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Research Article

Basics of Quality Control in Clinical Laboratory

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Abstract

The clinical laboratory involves processes and procedures that form an integral part of its management. Until quality control of the clinical laboratory is executed, performed and monitored continuously and progressively, the results generated from the clinical laboratory cannot be accepted or even relied upon. The main purpose of quality control is to rectify and make the entire functioning of clinical laboratory error-free. Until the importance and purpose of quality control is not appreciated and implemented; the international standards (ISO: 15189) shall not be fulfilled. The personnels working in the clinical laboratory should be aware, capable and trained in the various quality control methods and policies generated thereof. Quality Control is a systematic process which reduces as well as eradicates the various types of errors; measures that can be taken so as to facilitate and increase the quality standards of the clinical laboratory.

Key words: quality; quality control; errors, internal; external; control charts

Introduction

Clinical laboratories contribute significantly to the health care system. The important stakeholders such as patients, physicians, nurses etc. are provided with results in terms of "reports" supporting the diagnosis, prognosis, monitoring and treatment. They also provide the health authorities with statistical data. This data is utilized to develop, implement and evaluate national health policies. Additionally, clinical laboratories also enable the surveillance and monitoring of communicable diseases at the international and national level [1]. The clinical laboratory has major role in health as well as training the laboratory personnel. Without the presence and able support from the laboratory personnel; the following can happen:

a) Patients are less likely to receive the proper or even the best health care
b) Resistance to essential drugs will continue to spread
c) The disease neither its source can be identified
d) The check on epidemics nor communicable disease is possible
e) There will be ineffective control measures in the allocation of financeas and human resources [2]

The obstacle or challenge in providing the health –care is the lack of confidence in the medical laboratory results, especially in countries with poor economic resources. The delivery of health care in terms of reliable reports is critical for variety of diagnostic, treatment and control procedures. Major hindrances to the provision of such reports are the occurrence of errors during their generation [3].

Non-conforming reports or results are produced due to laboratory errors and mistakes. Non-conforming results with statistical meaning, caused due to non-human action are known as "errors". Whereas, mistakes are non-conformance with no statistical meaning; and includes all types of human errors.

These errors maybe classified on the basis of time and stage of their occurrence in the various stages of procedures of the clinical laboratory-as pre-analytical stage, analytical stage and post-analytical stage. Majority of the pre-analytical and post-analytical non-conformance are "mistakes" whereas analytical outliers are "errors".

Stages of the Analytical Procedure:

Pre-analytical stage: includes all the procedures occurring prior to analysis of patient's samples e.g. blood drawing, sample transportation, centrifuging, dilution etc.

Analytical stage: includes the procedure in which the intended analyte or parameter is measured.

Post-analytical stage: refers to the tr4ansmission of data to LIS and validation of the results to the physician [4].

In order to detect the errors and reduce their occurrence; a set of procedures have been developed known as " quality Control " for clinical laboratories [5].

Quality Control

The first recommendation of Quality Control was published in 1965. Now Quality Control is a major part of the total clinical laboratory

program.Quality Control is the control of the errors in the performance of the analytical tasks and verification of the test results. The check is on the reliability of the results as well as its correctness when compared to any laboratory in the world , provided that the same method is followed [6].

The types of procedures conducted in the clinical laboratory or analytical examinations are:

i) **Quantitative examination:** measures quantity of the analyte in terms of numeric value and particular unit of measurement.
ii) **Qualitative examination:** measures just the presence or absence of a substance or evaluate cellular characteristics, such as morphology; in terms such as "positive" or "negative". "reactive" or "non-reactive", "normal" or"abnormal" and "growth" and "no growth" are used
iii) **Semi quantitative:** to measure how much of the measured substance is present. Results maybe expressed as "trace amounts". "moderate amount" or 1+,2+, 3+ [7].

Terminologies used in Quality Control

Accuracy: it denotes the agreement or closeness between the test results obtained by a method to the true or acceptable reference value.

Analytical method: a laboratory procedure utilized to measure a physicochemical entity or its attribute.

Precision: the reproducibility and repeatability between two measurements on multiple sampling under the prescribed conditions. Classified as Repeatability –intraassay variability, Intermediate precision (Intra laboratory variability), Reproducibility (Inter Laboratory Variability)

Purity assay: quantitative analytical procedure used to measure the purity of an active ingredient

Purity method: a qualitative analytical procedure used to determine the purity of an active ingredient

Specificity: demonstrates the ability of a method to measure an analyte in the presence of components present such as impurities, degradants and matrix components of the sample utilized.

