPA by the NHS clinical laboratories. The EQA endorsement and compliance is aimed at providing high quality specifications for addressing the patient need. When EQA system is in place, a detailed assessment is done for all aspects of clinical laboratory and complete information is generated about QC. The EQAS is an elaborate system for sample analysis as well to develop a clinical context for the interpretation of test results and thus it not only guarantees accuracy of results but also ensures proper interpretation of result in relation to the clinical subject [56].

Sciacovelli1 & coworkers concluded that EQAS can regulate each aspect of EQA provided that the agencies involved in the system are dedicated and adhere to the principle of responsibility and accountability and thereby add value to the quality evaluation as well as devising an External Quality Assurance Program (EQAP) [56]. The prime goal of the EQAP is to retain the quality standards of clinical laboratory in long run for the benefit of patients.

9. Role of Inter-laboratory Quality Control

Comparing the internal quality results with other laboratories provide a tool to assess the proper functioning of internal QC that forms the basis of quality assurance of clinical laboratory and in the absence of regular between laboratory comparisons there is no other means to verify the validity of patient result beyond doubt. Such comparisons can be achieved by employing same instruments across the participating laboratories by comparing the within and between laboratories mean and SD for a particular test. Peer-reporting programs enable laboratories to compare their internal QC data to the findings from comparable peer-group laboratories, making it possible to evaluate and improve the quality of the analyses process of the testing [38, 34]. A design for inter-laboratory quality-control program was made wherein specimens are dispatched in duplicates to the peer laboratories [39]. The results generated by the peer participants are evaluated and compared among themselves and with the reference points and gross imprecision and inaccuracy, if any, is reported to the laboratory. Upon receiving several rounds of data linear regression analysis is done between the individual laboratory result and the reference result, which forms the basis for identifying the imprecision and systematic error of testing.

Rothenberg suggested following 5 steps for peer-reporting programs work [54]. An outside vendor supplies the laboratory with the QC materials used for daily QC processes. The QC data generated by each participating laboratory, using the same methods, are sent to the QC service provider on regular interval for comparison through statistical treatment of the data. The calculations result in a number of reports from which the laboratory can select those that best meet its needs. The reports are delivered to the laboratory by mail or e-mail, or can be made available for downloading via the internet. The laboratory evaluates the reports it receives, determines whether any corrective or preventive actions are required, and ensures that such actions are performed. The author further explained the benefits of inter-laboratory QC programs that are included to recognize trends, malfunctioning of equipments and chemicals as and when they arise, thus ascertaining the authenticity and enhancing level of accuracy of the test results.

10. Point-of-Care Quality-Control Practices

The QC in Point-of-Care (PoCT) can be simplified and systematized on the lines of regular laboratory testing by simple interventions to make it a coordinated system based on intelligent analysis without resorting to a complex process that hampers its operationality. Many PoCT's analyzers being relatively new to the system and tested under ideal conditions required to be evaluated more comprehensively.

The point of care analytical instruments have to comply with the QC standards. The system as such is not infallible and required to be tested for accuracy and reliability by alternative methods [22]. The PoCT can be mimicked as per the real situation and duplicate samples should be validated through alternated methods of testing to examine the QC for evaluating the progress of QC interventions. In a study of 88 units of PoCT for measurement of hematocrit levels through baseline correlation coefficient and regression analyses [36], it was observed that PoCT is very much reliant on skill of technician; however, discrepancies were largely removed with the targeted intervention and the correlation between bed-side versus core laboratory testing.

The PoCT results of blood glucose measured by PoCT devices can be altered at any point before starting analyses, during analyses and post-analyses. The pre-analytical factors can be arterial/ venous or capillary blood, improper maintenance of equipments, inadequate QC or external audit, extreme physiological conditions of the body. Erroneous data entry may account for post-analytical error whereas, technical faults, extreme limits of glucose, altered ratio RBC and WBC, mismatch in calibrations, intravenous intake of neuro-transmitters and low total protein oxygenation status may lead to changes during analytical process [35]. Martin has elaborated a working model for whole blood glucose testing wherein two levels of QC was recommended for every shift and a fasting test correlation for each technician within the limits of ±15% of laboratory mean. The other suggestions *viz.* values of less than 500 mg glucose/L to be authenticated by other laboratory methods; tri-monthly proficiency testing; recruitment of technologist through authorization and authentication of knowledge and proficiency and yearly skill validation. Martin advocated for QC programme that adequately controls the PoCT system without adding much to the cost and complicating the system of maintenance of instruments [42]. He emphasized the need of routine pre-analytical check-up work *viz.* information and good documentation of the instruments, operator training, monitoring, and analyzer maintenance programs. Gill & co-worker discussed the techniques adopted by clinical settings for applying of PoCT out of the periphery of laboratory and did not found a universal strategy that can be practiced by all [18]. The PoCT devises, though standardized and calibrated, yet not well defined and characterized for detecting errors at the point of care [24]. The utility of PoCT can be enhanced by customization, increased flexibility in application and adopting a reasonable approach in view of technological advancement, ease of use, reasonable cost and volume of PoCT network. Each laboratory should prepare a database for every PoCT analyzer with regard to the results of QC samples and electronic control, source of errors of equipments and error indicators [4]. Kathryn & co-workers examined PoCT and found that more than 90% adherence to prescribed QC protocol in PoCT documentation and about 96% cases were properly recorded. They emphasized that QC protocol and monitoring of out of range QC results as critical factor to obtain accurate results. Furthermore, it is important to train the technicians in order to assure high quality testing results in PoCT as per the compliance of regulators [32]. Katsuhiko summarized the internal quality control and external quality assessment and advocated for a coordinator and emphasized the importance of medical technologist in PoCT laboratory. Testing of instrument function is important for internal QC whereas, the authenticity of recent test results is reassured and transferability of assessment result among the laboratories is confirmed through external QC [33].

