Clinica Chimica Acta 571 (2025) 120240

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

# Ensuring internal quality control practices in medical Laboratories: IFCC recommendations for practical applications based on ISO 15189:2022

Jean-Marc Giannoli [a], Anne Vassault [b], Anna Carobene [c,*], Armand Perret Liaudet [d], Ivan M Blasutig [e,f,g], Pradeep Kumar Dabla [h], Ji Lin [i], Annette Thomas [j], José Antonio Tesser Poloni [k], Qing H Meng [l], Egon P Amann [m], on behalf of the International Federation of Clinical Chemistry, Laboratory Medicine Task Force on Global Lab Quality TF-GLQ

[a] Cerballiance Laboratory, CerbaHealthCare, AURA, Lyon, France
[b] University Paris City, Paris, France
[c] IRCCS Ospedale San Raffaele, Milan, Italy
[d] Hospices Civils de Lyon, Lyon, France
[e] Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[f] Children's Hospital of Eastern Ontario, Ottawa, Canada
[g] Eastern Ontario Regional Laboratory Association, Ottawa, Canada
[h] Department of Biochemistry, G. B Pant Institute of Postgraduate Medical Education & Research, Associated Maulana Azad Medical College, New Delhi, India
[i] AQR, Abbott Labs, Abbott Park, IL, USA
[j] Weqas, Cardiff and Vale University Health Board, Cardiff, UK
[k] Controllab, Rio de Janeiro, Brazil
[l] Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA
[m] University of Applied Sciences, Hamm-Lippstadt, Hamm, Germany

ARTICLE INFO

*Keywords*
IQC
ISO 15189:2022
Medical Laboratory
Quantitative results
Recommendation
Risk analysis

ABSTRACT

This document describes the guidance on implementing and monitoring an IQC strategy that fulfills the requirements of the Standard ISO 15189:2022. It also explores the practical application of these principles in daily IQC processes within medical laboratories. The goal is to provide a practical, user-friendly resource that not only explains the Standard's requirements but also equips laboratory professionals with the tools and knowledge needed to enhance diagnostic reliability.

To support laboratory professionals in this task, this document follows the structure and content of the ISO 15189:2022 Standard and provides a risk-based approach in consideration of the practical needs for quantitative results. Specific aspects such as the selection and assessment of IQC materials, the definition of control frequency, the definition of acceptable limits, the application of statistical rules, results from different sources comparability and strategies for handling non-conformities, quality indicators and determination of uncertainty of measurement are discussed in depth. Where relevant, excerpts from the ISO 15189:2022 Standard are included, with clarifications and actionable recommendations to facilitate implementation.

*Abbreviations:* AoN, average of normal; APS, Analytical Performance Specifications; BV, Biological Variation; CAP, Corrective Action Plan; ILC, Interlaboratory Comparison; CV, Coefficient of Variation; $CV_{90}$, 90th Percentile of the analytical Coefficient of Variation among a large group of users; $CV_I$, intra-subject Biological Variation; $CV_G$, inter-subjects Biological Variation; CVLT, Long Term Coefficient of Variation; DO, Optical Density; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; EQA, External Quality Assessment; EQAS, External Quality Assessment Scheme; EWMA, Exponentially Weighted Moving Average; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; IQC, Internal Quality Control; ISO, International Organization for Standardization; IT, Information Technology; IVD, In Vitro Diagnostic; LOQ, Limit of Quantification; MU, Measurement Uncertainty; NC, Non-Conformity; PBQRT, Proficiency-Based Quality Reference Testing; PED, Probability of Error Detection; PFR, Probability of False Rejection; POCT, Point-of-Care Testing; QIs, Quality Indicators; QC, Quality Control; SOP, Standard Operating Procedure; TAT, Turnaround Time; $TE_A$, Total Allowable Error.

* Corresponding author at: IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy.
*E-mail address:* carobene.anna@hsr.it (A. Carobene).

https://doi.org/10.1016/j.cca.2025.120240
Received 6 March 2025; Accepted 7 March 2025
Available online 8 March 2025

This document focuses on the crucial role of IQC in the accreditation process, particularly in the identification of risks, their mitigation through corrective actions and the implementation of improvements to prevent errors and control potential risks in the medical laboratory, ensuring patient safety in daily practice.

## 1. Introduction

One of the main goals of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is to enhance the quality and reliability of medical diagnostics provided by Medical Laboratories worldwide and to ensure optimal patient care. The ISO 15189:2022 standard has become a cornerstone in this endeavour, providing a comprehensive framework for quality and competence in medical laboratories [1]. Its adoption has highlighted the need for clear, harmonized guidance on implementing its provisions in everyday laboratory practice.

This document holds particular significance in the context of internal quality control (IQC) practices, considering the long-standing contributions of the IFCC to quality control in clinical laboratories. Decades ago, the IFCC set foundational recommendations on quality control in clinical chemistry [2], which outlined general principles and terminology in quality control. This series of six papers included a pivotal fourth paper entirely dedicated to IQC [3]. These historical recommendations provided the groundwork for quality assurance in laboratory testing at the time.

Since then, laboratory technologies, methodologies, and clinical requirements have evolved significantly. These advancements necessitate new and updated recommendations that reflect contemporary practices, incorporate modern standards such as ISO 15189:2022, and address the current needs of clinical laboratories.

## 2. Definitions

In the context of ISO 15189:2022, key terms and definitions play a crucial role in understanding and implementing the standard's requirements. For simplicity, we present *selected* definitions relevant to this document, omitting the detailed notes included in this ISO standard. For a comprehensive understanding and in-depth details, we recommend consulting the official ISO 15189:2022 document [1].

References for the definition shown are taken from the corresponding section EN ISO 15189:2022, *Medical laboratory – Requirements for quality and competence*, and are indicated in brackets. For terms not explicitly defined in this standard but included due to their importance, additional references are provided.

- Accuracy/Measurement accuracy/accuracy of measurement (3.18): closeness of agreement between a measured quantity value and a true quantity value of a measurand [4].
- Bias/measurement bias (3.1): estimate of a systematic measurement error.
- Clinical decision limit (3.3): examination (3.8) result that indicates a higher or adverse clinical outcome or is diagnostic for the presence of a specific disease.
- Commutability of a reference material/commutability (3.4): property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures and the relation obtained among the measurement results for other specified materials.
- Drift: a gradual change and consistent increase or decrease in results over time [5].
- Examination (3.8): set of operations having the objective of determining the numerical value, text value or characteristics of a property examination method.
- Examination procedure (3.9): specifically described set of operations used in the performance of an examination (3.8) according to a given method.
- External quality assessment (EQA) (3.10): evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons.
- Interlaboratory comparison (3.12): organization, performance and evaluation of measurements or examinations (3.8) on the same or similar materials by two or more independent laboratories in accordance with pre-determined conditions.
- Internal quality control (IQC)/Quality control QC (3.13): internal procedure which monitors the testing process to verify the system is working correctly and gives confidence that the results are reliable enough to be released.
- In vitro diagnostic (IVD) medical device (3.14): device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes and including reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.
- Measurement uncertainty (MU) (3.19): non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand based on the information used.
- Point-of-care testing (POCT) (3.22): examination (3.8) performed near or at the site of a patient.
- Precision: closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions time [4].
- Quality indicator (3.26): measure of the degree to which a large number of characteristics of an object fulfils requirements.
- Shift: a sudden change and constant deviation from the average. While precision is not affected, the plotted points consistently fall to one side or the other of the calculated mean value, indicating a shift in the distribution of control values resulting in a new mean [5].
- Trend: a progressive and consistent movement of results in one direction over time (unlike drift, a trend is typically identified through statistical analysis) [5].
- Trueness/measurement trueness (3.29): closeness of agreement between the average of an infinite number of replicates measured quantity values and a reference quantity value.
- Turnaround time (3.30): elapsed time between two specified points through pre-examination, examination, and post-examination processes.
- Validation (3.31): confirmation of plausibility for a specific intended use or application through the provision of objective evidence that specified requirements have been fulfilled.
- Verification (3.32): confirmation of truthfulness, through the provision of objective evidence that specified requirements have been fulfilled.

## 3. General principles (action to be taken according to ISO 15189: 2022 standard)

The recommendations outlined in this section are derived from Sections 7 and 8 of the ISO 15189:2022 standard, which serve as the foundation for ensuring the quality and competence of medical laboratory activities. These sections provide critical guidance on validating examination results, managing risks, and implementing effective quality management systems.

