

C24

Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions

This guideline provides definitions, principles, and approaches to laboratory quality control design, implementation, and assessment.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

Clinical and Laboratory Standards Institute

Setting the standard for quality in medical laboratory testing around the world.

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

Consensus Process

Consensus—the substantial agreement by materially affected, competent, and interested parties—is core to the development of all CLSI documents. It does not always connote unanimous agreement, but does mean that the participants in the development of a consensus document have considered and resolved all relevant objections and accept the resulting agreement.

Commenting on Documents

CLSI documents undergo periodic evaluation and modification to keep pace with advancements in technologies, procedures, methods, and protocols affecting the laboratory or health care.

CLSI's consensus process depends on experts who volunteer to serve as contributing authors and/or as participants in the reviewing and commenting process. At the end of each comment period, the committee that developed the document is obligated to review all comments, respond in writing to all substantive comments, and revise the draft document as appropriate.

Comments on published CLSI documents are equally essential, and may be submitted by anyone, at any time, on any document. All comments are managed according to the consensus process by a committee of experts.

Appeals Process

When it is believed that an objection has not been adequately considered and responded to, the process for appeals, documented in the CLSI Standards Development Policies and Processes, is followed.

All comments and responses submitted on draft and published documents are retained on file at CLSI and are available upon request.

Get Involved—Volunteer!

Do you use CLSI documents in your workplace? Do you see room for improvement? Would you like to get involved in the revision process? Or maybe you see a need to develop a new document for an emerging technology? CLSI wants to hear from you. We are always looking for volunteers. By donating your time and talents to improve the standards that affect your own work, you will play an active role in improving public health across the globe.

For additional information on committee participation or to submit comments, contact CLSI.

Clinical and Laboratory Standards Institute
950 West Valley Road, Suite 2500
Wayne, PA 19087 USA
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@clsi.org

Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions

Curtis A. Parvin, PhD
Nils B. Person, PhD, FACB
Nikola Baumann, PhD
Lili Duan, PhD
A. Paul Durham
Valerio M. Genta, MD
Jeremie Gras, MD
Greg Miller, PhD
Megan E. Sawchuk, MT(ASCP)

Abstract

Clinical and Laboratory Standards Institute guideline C24—*Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions* discusses the principles of statistical QC, with particular attention to the planning of a QC strategy and the application of statistical QC in a medical laboratory. Although these principles are of interest to manufacturers, this guideline is intended for use by medical laboratory personnel in order to provide a QC strategy that uses control materials that are external to a reagent kit, instrument, or measuring system and that are intended to simulate the measurement of a patient specimen.

Clinical and Laboratory Standards Institute (CLSI). *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions*. 4th ed. CLSI guideline C24 (ISBN 1-56238-946-7 [Print]; ISBN 1-56238-947-5 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2016.

The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org. If you or your organization is not a member and would like to become one, and to request a copy of the catalog, contact us at: Telephone: +1.610.688.0100; Fax: +1.610.688.0700; E-Mail: customerservice@clsi.org; Website: www.clsi.org.



Copyright ©2016 Clinical and Laboratory Standards Institute. Except as stated below, any reproduction of content from a CLSI copyrighted standard, guideline, companion product, or other material requires express written consent from CLSI. All rights reserved. Interested parties may send permission requests to permissions@clsi.org.

CLSI hereby grants permission to each individual member or purchaser to make a single reproduction of this publication for use in its laboratory procedures manual at a single site. To request permission to use this publication in any other manner, e-mail permissions@clsi.org.

Suggested Citation

CLSI. *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions*. 4th ed. CLSI guideline C24. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.