Standard deviation: the variation or the measure of the dispersion of the values from the average value or the mean

Mean: the average value of the analyte obtained post multiple analysis in clinical laboratory [8].

Sources of Laboratory Errors:

The potential errors occur which affect the quality of the laboratory results.The three distinct stages are prone to specific , characteristic types of errors

A] Errors in pre-analytical stage: Occur and impact prior to the analysis of the patient's sample , in the clinical laboratory.these types of errors include:

i) **Wrong patient identification:** The demographic details maybe noted wrongly which may finally affect the laboratory test results e.g., name, gender, age, patient 's posture, effects of exercise, dietary effects, medical history, effects of drugs, alcohol etc.
ii) **Improper collection of blood samples:** The blood sample maybe collected in another vacutainer than the one actually recommended e.g.; sodium citrate vacutainer utilized instead of fluoride vacutainer.
iii) **Inadequate quantity of sample:** the sample collected in vacutainer may not be adequate quantity required in order to test the analyte.
iv) **Improper handling of the sample:** if the sample in the vacutainer is not handled well may lead to hemolysis; which directly affects the biochemical testing.
v) **Incorrect sample storage:** the sample in the vacutainer should be stored properly in a refrigerator, if required to store for longer period of time
vi) **Other factors:** Heat or light exposure may lead to erroneous results of analytes in vacutainer on analysis e.g. photo-degradation of bilirubin by light exposure.

B] Errors in Analytical phase: the analytical phase means the period of analysis of the patient's specimen and between period involves both entry and exit of the patient's report. These patient's report are affected by the sample pre-treatment , reagent volume measurement, sample measurement, sample and reagent mixing time, incubation, reaction timing , dilutions and calculations involved. These errors are also dependent on the additional apparatuses used such as glassware, pipettes etc; which may not be washed or calibrated properly. The quality of the reagents and the deionized water used for the reconstitution of calibrators and controls has a direct influence on the values generated. The reagents should be prepared as per manufacturer's instructions. The accuracy and precision of the analytical method as well as proper maintenance of the equipment aid in the reduction of the analytical errors.

C] Errors in Post-analytical stage: After the analytical phase within the acceptable time frame or turnaround time (TAT), the reporting of the results is enabled in the post-analytical stage. The data, generated has to be presented in a format to be accepted clinically and comprehended and interpreted by the health –care professionals. The errors occurring are the typographical errors, delay in the transcript of reports, delay in the dispatch [9].

Quality Control Material: These are materials that are liquid in condition or freeze-dried (lyophilized) material. These are similar in condition containing the same analytes present as in human serum , plasma, blood , urine and cerebrospinal fluid. The QC materials ideally should be capable of long periods of storage and dispense, free from microbial antigens like bacterias, viruses, fungi and affordably priced. The abnormal level control material may be prepared at a concentration above or below the reference range of the analytes. Minimum two levels of the control materials are prepared by the reagent manufacturer or analyzer manufacturer or can be prepared even by the laboratory personnel [10].

Properties of Control Material

1) Quantity should be sufficient
2) Stability should extend to at least one year
3) Kept in aliquots (small measurable volumes)
4) Its concentration should vary minimally
5) Their composition should be homogenous in aliquots stored in vials
6) Control sample should be treated similar to test or patient sample [11]

The two levels of controls should be spaced by a time gap of 8hours. QC material should be run additionally after

1) After an instrument's servicing
2) Change in reagent lots

3) After calibration and
4) Whenever patient's sample seems inappropriate in order to confirm the results produced [10]

Purposes of Quality Control Process

1) To assess the precision of the results over a period of time
2) To give a prior warning of the control trends such that early action can be taken before actual mistakes occur
3) It provides an idea that the accuracy of the results by comparison with the known sera
4) It is important to test the performance of the analyser
5) Monitor the analytical methods so as toassess the accuracy
6) To monitor the technical skills of the laboratory personnel
7) Prevent the incorrect patient's value as compared to the known standards with the expected values [11]

Types of Quality Control

I] Internal Quality Control: set of procedures undertaken by a particular laboratory for continuously monitoring the operation and results of the measurements so as to assess its quality. Internal Quality Control involves the attempts and steps involved to ensure errors in the analytical data are of magnitude appropriate for usage.