The purpose of this list, detailed below, is to consolidate key actions required to align IQC practices with ISO 15189:2022, emphasizing the importance of maintaining analytical precision, detecting deviations, and ensuring patient safety. By following these principles, laboratories can systematically address potential risks, ensure compliance with the standard, and enhance the reliability and reproducibility of diagnostic outcomes.

- The IQC procedure shall include a clear definition of the records to be maintained along with a schedule for regular review intervals.
- The personnel involved in testing must be qualified and properly trained to minimize inter-operator variability.
- IQC materials have to be processed under the same conditions as patient samples to ensure consistency and accuracy.
- The purpose of IQC is to identify deviations in performance from a predefined normal state. Apart from gross errors such as incorrect sample handling, mislabeling of samples, equipment malfunctions, or errors in data entry, the detected errors are typically of a random or systematic nature in the examination procedure.
- The frequency of determinations should be set as often as necessary to maintain the stability of the analytical process, with a minimum of once per series or once per working day. This frequency represents a balance between ensuring quality and managing risk, cost, and workload, and it should be clearly defined in the IQC procedure.
- IQC materials should exhibit stability, homogeneity, and commutability, with concentration levels and matrix characteristics similar to those of patient samples. The number and concentration level of IQC samples should be determined based on the clinical decision limit for each specific examination. Ensuring the stability, homogeneity, and commutability of IQC materials is primarily the responsibility of the control material manufacturer. However, laboratory professionals are responsible for selecting appropriate control materials that meet these criteria, even though they do not directly control these properties.
- Use long-term material lots as far as possible, to minimize the need for lot changes and lot-to-lot variation.
- Define specific criteria and analytical performance specifications (APS) according to different clinical situations, including the definition of clinical application and pertinent validity necessary to support informed clinical decision making.
- For non-conformities, re-examination should be conducted after implementing appropriate correction, followed by corrective actions if relevant, and the impact on other results should be assessed after achieving the most appropriate IQC result.
- Consider the use of third-party IQC materials as an alternative to, or in addition to, controls provided by the reagent supplier.
- Immediate action is required to control and correct the nonconformity.
- Provide clear instructions and define accountability to ensure operators have access to a Corrective Action Plan (CAP) in the event of an alert.
- IQC rules are partially based on statistical principles, *Westgard rules* being widely used [6,7].
- Conduct regular evaluations of current performance of methods and include peer review.
- Alternative options in case of unavailability of IQC materials:
  - The moving average of patient results [8].
  - Comparison of patient sample results with those obtained by an alternative procedure or retesting of stored patient samples.
- The use of unassayed IQC samples is effective for assessing the consistency of daily results (precision), but it is not suitable for evaluating the accuracy of the method.
- Participation in an IQC program associated with interlaboratory comparison using samples of known values is highly beneficial for promptly taking corrective actions and eliminating the root cause of the non-conformities (NC).
- Indicators, such as the number of NC per examination and level ratio, should be evaluated over different periods (e.g. day/night etc.).

To systematically address potential risks and opportunities for improvement, laboratories should refer to standardized risk management frameworks [9]. A detailed summary of analytical risks and mitigation strategies is provided in Table 1.

## 4. Objectives of IQC

The objectives of IQC outlined in this section are drawn from Sections 7.3.7 and 8.6 of the ISO 15189:2022 standard, which emphasize ensuring the validity of examination results and driving continual improvement in laboratory practices. These objectives define the purpose of IQC as a critical tool for maintaining accuracy and reproducibility in laboratory testing.

This section highlights the key goals of IQC, including monitoring analytical performance, detecting trends or shifts, identifying risks and improvements, implementing corrective actions, and ensuring the quality of results before their release. By adhering to these objectives, laboratories can proactively identify and mitigate risks, demonstrate ongoing improvements, and maintain compliance with ISO 15189:2022 requirements, thereby supporting optimal patient care and diagnostic accuracy.

The primary objective of IQC is to ensure that each analytical result is appropriately reproducible and accurate according to the criteria defined at the time of testing, thereby confirming the quality of the examination results before they are released for clinical use.

- To monitor the analytical process and detect early signs of performance changes (such as trends or shifts in QC values) which could compromise the reliability of the examination results, IQC monitors the consistency of analytical performance of laboratory measurement systems.
- To implement improvement actions based on the detection of trends or deviations, IQC enables the laboratory to proactively implement corrective and identify risks and opportunities for improvement, reducing the risk of future non-conformities and ensuring consistent test performance.
- To monitor the effectiveness of any corrective actions or improvements, IQC serves to assess the effectiveness of these actions by comparing current performance against predefined criteria, ensuring that the desired quality standards are maintained.
- To demonstrate improvements, IQC provides a framework for documenting continuous improvement in the laboratory's performance by demonstrating a reduction in errors or deviations over time, thereby enhancing overall diagnostic accuracy and appropriate patient care.

The laboratory shall have a procedure for monitoring the validity of results. The resulting data shall be recorded in such a way that trends and shifts are detectable and, where practicable, statistical techniques shall be applied to review the results. This monitoring shall be planned and reviewed (ISO 15189: 2022 7.3.7.1).

For those purposes, results obtained with control materials are interpreted as follows:

- *Immediate interpretation*

This involves analysing the control results as soon as they are available, to promptly identify any deviations or errors that could affect the current batch of patient results. Immediate interpretation allows for quick curative actions to prevent the release of inaccurate results.

- *Short-term interpretation*

**Table 1**
Identification and Management of Analytical Risks in Internal Quality Control (IQC).

| Risk | Identification of risk and potentially erroneous result | Recommendations: suppliers or best practices | Limitations of these recommendations | Effectiveness of correction | Other possible actions (master plan) | Residual risk | Indicators |
|---|---|---|---|---|---|---|---|
| 1 | Deterioration of reagent during transport.<br><br>Degradation of reagents due to improper handling or temperature fluctuations during shipping, leading to potential inaccurate test results or delayed reporting. | − Use separate shipments for reagents and control materials to minimize widespread quality issues.<br>− Conduct thorough inspections upon receipt to identify potential risks, including damage or temperature deviations.<br>− Implement real-time temperature monitoring and tracking during transport.<br>−Require suppliers to provide validated shipping conditions and stability data. | − Temperature deviations may occur despite validated shipping conditions.<br>− Inspection at receipt may not always detect early-stage reagent degradation.<br>− Internal control materials may not always identify reagent instability immediately. | Partial. | − Separate reagents and IQC materials when ordering.<br>− Monitor the storage of IQCs (temperature) and be aware of acceptance tests.<br>− Check the expiry date before and after the vials are opened.<br>− Use multiple control levels (LOQ, threshold value, linearity limit) to detect potential degradation effects over time.<br>− Acceptable limits adapted to detect trend and shift.<br>− Acceptable limits adapted to clinical needs.<br>− Implement supplier audits for compliance with transport standards. | Acceptable. | − Number of non-conformities reported upon reagent receipt.<br>− Number of non-conformities due to inappropriate storage.<br>− Non-conformities detected during the internal technical audit.<br>− IQC CV monitoring.<br>− Recording of EQA compliance and non-compliance and periodic review. |
| 2 | Inappropriate calibration data.<br><br>Potentially erroneous result and delayed reporting of results. | − Acceptable limits of the calibrator signal (software).<br>− Verification of calibration data with appropriate acceptable criteria.<br>− Utilize automated calibration verification tools to detect anomalies promptly.<br>− Systematic IQC post-calibration.<br>− Define and implement SOPs for calibration verification. | Possible drift or shift between 2 IQC results (with new batches). | Partial. | − IQC before/after recalibration.<br>− Analyse multiple patient samples before and after calibration.<br>− Frequency strategy for performing IQC based on the number of analyses and the criticality of the analyte.<br>− Participation in EQA.<br>− Monitoring of temperature and temperature variations.<br>−Implement automated trend analysis to detect systematic deviations. | Acceptable. | −Number of calibration failures.<br>− Number of additional calibrations as compared to the supplier specification.<br>− Number of calibrations outside the supplier's specifications.<br>− Number of extra-calibrations.<br>− IQC CV data and follow-up.<br>− Conformity of EQA results. |
| 3 | Micro clogging that totally or partially obstructs the system.<br><br>Potentially erroneous result and instrument shutdown. | − Measurement of the pressure in the pipetting system (if available and if the analyser alarm exists).<br>− Optical detection for checking the volume of the sample taken.<br>− Use preemptive system flushing and self-cleaning mechanisms.<br>− Implement automated clogging detection and alert system. | Micro-clots are not detected. | Partial. | − Time management before centrifugation.<br>− Visual inspection of samples.<br>− Monitor the frequency of clogging problems.<br>− IQC before and after maintenance (syringe exchange, decontamination).<br>− Implement preventive maintenance schedules to minimize clogging risks. | Acceptable. | Number of non-conformities due to total or partial fouling or clogging. |
| 4 | Defective maintenance.<br><br>Instrument malfunction or shutdown due to inadequate or irregular maintenance, potentially leading to delayed results,. | − Establish a preventive maintenance schedule aligned with manufacturer recommendations.<br>− Implement a maintenance log and quality assurance | − Unexpected failures may still occur despite preventive maintenance.<br>− Variability in operator compliance with maintenance protocols.<br>Maintenance-induced drift or instability may | Partial. | − Conduct IQC testing before and after maintenance to assess instrument stability (syringe exchange, decontamination).<br>− Analyse several patient samples that | Acceptable. | − Number of IQCs failures following maintenance.<br>− Frequency of maintenance-related system malfunctions. |