11. Conclusion

The QC of laboratories have covered long distance from "Shewhart cycle" to six sigma quality management system [57, 67]. The clinical biochemistry laboratory has grown strength to strength in managing, conducting and reporting of clinical diagnostic tests. The role of clinical biochemistry laboratory has transformed from mere supportive activity to an active partner in patient care [58]. While the clinical laboratories have been modernized with sophisticated equipments, the reliability of test remains an issue.

With the enhanced awareness among the general public and increased legal hassles there is need for laboratories to adhere to strict quality assurance policy and generation of quality reports [59]. Assuring quality has become utmost important by delivering relevant, true to type result and effective patient care in accordance with standards. The goal of effective quality assurance program is to ensure execution of all required activities in a proper, professionally acceptable manner [3]. QC ensures that the testing protocol is under control and the test results are reliable and meet the required quality standards as specified by the regulatory authority. The purity and truthfulness of control samples for QC are not only required for proficiency testing but also of prime importance for managing the overall quality. The patient's results are vulnerable to a variety of errors, encompassing reagent matrix effects to instrument calibration as per the required testing function, that need to be addressed in QC for the proper identification of potential errors in test results.

The prime objective of QC management is to reduce the systematic errors and non-reporting of flawed results by employing adequate checks and balances without too much repeating the analytical runs. Quality control standards should match the physical parameters of actual samples taken from the patient in terms of colour, opacity, viscosity, refractivity and constituents. Both assayed and unassayed control material are available can act as a control sample. The mean of new batch of control samples are calculated and compared with the previous batch of outgoing QC sample material and accepted as QC reference, if the mean does not show significant deviation. Both laboratory reagents and faulty equipments can lead to inconsistency in repeatability of QC or patients result. Precision of the test may be judged from standard deviation. Low standard deviation implies that repeatability of a test is consistent whereas high standard deviation indicates inconsistency and high imprecision. Coefficient of variation is also used under specific conditions as it allows easy judgment on general precision of the tests by comparing the various results.

A relatively easy way of assessing the authenticity and inaccuracies is to compare the within and between laboratories means and standard deviations provided that different laboratories are employing same instruments and procedures for analyses. The inter-laboratory QC programs are efficient in observing trends, detecting malfunctioning of instruments and quality of reagents, as and when they arise, thereby assuring validity of tests performed and enhancing the reliability and accuracy of test results [40].

The use of multirule QC procedures optimizes the QC system which not only decreases the repeat of tests and chances of false rejection but also enhances the error detection.

A system of QC database, created by performing routine testing of quality control samples, enables to draw QC statistics for the tests conducted in the clinical laboratory. Once the database is created it can be applied for effectively validating testing QC system. An error proof QC is required to include both normal and abnormal controls to define a range of QC values in a laboratory whereupon daily QC results can be validated. The QC can be assessed by Westgard's quality-control selection grids [65]. A chart akin to method decision chart namely, Operating Specifications (OPS pecs chart) may be of more use and choice [71]. Westgards quality-control microcomputer program [72] is amenable to automation.

The Sigma Quality Assessment Chart, a graphical tool, is recommended for demonstrating the quality of current examination procedures on the sigma scale [67]. At present the coefficient of biological variation, introduced Ricos & co-workers, has limited use QC.

The overall quality assessment of the clinical biochemistry laboratory has evolved, wherein internal quality control has been the core of QC that is reinforced by integral external quality assessment that ensures functional competence of clinical laboratories in conducting test and overall performance of the laboratory. Measurement of instrument function is important for internal QC whereas, the authenticity of recent test results is reassured and transferability of assessment result among the laboratories is confirmed through external QC.

QC programme is also necessary for the point of care testing (PoCT) that adequately controls the system without adding much to the cost and complicating the system of maintenance of instruments. In PoCT too, there is need of routine pre-analytical check-up work *viz.* information and good documentation of the instruments, regular training of technicians, evaluation and maintenance of equipments and analyses software.

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