It involves two approaches a) the analysis of the reference materials to monitor trueness and statistical control b) duplication to monitor precision

The basic approach to Internal Quality Control involves the analysis of control materials alongside the analyte under examination. The outcome forms the basis of decision of acceptability of the data produced. However, the interpretation of the control data should be documented based on objective, criteria and on statistical principles. The results of control analyses are indicators of the performance of the analytical system, also as guide to errors to individual test results [12].

According to ISO 15189 (International requirements) "The laboratory shall design internal quality control systems that verify the attainment of the intended quality of the results [13].

Pre-requisites for Internal Quality Control Program

It is primarily essential to set up QC protocols to implement that are statistical tools or control rules, number of control measurements as per the required quality of analytical test. The following is necessary to implement an internal quality control program.

1) Create standard operative procedures and policy
2) Assign personnel or staff for monitoring and reviewing
3) All staff should be trained
4) Obtain the control materials
5) Collect the data
6) Set target or true values and calculate mean and SD
7) Establish Levy-Jenning charts
8) Plot the control data
9) Establish , implement, troubleshoot and corrective action protocols
10) Document the entire procedure
11) Control specimens should be tested in the same manner as the test samples by the same staff of the laboratory
12) The calibrator obtained from the obtained from the manufacturer and used as control, it should be a diffe3rent lot no from that used to calibrate
13) For a new lot QC material, numeric QC data, QC statistics (mean , SD and CV) should be calculated at least 20-30 data interval to dete3ct the precision.
14) The data of the control should be recorded or plotted to detect a malfunction in the instrument or the analytic system. The control records must be readily available to the laboratory staff performing the analytic method.
15) To detect problems and trends the staff must review QC data on days when control are run
16) The results of control should be verified for acceptability before patient
17) The results of the control should be verified for acceptability
18) The laboratory director should review the Internal Quality Control at least monthly
19) Controls must be run prior to reporting patient's results after critical changes [14]

Calculation and Use of Quality Control Statistics

1. **Mean:** Is the average or the laboratory's best estimate of the value of estimated specific level of control
2. **Standard deviation:** is a statistic that quantifies the closeness between the3 numerical values (QC values) are in relation to each other. It gives an idea with regards to repeatability or consistency; where the consistency may vary when repeatability is obtained
3. **Co-efficient of Variation:** Is the ration of the standard deviation to the mean expressed in the form of percentage
4. **Westgard Rules:** Dr.James Westgard of the University of Wisconsin established clinical laboratory quality control rules on the basis of evaluation of quality of analytical run for medical laboratories. These quality control rules are used since 1950s

a) **Rule 12s:** This is a warning rule that is violated when a single control observation is outside the ± 2s limits
b) **Rule 13s:** This rule identifies unacceptable random error and is a rule for action plan to remove the error
c) **Rule 22s:** This rule identifies systematic error only. The criteria for violation are Two consecutive QC results greater than 2s are on the same side of the mean
d) **Rule R4s:** This rule applies for the random error in a single run. If there is a 4s difference between control values within a single run
e) **Rule31s:**This rule is violated when three consecutive results are on one side of mean greater than 1s on the same side of the mean
f) **Rule41s:** This rule is violated when four consecutive results greater than 1 s are on the same side of the mean
g) **Rules :7 χ,8 χ,9 χ,10 χ,12 χ:** these rules are violated when there are 7 or 8or 9 or 10 or 12 control results on the same side of the mean; regardless of the specific standard deviation in which they are located
h) **Levy-Jennings Chart:** The graphical representation of the quality control data (QC data) in order to analyze it on statistical basis by the application of QC rules such as Westgard Rules [15].
i) **Standard Deviation Index (SDI):** It is a peer –based estimate of reliability.

It is calculated as SDI = (Lab- Group)/s Group

Where 1.25 or less is considered acceptable

1.25 -1.49 is considered accepted marginally

1.5 -1.99 is considered marginal performance and investigation of the test system is recommended

2.0 or greater unacceptable performance and remedial action is usually required [15]

II] External Quality Control: Widely known as External Quality Assessment Scheme (EQAS) in the late 1940s pioneered by Belk and Sunderman. It is an integral part of Total Quality Management System. EQA is a continuous process for quality improvement in which the participating laboratory was an outside, unbiased source to compare the quality of the patient's results.