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**Table 1** (*continued*)

| Risk | Identification of risk and potentially erroneous result | Recommendations: suppliers or best practices | Limitations of these recommendations | Effectiveness of correction | Other possible actions (master plan) | Residual risk | Indicators |
|---|---|---|---|---|---|---|---|
| | | checklist.<br>− Require recalibration and IQC verification after maintenance interventions. | not be immediately detectable. | | were analyzed prior to maintenance.<br>− Implement a sentinel test strategy to detect subtle performance variations post-maintenance.<br>−Control of maintenance operations in terms of system stability.<br>− Require periodic training for maintenance personnel. | | − Number of unexpected instrument downtimes due to maintenance issues.<br>− Non-conformities detected during an internal audit. |
| 5 | Deterioration of the reagent during storage or use; use of expired reagents.<br><br>Potentially erroneous result and possible delayed reporting of results. | − Reagent degradation over time, improper storage conditions, or use beyond the expiration date.<br>− Software to signal error detection (baseline, DO calibration).<br>− IQC strategy.<br>−Implement automated tracking of reagent usage and expiry dates. | − Automated tracking may not detect degradation in open reagents over time.<br>− IQC monitoring may not immediately capture gradual reagent instability.<br>− Variability in environmental conditions may accelerate reagent deterioration. | Partial for open reagents. | −Training, user qualification.<br>−Maintain traceability of reagent usage, including date of opening and storage conditions.<br>−Maintain traceability of reagent usage, including date of opening and storage conditions.<br>− Introduce a redundancy system, such as multiple QC levels, to detect reagent degradation. | Acceptable. | − Internal audit findings on reagent handling and storage compliance.<br><br>− Frequency of IQC failures linked to reagent degradation.<br><br>− Internal audit findings on reagent handling and storage compliance |
| 6 | System failure (locking and non-locking).<br><br>Instrument shutdown and possible delayed reporting of results. | − Implement redundant system monitoring tools.<br>− Utilize predictive maintenance software to detect early signs of failure. | − No detection of abnormalities prior to failure. | Partial for failure blocking. | − IQC after maintenance.<br>− Retesting patient samples after resolving the problem.<br>− Develop a contingency plan to ensure continuity in case of system failure.<br>. | Acceptable. | − Number of patient reports recalled.<br>− Number of blocking failures. |
| 7 | Uncontrolled environmental conditions (temperature drift over time).<br><br>Potentially erroneous result. | − Definition of minimum/maximum temperature limits.<br>− Variation of the temperature between the calibration phase and the analysis phase and during the analysis phase.<br>− Require real-time temperature monitoring systems. | Lack of monitoring of temperature changes over time. | Partial if variations are within acceptable temperature limits. | − Traceability of temperature variations as a function of operations (calibration, IQC, patient samples).<br>− Bracketed series by additional controls or tests on patient samples.<br>− Install automated environmental monitoring systems with alerts. | Acceptable. | − Use of temperature monitoring data during the analysis process.<br>− Monitoring of temperature control cards. |
| 8 | Deviations over time (drift).<br><br>Gradual changes in test results due to instrument wear, reagent degradation, calibration drift, or environmental influences, potentially leading to clinically significant errors if not detected in time. | − Implement a structured IQC strategy tailored to reagent and analyte stability.<br>− Define appropriate IQC frequency based on analytical robustness and clinical risk.<br>− Utilize *Westgard rules* or advanced statistical methods to identify systematic trends.<br>− Establish acceptable control limits aligned with method performance and clinical decision-making needs. | − IQC intervals may not always capture subtle trends in real-time.<br>−Frequency too low.<br>− Wide acceptable limits may delay drift detection.<br>− Inadequate *Westgard rules*. | Partial. | −Use advanced statistical techniques for drift analysis.<br>− IQC with acceptable limits adapted to the actual performance of the analyser and clinical needs.<br>− Visual assessment of drift and trend control charts.<br>− Monitoring of CVs according to relevant specifications.<br>− 6 Sigma calculation;<br>− Monitoring of patient mean values.<br>− If several analysers, | Acceptable. | − Frequency of long-term CV monitoring by analyte and instrument.<br>− Percentage of IQC failures attributed to drift.<br>− Conformity of CVs with established APS.<br>− Number of corrective actions initiated due to detected drift. |

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**Table 1** (*continued*)

| Risk | Identification of risk and potentially erroneous result | Recommendations: suppliers or best practices | Limitations of these recommendations | Effectiveness of correction | Other possible actions (master plan) | Residual risk | Indicators |
|---|---|---|---|---|---|---|---|
| | | | | | check for comparability.<br>– Implement systematic bias evaluation with peer groups. | | |
| 9 | Operator error (manual techniques).<br><br>Inconsistent or inaccurate test results due to human errors in manual procedures. | – Authorization of qualification (skills assessment). | – Diversion of practices.<br>– Variability in adherence to standardized procedures. | Partial. | – Appropriate frequency of authorizations.<br>– Audit with observation of practices (inter-operator variability).<br>– Checking manual entry.<br>– Implement refresher training at regular intervals. | Acceptable. | – Monitoring of IQC and EQA per operator. |
| 10 | Operator error (automatic techniques).<br><br>Potentially erroneous results due to unintended or unauthorized modifications to system settings, misinterpretation of automated alerts, or improper interaction with the system interface. | – Implement role-based access control with unique user authentication.<br>– Require frequent password updates and administrator-level authentication for configuration changes.<br>– Enable automatic logging of user activities and access to maintain traceability and accountability. | – Security measures prevent unauthorized modifications but do not eliminate operator mistakes in following procedures. | Partial. | – Password security.<br>– Implement IT security protocols to prevent unauthorized system modifications.<br>–Conduct regular audits of system logs to detect irregular activity. | Acceptable. | – Number of unauthorized or erroneous system modifications detected.<br>– IT security audit results.<br>– Frequency of system configuration changes. |

Abbreviation list: APS. Analytical Performance Specifications, CV, coefficient of variation; DO, Optical Density; EQA, External quality Assessment; IQC, internal quality control; IT, Information Technology; LOQ, Limit of Quantification; SOPs, standard operating procedures.

Short-term interpretation focuses on monitoring control results over a shorter timeframe, such as a single day or series of runs, to detect any trends or patterns that may indicate a potential issue. This approach helps identify issues that may not be immediately obvious but could compromise quality if left unaddressed.

- *Long-term interpretation*

Long-term interpretation involves evaluating control results over extended periods, such as weeks or months, to assess the overall stability and reliability of the analytical process. This approach helps to understand the cumulative performance trends and identify persistent biases or systematic errors that require process optimization or recalibration.

One goal of IQC is to detect trends, shifts or deviations of analytical performance where results begin to diverge from established statistical norms.

Another goal is to prevent the release of non-conforming results that could negatively impact patient care when IQC results fall outside the defined allowable limits based on clinical data. Therefore, the laboratory should define specific allowable limits both for the early detection of performance changes, such as trends and shifts and for the rejection of abnormal results to ensure the highest standards of diagnostic accuracy and patient safety.

## 5. Quality control materials

The recommendations provided in this section are based on Sections 7.3.7.2 and 6.6 of the ISO 15189:2022 standard, which outline the requirements for selecting, acceptance testing, and managing quality control (QC) materials in medical laboratories. These guidelines emphasize the critical role of QC materials in ensuring the accuracy and consistency of laboratory results.

This section focuses on the selection criteria for QC materials, including their stability, homogeneity, and commutability, as well as their alignment with clinical decision levels.

### 5.1. Selection of control materials

According to ISO 15189:2022 (7.3.7.2.b), IQC materials shall meet the specific requirements to ensure reliable laboratory performance. The Standard outlines the following key criteria:

- Matrix: control materials should be similar to that of patient samples as closely as possible. The non-commutability of IQCs is not prohibitive, provided they are more sensitive to analytical issues than patient samples (for intra-laboratory reproducibility monitoring).
- Frequency of result review: the review of IQC results should be conducted as frequently as necessary according to the stability of the method and the risk of impact on the patient care in the event of an erroneous result.
- Control concentration levels: the concentrations of control materials should be as close as possible to clinical decision levels and cover the measurement range where possible.

Note: For those interested in understanding the topic of commutability in greater detail, several relevant papers by the IFCC provide comprehensive insights [10–12].

The ISO 15189: 2022 standard recommends the use of (or in addition to) IQCs that are independent of the reagent's supplier to control a potential risk of non-detection of drift when changing reagent. However, in this case, fresh (or frozen) aliquot of patient samples can also be used.

Consideration should be given to the following:

- *Nature of the sample*

- o Frozen form: Thawing conditions may need to be considered such as temperature and time as well as ensuring adequate mixing.
- o Lyophilized form: Consideration need to be given to the nature, purity and volume of the reconstitution liquid as well as the accuracy and reproducibility of the pipette used. Homogenization of the final solution can be checked by visual inspection or absorbance stability.
- o Liquid form: Homogeneity can be assessed by visual inspection.

- *Concentration levels*

The number and concentration levels of IQCs materials shall be defined to ensure they cover the clinically relevant range of measurements, including the clinical decision limits as well as an analytical range to allow for verification of calibration.

- *Commutability*

The matrix of the QC materials selected should be as close as possible to the patient sample matrix. It should provide the same result as clinical samples containing the same amount of an analyte when measured using different reagent lots or different measurement procedures [13,14].

- *Stability*
  - o Stability can be defined as shelf-life and open vial (in-use) at various storage temperature conditions (room temperature, refrigerator, freezer) and before and after pre-treatment of the control materials at various storage.
  - o The IQC procedure has to be defined depending on the length of stability of the IQC material.
- *Homogeneity*
  - o It is essential to keep sample-to-sample variation as low as possible.
  - o Vial-to-vial variation needs to be checked for each lot especially for lyophilized materials.

### 5.2. Verification of conformity of IQC materials for intended use

In accordance with ISO 15189:2022 (7.3.7.2) and ISO 15189:2022 (6.6.3) on acceptance testing, laboratories shall implement a structured approach to verify the performance of reagents and consumables. This involves establishing an acceptance strategy based on risk analysis, which may include supplier-provided data, certificates of conformity, and a comprehensive quality control plan.

For each change in the IQC control lot, the laboratory must calculate and establish new target values and interpretation thresholds. These values are determined through preliminary testing, as defined by the laboratory, taking into account the specificity of the test and the validity period of the batch.

During this acceptance testing phase, the conformity of the method is maintained using the existing control lot in use and assessed to confirm method performance stability and acceptability.

The average of the results is used to determine the initial target value, and thresholds for new control charts may be adjusted if necessary.

The number of preliminary determinations is adapted on the duration of IQC batch use, which can range from very short periods (e.g. 1 to 2 days for hematology) to longer durations for fields like hemostasis or biochemistry, where IQC batches may last several months. In cases where direct empirical data are limited, statistical methods such as Bayesian approaches can help refine estimates of target values and acceptable limits by incorporating prior knowledge and observed data [15,16].

The objective of acceptance testing is to ensure that the product (reagent, IQC material or consumable) meets the laboratory's requirements before it is authorized for use. The testing should be conducted early enough to allow sufficient time for obtaining a new batch, organizing a backup plan, or subcontracting, thereby avoiding any production interruption that could pose risks to patients during critical testing. The testing strategy for each analyte is defined based on available data and an assessment of identified risks.

### 5.3. New batch of IQC materials

When introducing a new batch of IQC materials, laboratories must establish baseline performance parameters to ensure consistency and reliability in quality control processes. The following recommendations, outlined in [17], provide a structured approach for determining key analytical values:

- Determination of the target value by the laboratory through a minimum of 10 measurements over 10 days.
- Calculation of the standard deviation by the laboratory based on a minimum of 20 measurements.
- Calculation of the control limits using the means and standard deviation from laboratory results, or apply a standard deviation defined by the laboratory based on its experience.

These data should be updated after a few weeks to incorporate greater real-world variability, accounting for factors such as maintenance and calibrations. Additionally, the laboratory may utilize results from peer group methods as part of a trueness assessment approach (external comparison of IQC program) and to reduce the duration of the probationary phase [18].

### 5.4. New reagent batch and formulation change

When introducing a new reagent batch or formulation, laboratories must conduct a thorough assessment to ensure analytical consistency and minimize the impact of potential variations. The following guidelines outline the necessary steps for evaluating both new reagent batches and new reagent formulations or references:

*New reagent batch.*

- Risk analysis must be conducted during method verification or validation to assess the impact of the change of the product lot (e.g., diluent, reagent, calibrator).
- Consider whether the product is critical and assess its robustness. (see definition of robustness below).
- The analysis of "fresh" patient samples remains the gold standard; however, alternative methods, such as averaging patient results or using pooled samples, can also be employed.
- Isolated measurements of IQC materials to validate new batch of reagents are generally not recommended.
- For certain substrate tests (e.g. serum/plasma glucose, cholesterol, etc.), the commutability of IQCs is often sufficient. In endocrinology, lot-to-lot variability is common, and IQC comparison may not always be relevant. For tumour markers, where IQC materials are often non-commutable, the use of fresh patient samples is strongly recommended [19].

*New reagent formulation or new reference.*

When a reagent formulation or a reference value is modified by the supplier, the laboratory must conduct an impact assessment, based on the supplier's documentation. This assessment may include:

- A straightforward bibliographic review, which verifies whether changes, such as packaging, change of storage conditions, have a negligible impact on the method. The aim is to confirm that these modifications do not affect the analytical process or results.
- Comparative evaluations of results if a new calibrator is introduced. These evaluations should investigate potential impacts on accuracy, precision and reference values.

- A method verification in case of major changes.

## 6. Definition of IQC frequency

The recommendations in this section are derived from Section 7.3.7.2(d) of the ISO 15189:2022 standard, which provides guidance on determining the frequency of IQC procedures. This aspect is essential to maintaining the stability and reliability of analytical processes while balancing workload, cost, and patient safety [20].

This section emphasizes the need to define the frequency of IQC based on method robustness, clinical criticality, and risk analysis. It also outlines strategies for determining IQC scheduling, incorporating key factors such as calibration, critical events, calibrator and reagent stability. By following these principles, laboratories can ensure continuous monitoring of analytical performance in compliance with ISO 15189:2022, safeguarding the quality of test results and enabling timely identification of performance deviations.

### 6.1. Evaluation of the robustness of the method

In accordance with ISO 15189:2022 (7.3.7.2.d), laboratories must assess the robustness of analytical methods to ensure consistent performance and reliability.

One widely used approach for this evaluation is the Six Sigma methodology [21], which quantifies analytical quality using the formula:

$\text{Sigma} = (TE_A - \text{Bias})/CV$.

where $TE_A$ (total allowable error) represents the predefined analytical quality specification chosen by the laboratory, Bias indicates systematic deviation from the true value, and CV (Coefficient of variation) measures method precision. The difficulty lies in the choice of the $TE_A$, which has a significant impact on the Sigma value. There is no general consensus as to the selection of $TE_A$, although the Milan models for establishing APS may offer a solution in the future [22,23]. There is also currently a debate on the sigma calculation formula taking or not the bias into account [24,25].

The Sigma calculation can be used to define the IQCs strategy for establishing the frequency of testing QC materials. The Six Sigma approach is also suitable for large series.

### 6.2. IQC planning

In accordance with ISO 15189:2022 (7.3.7.2.d), laboratories must establish a structured approach for planning IQC procedures, including determining the number of tests in a series and the frequency of IQC assessments.