By comparison the similarity and variation if any is recorded on a fortnight , monthly or six-monthly basis with the outside laboratory.

Steps in EQAS

1) Providing and sending QC material to all the participating laboratories
2) Measurement of the analytes to send best value and results by the participating laboratories
3) Data analysis and reporting the results to the laboratories participating
4) Interpretation of the evaluation report and take corrective actions for unacceptable results by each of the respective participating laboratory

Proficiency testing or External Quality Assurance (EQA) are terms used synonymously but there are slight differences between the two. The former is utilized in accreditation purposes whereas the later for quality control by an external agency [16].

Types of errors which is a measured of inaccuracy in the EQA results are transcription errors, pre –survey issues of outside laboratory (provider), sample receipt /handling ,test performance, data handling of EQA by provider , report and interpretation [17].

EQA is an important component of a laboratory's total Quality Management and is required by many national regulations of International Organization for Standardization (ISO) 15189 accreditation and by the Clinical and Laboratory Standards institute (CLSI) .QMS 24 document.

Although EQA is applied to analytical performances, the EQA process is also applied to pre-analytical stage.

Type I : registration of procedures by means of questionnaires .Few resources are required to organize and participate and relevant recommendations included.

Type II : sample analysis with simulated problems. However, only limited pre-analytical deviations can be assessed.

Type II : registration of incidences. This is utilized for harmonization of quality indicators (QIs) to pre-analytical stage to EQA providers.

Pre-analytical EQA schemes are more difficult to standardize however requires attention and improvement since the pre-analytical stage in error-prone and subjected to maximum chances of error [18].

External Quality Assurance Scheme program enables to improve the efficiency of the laboratory services, thereby optimizing the quality of the health –care facilities. It enables the participating laboratories to compare activities and modify their practices based on their own interpretations and provider laboratory. In clinical laboratory, EQAS evaluates the performance of procedures, equipment, materials, personnel and recommends areas of improvement. In India, CMC Vellore Christian Medical College , Vellore is one of the provider for EQAS program [19].

Calculation in EQA: Although there are variopus calculation methods wherein the final results maybe expressed in terms of Standard Deviation Index, Precision Index (PI) or Co-efficient of Variation Ratio or Z-score. However, an EQAS co-ordinator normally takes the following steps

1) The EQAS co-ordinator calculates the mean value (μ) and the standard deviation (s) of each peer group (individual participating laboratories)
2) Calculates the range μ ± 3s (Mean ± 3SD)
3) If the participating laboratories results are over 3s , these results are rejected
4) Calculates the range μ ± 2s (Mean ± 2SD)
5) If the participating laboratories results are over 2s , these results are rejected
6) The steps 4-5 are repeated until no values are outside the new range μ± 2s
7) Standard deviation Index is calculated
   $$SDI = \frac{\text{Laboratory result- Mean value of peer group}}{\text{Standard deviation of peer group}}$$
8) Precision Index (PI) = $\frac{\text{Standard deviation of the laboratory}}{\text{Standard deviation of peer group}}$
9) Co-efficient of Variation Ratio: $\frac{\text{CV of laboratory /month}}{\text{CV of Peer group /month (4)}}$

Maintenance of Quality or State of Control involves overall controlled

i) Chemical and critical reagents
ii) Compliance audits
iii) Instruments Maintenance & Qualification
iv) Laboratory Investigations
v) Analyst training and certification
vi) Assay Quality, Validation and Performance Evaluation (8)

Conclusions:

The modern clinical laboratory plays an active role in the health –care settings. Since the basis of diagnosis , prognosis , treatment and monitoring in the laboratory reports generated by the clinical laboratory. To prevent legal hassles and to satisfy the aware general public ; it becomes imperative to implement quality control policies and adhere to generating quality reports (20).

This article is an insight into the basics of the quality control and the processes and procedures directly and indirectly related to it. It is to understand that quality control is only a part of Total Quality Management system. However, it does contribute to a major role in producing results of clinical laboratory which can be relied upon due to the simultaneous Internal and External Quality Control Program which are administered simultaneously and continuously. Also due importance should be given to the procurement and maintenance of Control materials. The retrospective and progressive monitoring of Internal Quality control charts and EQAS program results further lays emphasis on the purpose of Quality control to take necessary corrective and preventive actions in the present and for the future .

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Conflict of Interest -None

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