The laboratory must determine both the frequency of IQCs and the size of the series, which refers to the number of patient sample analyses performed for an analyte between two IQCs events. While the sigma level serves as a valuable tool for assessing the robustness of the method, additional factors must be considered as part of a comprehensive risk analysis:

- The clinical significance and criticality of the analyte.
- The time frame required for the result release and subsequent use.
- The feasibility of re-analysing samples, particularly for tests with strict pre-analytical requirements (e.g. blood gas analysis, where re-testing may not be possible).

Note: Some authors, in recent publications, propose to adapt the size of the series according to the Sigma level and the choice of *Westgard rules* [6,7].

### 6.3. IQC's scheduling frequency/ establishing the series and critical events

The laboratory must identify factors that could potentially affect the robustness of the method. Critical events or critical control points, such as calibration, instrument maintenance, replacement of parts, adjustments, change of reagents, batches or calibrators, should be defined to determine when a series concludes.

- *The strategy for scheduling IQC should be based on:*
  - o Defining the frequency of IQC material usage [26].
  - o Determining the number of QC materials levels used.
  - o Positioning IQC within the series (e.g. just after the calibration process, at the end of the series, one QC material each given number of patient samples according to the risk analysis).
  - o Identifying any events that may have an impact.
  - o Establishing acceptable limits and choosing rules for interpreting control charts.
- *Key considerations when establishing the series include:*
  - o Sample stability, with risk analysis for the analyte that do not allow re-testing (e.g. bicarbonates).
  - o The criticality of tests in emergency cases (e.g. troponin, D-Dimer, complete blood count, etc.) ensuring IQC is performed before closing the series.
  - o The robustness of the analytical method employed.
  - o Manufacturer recommendations.
  - o Regional regulations.

The laboratory therefore defines the series strategy based on IQCs practices. It can be reasonably assumed that the method is stable and in control for that pre-determined time period and number of samples.

This pre-determined time period needs to be defined by the laboratory during the method verification or validation period.

- *Position of maintenance activities (manufacturer or and (or) in-house) in the IQCs schedule*
  - o Maintenance activities may impact the performance of the method, and it is crucial to document and evaluate these impacts according to the supplier's recommendation.
  - o To proactively implement corrective action and identify risks and opportunities for improvement, reducing the risk of future non-conformities and ensuring consistent test performance, the impact of maintenance on system stability should be assessed.
  - o The simplest way to monitor these impacts is to perform IQC testing both before and after maintenance activities.
  - o Alternatively, other methods, such as re-testing patient samples, may also be employed to monitor stability.
- *Positioning of the curative maintenance*

Curative maintenance may unexpectedly impact the system potentially requiring the series to end prematurely. It is essential for the laboratory to verify that no drift or significant deviation occurred before failure.

## 7. Defining acceptability criteria

The recommendations in this section are based on Section 7.3.7.2(e) of the ISO 15189:2022 standard, which highlights the importance of defining specific criteria for acceptable analytical performance. These criteria are essential for identifying abnormalities, trends and shifts, and deviations in test results to ensure the reliability and validity of laboratory measurements.

This section focuses on establishing acceptable limits for precision, bias, and other performance metrics using tools such as control charts and statistical rules. By adhering to these guidelines, laboratories can maintain compliance with ISO 15189:2022, enhance diagnostic accuracy, and minimize the risk of releasing non-conforming results.

### 7.1. Acceptability criteria based on precision data

The main objective is to detect abnormalities and trends (e.g., shift and drift) and to ensure that results meet the required quality specifications.

It is important not to confuse drift and shift: drift refers to a gradual and consistent increase or decrease in results over time, whereas shift indicates a sudden and constant deviation from the average.

The laboratory should select precision criteria (expressed as CVs) for each analyte according to the performance of the usual situation (evaluation from long-term previous batches). These CVs, referred to as the laboratory's long-term CVs (CVLT) calculated using results observed during several months, account for all sources of variability in the method and are used to define acceptable limits for control charts.

When multiple identical instruments are used, a number of approaches can be used to establish the imprecision (CV). One approach is to use the $CV_{90}$, which represents the 90th percentile of the observed analytical CV among a large number of users of the same analytical system, this provides a robust estimate of what is achievable. A second approach relies on using an objectively derived APS based on biological variation (BV), which is used to derive APS objectively. A third approach seeks a compromise between BV and the state-of-the-art methods. This method accounts for both BV and the most current analytical capabilities, ensuring that realistic yet stringent quality standards are applied [26–30].

It may be useful to undertake an exercise to compare the observed CVs to those from other sources which might include:

- Primarily, the CV established as standard for the specific analytical system in use.
- CVs resulting from BV estimated as reported by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) BV database [31,32].
- CVs reported by the manufacturer.
- CVs from peer groups where IQC is associated with interlaboratory comparison (ILC) or external comparison of IQCs.
- CVs based on recommendations from international or national organizations.
- CVs from the EQAS providers [33,34].

### 7.2. Establishing the Levey-Jennings Control Chart

The use of Levey-Jennings charts in QC is based on identifying whether a given value falls within the expected "normal" distribution or deviates from the usual defined situation. A deviation typically manifests as either a random or a systematic error, both of which may indicate a malfunction in the analytical process.

Estimating statistical parameters, such as the mean, standard deviation, or CV, relies on sampling data to infer population characteristics. However, if the dataset includes values from two different populations, the calculation becomes unreliable. In a well-controlled analytical process, the "normal" dispersion of the observed values is attributed to the "common" causes, meaning that IQC results should accurately reflect the method's inherent performance.

If an analytical malfunction is identified through out-of-control values – such as deviations of statistical QC rules (e.g. 1-3S, 2-2S, R-4S) – it indicates the presence of an "exceptional" cause. Values obtained under these conditions fall outside the expected "normal" range, indicating that the IQC is out of control. As a result, patient results should not be released until the underlying issue has been identified and resolved.

However, if the re-running IQC yields results that fall within the predefined acceptable limits, the previously flagged value may be reassessed. In this case, if no persistent issue is identified, the value can be reintegrated into the dataset for CV calculation.

IQC results included in the calculation of the laboratory's intermediate precision expressed as CV should accurately represent the actual performance of the analytical method and remain consistent with patient results.

Major errors, such as incorrect assignment of IQC levels or the use of vial beyond its shelf life, do not provide a reliable measure of the method performance and should therefore be omitted from the CV calculation. Similarly, if there are significant change in the conditions of applying the method, such as the introduction of a new reagent batch or recalibration, non-compliant IQC values obtained before the transition should be excluded from the CV. However, if a deviation is systematic and justified, the laboratory may reassign or adjust the target value accordingly (see below, paragraph 8.3).

Conversely, in the absence of any change in the conditions of applying the method, and if the same IQC material remains in use, there is no valid justification for omitting IQC results from the CV calculation.

### 7.3. Establishing IQC target values

Each laboratory determines the target value by calculating the average of measurements obtained during the acceptance testing period. This target value serves as the baseline for the establishment of the control chart. If the peer group average is available, the target value may be adjusted accordingly. The calculation of the target value should be based on a sufficiently large dataset collected over an adequate timeframe.

When adjustments to the target value are made, the laboratory is required to document the retargeting process, including comparative evaluations with peer groups or EQAs.

Any "retargeting" must be supported by an in-depth investigation into potential sources of variation, such as personnel change, QC material stability, calibration issue, reagent batch changes, or maintenance activities.

If after making changes, the IQC mean shows a shift exceeding one standard deviation, the laboratory must retarget the mean to reduce the risk of false rejection and false acceptances.

Additionally, the laboratory has to check that no trueness errors (e.g., deviation from the peer group average, if available) or accuracy (as assessed through EQAS data) have occurred.

## 8. Statistical control rules (Risks 2, 5, 6, 8)

The recommendations in this section are based on Section 7.3.7.2 (e) of the ISO 15189:2022 standard, which underpins the importance of applying statistical principles to monitor and maintain the validity of laboratory examination results. Statistical control rules provide a structured approach to detecting trends, shifts, and deviations in analytical performance.

This section outlines the application of statistical tools, including widely used control rules such as Westgard rules, to assess the stability and reliability of analytical methods [35,36].

The *Westgard rules* are designed to ensure analytical reliability by achieving the following objectives:

- Detection of errors: identifying gross error, systematic and random analytical error.
- Prevention of erroneous result release: halting the reporting of patient results in the event of a proven error.
- Bias estimation and impact assessment: evaluating the extent of bias (error) introduced in previously reported results to determine its potential impact on patient care.

From a statistical perspective, the goals of implementing the *Westgard rules* include:

- High probability of error detection (PED $\geq$ 90 %): ensuring that in case of analytical issue dysfunction, the system is highly likely to detect it. A PED above 90 % is recommended to maximize reliability.
- Low probability of false rejection (PFR $\leq$ 5 %): minimizing the risk of incorrectly rejecting a valid analytical run. A PFR below 5 % helps prevent unnecessary repeat testing and workflow disruptions.

Some international recommendations allow choosing, as a minimum, the rejection rules —such as 1-3S, 2-2S, and R4S—without necessarily considering the robustness of the analytical method [37]. However, this approach carries the risk of imposing overly stringent quality requirements ("over-quality"), potentially leading to unnecessary rejections and inefficiencies [38].

Due to the significant improvement of precision for some analytes since the publication of these rules, which are based only on standard deviation values, some reported discrepancies may lack clinical relevance. These discrepancies could be due to by minor variations in environmental conditions that are unrelated to the analytical system.

Other approaches propose adapting the *Westgard rules* based on the Sigma level and error detection probabilities, adjusting control strategies according to the analytical performance of the method [39,40]. However, this adaptation does not necessarily consider the clinical impact of an analytical performance issue.

In cases of non-conformity at the end of an analytical series, laboratories have to assess the deviation not only in terms of analytical performance and improvement actions but also concerning clinical decision-making. The significance of the deviation will vary depending on the clinical application—whether for interpretation, diagnosis, prevention, monitoring, screening, prognosis, or epidemiological studies.

Thus, two levels of assessment should be considered:

- Analytical Acceptable Limits – based on statistical performance and predefined quality specifications.
- Clinically Acceptable Limits – determined by the potential medical impact of an analytical deviation on patient care.

In cases where IQC rules indicate failure, laboratories must ensure traceability and corrective/improvement actions to identify and mitigate risk to prevent recurrences. The workflow for handling IQC failures is demonstrated in Supplementary Material, *A routine day in a Clinical Lab*.doc and Fig. 2.

## 9. Alternative methods for monitoring performance

The recommendations in this section are based on Section 7.3.7 of the ISO 15189:2022 standard, which provides flexibility for laboratories to implement alternative approaches to monitor analytical performance when traditional IQC methods are not feasible or sufficient. These alternative methods can enhance the laboratory's ability to ensure the validity of results under varying conditions.

This section highlights techniques such as the moving average of patient results, retesting stored samples, or comparing patient sample results with alternative methods.

These strategies can also complement the standard methods described in this paper for IQCs and offers an additional tool to external evaluation of the IQC and EQAs.

They are not mandatory but may provide additional information if used correctly [13].

### 9.1. Proficiency-based quality reference testing (PBQRT)

To enhance the detection of subtle trends, in 1959 Roberts introduced the exponentially weighted moving average (EWMA), a statistical method based on Bayesian principles [41]. This approach assigns greater weight to recent data points while gradually reducing the influence of older values, making it particularly effective in identifying gradual shifts in analytical performance. More recently, Badrick expanded on this concept by developing Proficiency-based quality reference testing (PBQRT) [42]. This method applies the EWMA principle to laboratory quality control, prioritizing the most recent results to enable earlier detection of small deviations and systematic errors. By emphasizing recent trends, PBQRT enhances the sensitivity of quality control monitoring, allowing laboratories to identify performance issues more efficiently and implement curative actions promptly.

### 9.2. Moving mean or average of normal (AoN)

Monitoring through the moving mean of through patient results or AoN (that use bulls' algorithm) can serve as a valuable Supplementary tool for the early detection of drift or shift in an analytical system [43,44]. This method has the advantage of evaluating potential bias in an assay relative to a human sample matrix, making it particularly useful in addressing commutability issues or detecting the deterioration of IQC materials. However, its applicability is test-dependent, and it is not suitable for all analytes, such as infectious serology or tumour markers, where population variability may compromise its effectiveness.

When implementing AoN, the following considerations are crucial:

- Population size & stability: The dataset must be sufficiently large to ensure reliable statistical calculations, and patient populations should remain stable over time. Certain patient groups—such as those in dialysis, intensive care, or emergency departments—should be excluded, as they may introduce significant variability. Additionally, AoN is not suitable for weekend hospital laboratories, where only critically ill patients may be tested, leading to biased averages.
- Definition of acceptable limits: the laboratory must establish control limits for AoN monitoring. While the CV derived from patient samples may differ from that of IQCs, the defined limits should be at least comparable to ensure meaningful quality control.
- Response to alerts: a predefined action plan must be in place for instances where patient mean values deviate beyond acceptable thresholds. This should include investigation protocols, verification with alternative quality control measures, and corrective actions if an analytical issue is confirmed.

### 9.3. Retesting of patient samples

Repeated analysis of patient samples throughout the day—within the constraints of analyte stability—can serve as a performance control tool, often referred to as a "patient reference sample" or "patient QC". By applying an acceptance criterion of 2.8 times the standard deviation (SD) of the method, this approach provides a robust means of monitoring analytical performance system [45 –47]. This method is particularly useful in compensating for the non-commutability of certain IQC materials, ensuring that the analytical system remains stable when applied to actual patient specimens. Additionally, systematic retesting may provide further insight into commutability issues, allowing laboratories to evaluate and compare performance across different sample types.

### 9.4. Pooled patient samples

The use of pooled patient samples may be a viable strategy for laboratories, particularly in situations where IQC materials are unavailable or as a supplementary control measure, for example to check data at some defined critical level [48]. This approach is especially relevant for assessing commutability in analytes such as immunoassays (tumour markers or hormones), where standard IQCs may not fully reflect patient sample behaviour. The integrity and stability of pooled samples—which are often stored frozen—must be evaluated and documented. Additionally, appropriate safety precautions should be implemented to maintain sample integrity and prevent contamination or degradation

over time.

### 9.5. "Sentinel tests"

On a multi-test analyser, certain assays are inherently more sensitive to variability due to differences in instrument components and operational parameters – such as low-volume pipetting, specific wavelength, reagent stability, or reaction time, etc. These variations can affect the analytical performance of specific tests more than others [49].

By strategically scheduling IQCs runs or patient sample controls for these high-sensitivity tests, laboratories can effectively monitor the overall performance of the analyser, particularly when more robust methods are in use. Furthermore, "sentinel tests" can be used as a risk control measure for evaluating the impact of both internal maintenance procedures and manufacturer-performed servicing (after-sales service). This approach allows for rapid verification that maintenance activities have not adversely affected critical instrument components. However, in cases where major maintenance requires recalibration, this strategy becomes unreliable and should not be implemented as the primary quality control measure.

## 10. Post-IQC impact assessment

The recommendations in this section are derived from Sections 7.3.7.1, 7.3.7.2.(g) and 8.7 of the ISO 15189:2022 standard, which emphasize the importance of assessing the impact of IQC results that fall outside acceptable limits.

These evaluations are essential for preserving the integrity of laboratory processes and ensuring the reliability of results. The identification of potential risks and the assessment of corrective actions' effectiveness can be guided by established analytical risk frameworks, as detailed in Table 1.

This section focuses on procedures to be followed when IQC results indicate non-conformance, including the immediate implementation of curative remedial actions, re-examination of affected results, evaluation of potential impacts on previously released patient data and implementation of corrective action to avoid recurrence.

Where quality control rules aren't fulfilled and indicate that the examination results are likely to contain clinically significant errors, the results are rejected, and the relevant patient samples are re-examined after the error condition has been corrected and performance in accordance with specifications has been verified.

The laboratory must also evaluate the results of patient specimens that have been examined after the last successful quality control.

A systematic approach to IQC failure traceability and impact analysis is essential to ensure patient safety and analytical accuracy. Supplementary Material (*A routine day in a Clinical Lab.doc*, Fig. 1 and Fig. 2) provides an example of a structured IQC validation and curative action workflow.

### 10.1. Reason for method drift

The laboratory must verify that an out-of-range IQC is indicative of a malfunction in the analytical system. To prevent false rejection, the first step is to rule out an IQC related issue by verifying whether a freshly prepared control remains non-compliant or if the retesting of fresh patient samples confirms the anomaly. Failing to do so may lead to unnecessary troubleshooting, causing delays and additional costs for the laboratory.

Once the IQC issue has been ruled out, a systematic investigation must be conducted to determine the causes and the extent of the problem:

- Which analytes are involved, and to what extent?
- Verification of IQC analysis across all levels and/or re-testing of patient samples.
- Identification of probable causes. Was an explicit system alarm triggered, or is the deviation occurring without an alert?
- Duration of the issue. How long has this been a problem? Review IQC trends, system alarms, and floating mean calculations to detect potential drift over time.

A comprehensive scope analysis should quantify the severity of the issue and establish which patient samples may have been impacted.

### 10.2. Impact study strategy: Interpretation of the results

To ensure the validity of patient results and assess the impact of potential analytical deviations, a structured approach must be followed. This process involves two key steps:

*Step 1: Selection of samples for re-analysis.*

The selection of samples for re-analysis should be guided by the extent of the potential impact on patient results. To assess the validity of results, re-analysed sample data should be compared against predefined analytical acceptance limits, ensuring that deviations remain within 2.8 times the standard deviation (or CV). This threshold serves as a reference for determining whether analytical performance remains within acceptable quality specifications.

*Step 2: Defining clinical acceptance limits.*

If analytical agreement cannot be established, the laboratory should define clinical acceptance limits to assess the potential impact on patient care. This evaluation should be based on established quality standards:

- Application of the *Milan Consensus* objectives: despite limited clinical studies, the $TE_A$ derived from desirable BV estimates can serve as a reference for determining acceptable clinical performance [50].
- Use of EQA acceptance limits: EQA limits provide a clinically relevant benchmark for evaluating result validity, as they are designed to reflect the impact of deviations on medical decision-making.

If clinical acceptance limits are exceeded, curative actions must be taken followed with corrective actions if relevant:

- A recall of previously reported test results may be necessary if they have already been issued.
- Modification should follow ISO 15189:2022 standard (Section 7.3.7.2.(g)) guidelines for test report corrections.
- The responsible healthcare professional must be promptly informed to ensure appropriate patient management.

## 11. Analysers results comparability

The recommendations in this section are based on Sections 7.3.7.4 of the ISO 15189:2022 standard, which address the need to ensure consistency and comparability between the results provided by different analysers used within the laboratory. Establishing comparability is essential for maintaining uniformity in results, especially when multiple instruments are used for the same tests [51,52].

This section emphasizes methods for verifying analyser performance, including inter-analyser comparisons between results provided by different analysers, alignment with calibration standards, and the use of shared IQC materials. By following these guidelines, laboratories can reduce variability and enhance confidence in the accuracy of results whatever the across all instruments, thereby supporting appropriate diagnostic outcomes.

If several analytical systems are used to perform the same tests in the laboratory, comparability of the results provided by the different systems must be ensured. POCT devices are also included in this comparability study.

The first objective is to ensure equivalence of the results within the same laboratory especially with several instruments [53].

### 11.1. Frequency of monitoring

The laboratory must establish an appropriate frequency for review and monitoring of comparability of results between analysers. While there is no universally mandated recommendation, the chosen frequency must be justified through a risk-based approach.

Key factors to consider when determining the monitoring frequency include:

- Test volume: the number of analyses performed daily.
- Method robustness: the inherent stability of the performance of the analytical system.
- Potential impact of analytical drift: the clinical consequences of undetected deviations.
- Additional quality control measures in place: such as IQC with shared acceptance limits, moving average comparisons, or other statistical tools.

The laboratory must document and validate its chosen frequency, ensuring that it effectively mitigates risks and maintains result reliability.

### 11.2. Possible materials for ensuring analytical comparability

To maintain analytical comparability across different systems or instruments, laboratories can utilize various materials and methodologies, including:

- IQC materials: standardized control samples used routinely to monitor assay performance.
- Fresh patient samples: real-time comparisons using newly collected patient specimens.
- Pooled stored samples: pre-collected patient specimens, often frozen, to assess consistency over time.
- EQA samples: standardized proficiency testing materials for inter-laboratory comparisons.
- Statistical analyses of patient results: methods such as patient averages or moving averages to detect trends and systematic biases.

Selecting the appropriate material depends on the test type, analytical objective, and required level of comparability, ensuring robust and clinically reliable results [54].

### 11.3. Indicators for detecting system drift

To enable the early detection of system drift between analysers, laboratories can implement various performance indicators that signal potential issues requiring investigation. These include:

- Percentage of rejected IQCs per system – Evaluating the frequency of QC failures across different analysers.
- Monitoring of CVs for each system – Tracking variations in precision over time.
- CV ratio between systems– Comparing the CV between different analysers to assess analytical consistency.
- Percentage of rejected results relative to total data points – Identifying trends in abnormal result frequencies.
- Number of EQA failures – Monitoring participation in EQA schemes to detect performance deviations.
- Percentage of rejections in re-analyzed patient samples – Assessing the rate of invalidated patient results based on re-analysis criteria.
- Percentage of qualitative alarms per analyser – Evaluating the occurrence of instrument-generated warnings in assays.

These early-warning indicators help laboratories proactively identify and address potential analytical issues before they compromise result reliability.

### 11.4. Assessment of clinical impact

When an analytical discrepancy is identified, the laboratory must assess its clinical impact to determine whether curative actions, such as test report modifications or recalls, are necessary, followed by corrective actions if relevant.

The decision to recall a report depends on the critical difference between the original and re-evaluated results, which defines the potential impact on clinical interpretation and patient management. To establish acceptable limits, laboratories can refer to:

- The EQA providers, which set performance thresholds based on international guidelines.
- The *Milan Model* which defines analytical quality specifications according to BV estimates and clinical needs [50].
- $TE_A$ limits, as determined by expert consensus or EQA/PT providers' experience for specific analytes.

This structured approach ensures that corrective actions are clinically justified, and that patient safety remains the primary consideration in laboratory decision-making.

### 11.5. External comparison of IQCs

The external comparison of the IQCs results serves as a valuable complementary tool for assessment of analytical performance. This approach allows laboratories to:

- Assess trueness. Compare the laboratory's results against the peer group mean and the peer SD or CV to verify method accuracy.
- Facilitate retargeting. Adjust target values when internal conditions change or establish a control chart when no probationary period data is available.
- Determine method performance specifications. Evaluate key parameters such as long-term CV, bias, measurement uncertainty, and overall analytical stability.

By incorporating external IQC comparisons, laboratories can enhance quality assurance, benchmark performance against peers, and improve the reliability of patient results.

## 12. Handling of different types of abnormalities detected (Risk 5)

The recommendations in this section are informed by Section 7.3.7 of the ISO 15189:2022 standard, which emphasizes the need to identify and categorize different types of abnormalities in analytical performance to maintain the validity of examination results. Recognizing these abnormalities is crucial for ensuring timely corrective actions and preserving the quality of diagnostic processes [20].

This section outlines various types of abnormalities, including random errors, systematic errors, trends, and shifts, which can impact the reliability of test results.

The laboratory has to record all the events that lead to non-conformities.

Laboratories frequently encounter non-conformities that can affect analytical performance and result accuracy. Some of the most common issues include:

- Control material issues: errors in preparation, processing, stability, evaporation, contamination or identification that compromise IQC integrity.
- Analytical system failures: calibration errors or contamination.

- Reagents –related problems: instability, incorrect reagent assignment (inversion) or inadequate mixing, leading to poor homogenization and inconsistent results.
- Analyser malfunctions: outdated maintenance, temperature dysfunction, sampling errors affecting instrument precision.
- Incorrect analytical procedure: use of incorrect settings, leading to deviations from expected values.
- IQC protocol deviations: failure to follow standard operating procedures by the operators.
- Target values definition issue: detection of an unexpected trend or shift, requiring reassessment and corrective action.
- Inappropriate acceptable limits: poorly defined control thresholds, which may not align with method performance or clinical requirements.
- Insufficient staff training: lack of operator competency in performing and interpreting QC procedures.
- Lack of information: Incomplete documentation or unclear procedural guidelines, affecting workflow and decision-making.

Proper quality control measurement, staff training, and procedural standardization are essential to mitigate these risks and ensure consistent, high-quality laboratory results.

At least once or twice a year, the laboratory will conduct a comprehensive review of quality control data to identify the most frequent and high-risk non-conformities affecting analytical performances. Regular trend analysis and corrective action implementation ensure continuous quality improvement, regulatory compliance, and enhanced patient care.

## 13. Quality indicators for IQC (Risks 1, 2, 6, 7, 8)

The recommendations here reported, are derived from Section 8.8.2 of the ISO 15189:2022 standard, which highlights the importance of defining and monitoring quality indicators to evaluate the effectiveness of laboratory processes. Indicators serve as measurable metrics that enable laboratories to assess performance, identify trends, and drive continual improvement.

This section focuses on selecting relevant indicators, such as the frequency of non-conformities, turnaround times, or error rates to monitor key aspects of analytical processes [55].

To ensure comprehensive quality monitoring, laboratories should use key indicators that assess system failures, calibration errors, and operator mistakes. A summary of potential risks and corresponding indicators can be found in Table 1.

### 13.1. Key objectives of IQC QIs

The following key objectives outline the primary roles of QIs in IQC management:

- *Error Identification and Reduction*: QIs help identify and reduce errors across all analytical phases, with particular emphasis on the pre-analytical and post-analytical phases where errors are more frequent. Examples include sample misidentification and incorrect result interpretation.
- *Benchmarking and Performance Comparison*: By utilizing harmonized QIs, laboratories can benchmark their performance against peers through participation in inter-laboratory EQAs.
- *Continuous Quality Improvement*: QIs enable systematic monitoring of trends and deviations, providing a foundation for implementing corrective actions, identifying risks and opportunities for improvement, and documenting performance enhancements over time.
- *Trend analyses:* Detect any drift in the analytical system at the earliest possible stage and implement the necessary corrective actions to proactively address risks and ensure consistent test performance (monitoring both random and systematic error):
  - o *Increasing random error*: An increase in the dispersion of the method can be identified through regular monitoring, with the frequency adapted based on factors such as the method's robustness, clinical significance, and performance frequency. For routine examinations, it is recommended to monitor the CV regularly and compare it with laboratory specifications, at an appropriate interval, typically monthly, depending on the examinations, to enable timely correction actions.
  - o *Systematic error (bias)*: An increase in bias can be evaluated through an external comparison of IQC results, using metrics such as regular monitoring of the Z-score or standard deviation index.

### 13.2. Recommended QIs for IQC in laboratories

The following QIs are recommended for effective monitoring and enhancement of IQC practices:

- Frequency and Results of IQC:
  1. Number of IQC tests performed within a defined time frame.
  2. The percentage of IQC results falling outside acceptable control limits.
- Error Reporting:
  1. Rate of IQC failures and their classification (e.g., systematic vs. random errors) and root cause: identification of the samples, reagents, settings, operators, procedures, calibrators, environment.
  2. Time taken to resolve IQC-related issues and re-establish control (time during which the machine is not available)
- Stability and Accuracy:
  1. Monitoring of IQC stability over time to detect trends or shifts.
  2. Assessment of IQC accuracy against established benchmarks or trueness evaluation through peer group comparisons.
- Turnaround Time (TAT):
  TAT for IQC processes to ensure timely detection and correction of analytical issues.
- Pre-analytical and post-analytical QIs:
  Rate of IQC-related issues linked to sample collection, handling, or reporting stages.

### 13.3. Implementation strategy

To implement QIs effectively, laboratories should:

- Establish a structured reporting system that defines the responsibility for data collection, analysis, curative and corrective action.
- Utilize software tools for standardized data collection and trend analysis.
- Regularly review QI outcomes in management review to identify areas for improvement.
- Participate in harmonized EQA programs to compare results and foster collaborative learning.

By incorporating these QIs into routine IQC practices, laboratories can ensure a robust quality management system that supports patient safety, diagnostic accuracy, and continuous performance improvement.

## 14. Uncertainty: Interpretation of measurement uncertainties and their estimation

The recommendations in this section are based on Section 7.3.4 of the ISO 15189:2022 standard, which emphasizes the need to evaluate, interpret, and document measurement uncertainty (MU) to ensure the appropriate interpretation of laboratory results. Understanding MU is essential for supporting clinical decision-making and maintaining confidence in analytical processes. Other sources of uncertainty, pre and post analytical must be evaluated and monitored according to a risk analysis [9].

This section guides the calculation and interpretation of MU, including the identification of contributing factors such as imprecision and bias. By following these principles, laboratories can enhance the transparency of reported results, and support clinicians in making informed decisions for improved patient care.

Care should be taken not to confuse total error with MU.

$TE_A$ is calculated from the intra-subject ($CV_I$) and inter-subjects ($CV_G$) BV estimates, while the MU is an analytical uncertainty based on the quadratic combination of two terms: imprecision and bias. Bias should, in principle, be eliminated and all the remaining sources of variation added linearly as variances [56].

A measurement result therefore can comprise two uncertainties: the uncertainty associated with bias correction and the uncertainty due to imprecision [57,58]. For the bias, one can use the mean bias (with the standard deviation of the bias) or the maximum bias. Nevertheless, the major component of uncertainty is imprecision. So, where the bias is deemed acceptable from data from EQA, or so small as compared to precision CV, it could be permissible to calculate the MU considering only two times the standard deviation (or CV) calculated within a long period. Results of IQC can be used for the evaluation as long-term evaluation of precision.

If the two components of the measurement uncertainty (standard deviation and bias) monitored regularly have not changed, the monitoring can be spaced out. Nevertheless, the EQAS bodies that provide an estimate of the MU carry out an annual review with a comparison of all the participating laboratories.

Measurement uncertainty is particularly important when interpreting the result concerning a decision threshold with consequences for the medical impact of patient care (hemoglobin level and transfusion, drug dosage and dosage adjustment, etc.) or monitoring a treatment or disease.

The MU shall be evaluated according to the clinical interpretation required by clinicians, considering the clinical needs.

Finally, the choice of performance requirements is difficult: the total error is not rigorously statistically comparable and there is little other recent data in the literature.

## 15. Conclusion

IQC remains a cornerstone of laboratory medicine, ensuring the trueness, and reproducibility of results for prevention, diagnostic, monitoring, and screening of diseases.

This document, grounded in the ISO 15189:2022 standard, provides practical recommendations that align with the evolving landscape of medical laboratories. It outlines guidelines for IQC material selection, frequency definition, statistical rule application, and the definition of acceptable limits for immediate interpretation—leading to the implementation of corrective actions, proactive risk identification, and opportunities for improvement on the one hand, and clinical acceptable limits interpretation on the other—alongside the non-conformity management process.

The importance of updated IQC guidance cannot be overstated, especially considering the historical contributions of the IFCC through foundational recommendations in the late 20th century. The laboratory environment has changed significantly since the publication of the recommendations [2,3], and with the advent of new technologies and methodologies, automation, informatics and clinical demands, contemporary approaches are needed to address the challenges laboratories face today.

This document provides a comprehensive and user-friendly resource for laboratory professionals to enhance their IQC practices, adapt to new developments, and maintain compliance with international standards. By following these recommendations, laboratories can mitigate risks, improve analytical processes, and ensure optimal patient care. Ultimately, the implementation of robust IQC systems not only safeguards the integrity of diagnostic results but also upholds the trust placed in medical laboratories as critical contributors to modern healthcare.

The future of IQC will require continuous adaptation as laboratory technologies and clinical requirements evolve. Therefore, this document serves as a foundation for laboratories to not only meet current standards but also remain agile in addressing emerging needs and advancing the quality of patient care.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 4o/ Open AI for language refinement and rephrasing of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

## CRediT authorship contribution statement

**Jean-Marc Giannoli:** Conceptualization, Writing – original draft, Writing – review & editing. **Anne Vassault:** Conceptualization, Supervision, Writing – review & editing. **Anna Carobene:** Conceptualization, Supervision, Writing – review & editing. **Armand Perret Liaudet:** Conceptualization, Writing – review & editing. **Ivan M Blasutig:** Conceptualization, Writing – review & editing. **Pradeep Kumar Dabla:** Conceptualization, Writing – review & editing. **Ji Lin:** Conceptualization, Writing – review & editing. **Annette Thomas:** Conceptualization, Writing – review & editing. **José Antonio Tesser Poloni:** Conceptualization, Writing – review & editing. **Qing H Meng:** Conceptualization, Supervision, Writing – review & editing. **Egon P Amann:** Conceptualization, Supervision, Writing – review & editing.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2025.120240.

## Data availability

No data was used for the research described in the article.

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