Previous Editions:

March 1985, September 1986, May 1991, February 1999, June 2006

ISBN 1-56238-946-7 (Print)
ISBN 1-56238-947-5 (Electronic)
ISSN 1558-6502 (Print)
ISSN 2162-2914 (Electronic)

Volume 36, Number 12

Contents

Abstract.....	i
Committee Membership.....	iii
Foreword.....	vii
Chapter 1: Introduction.....	1
1.1 Scope.....	1
1.2 Background.....	2
1.3 Standard Precautions.....	2
1.4 Terminology.....	3
Chapter 2: Path of Workflow.....	9
Chapter 3: Purpose of Statistical Quality Control.....	11
3.1 Quality Control and Patient Risk.....	11
3.2 Quality Requirements.....	12
3.3 Method Performance Relative to Quality Requirements.....	14
3.4 Types of Out-of-Control Conditions.....	17
3.5 Quality Control Rules.....	17
Chapter 4: Assessing Quality Control Performance.....	19
4.1 False Rejection Rate.....	19
4.2 Detection of Out-of-Control Conditions.....	20
Chapter 5: Planning a Statistical Quality Control Strategy.....	23
5.1 Define the Quality Requirements.....	23
5.2 Select Control Materials.....	24
5.3 Determine Target Values and Standard Deviations for Quality Control Materials That Represent Stable Analytical Performance.....	27
5.4 Set Goals for Quality Control Performance.....	31
5.5 Select a Quality Control Strategy Based on Performance Goals.....	32
5.6 Design a Quality Control Strategy for Multiple Instruments.....	37
Chapter 6: Recovering From an Out-of-Control Condition.....	39
6.1 Responding to an Out-of-Control Quality Control Event.....	39
6.2 Responding to an Out-of-Control Condition.....	39
6.3 Identifying and Correcting Reported Erroneous Patient Results.....	39
Chapter 7: Ongoing Assessment of Quality Control Programs.....	41
7.1 Assessment of the Internal Quality Control Program.....	41
7.2 Using Interlaboratory Quality Control to Assess a Quality Control Program.....	41
Chapter 8: Worked Examples.....	43
8.1 Define the Quality Requirement.....	43
8.2 Select Quality Control Materials.....	43
8.3 Determine Target Values and Standard Deviations.....	43
8.4 Select Quality Control Strategy.....	44
Chapter 9: Conclusion.....	46
Chapter 10: Supplemental Information.....	46
References.....	47

Contents (Continued)

Appendix A. Levey-Jennings Chart.....	50
Appendix B. Medical Laboratory Quality Control Shift and Trend Troubleshooting Checklist	55
The Quality Management System Approach	60
Related CLSI Reference Materials	61

SAMPLE

Foreword

The medical laboratory community has used C24, now in its fourth edition, for more than 20 years. Today, statistical QC is still critically important to ensure the quality of the results of any laboratory measurement procedure. The almost universal applicability of statistical QC to quantitative measurement procedures provides laboratories with an essential quality management tool that can be used to monitor the effects of many instrument, reagent, environment, and operator variables on the outcome of a measurement process.

The laboratory director is generally responsible for the laboratory QC program. The definition of quality requirements for the tests being performed is particularly important because laboratory managers, supervisors, scientists, and quality specialists often use those quality requirements to select and validate appropriate measurement and control procedures. C24's approach provides medical laboratory scientists with practical guidance on how to satisfy recommendations by authorities and/or accreditation organizations.¹

The concepts, approaches, and practices discussed in this guideline are interdependent and all should be carefully studied and considered when developing the specific QC strategy for any measurement procedure, system, or laboratory. C24 highlights the technical issues that need a careful scientific approach to designing, implementing, and assessing QC strategies in order for laboratories to achieve the quality requirements needed by the physicians and patients they serve.

Overview of Changes

This guideline replaces the previous edition of the approved guideline, C24-A3, published in 2006. The fourth edition maintains the focus on principles and approaches to laboratory QC design, implementation, and assessment that reflect the realities of the modern medical laboratory and its role within the health care enterprise. Several changes were made in this edition, including:

- The alignment of principles and definitions to be consistent with and to supplement the general patient risk model described in CLSI document EP23^{TM2}
- The introduction of additional performance measures useful for evaluating the performance characteristics of a QC strategy (see Chapter 5)
- Expanded guidance on setting target values and SDs for QC materials (see Subchapter 5.3)
- A greater focus on QC frequency and QC schedules as a critical part of a QC strategy (see Subchapter 5.5)
- A substantive chapter on recovering from an out-of-control condition (see Chapter 6), including sections on:
 - Responding to an out-of-control QC event
 - Responding to an out-of-control condition
 - Identifying and correcting reported erroneous patient results

NOTE: The content of this guideline is supported by the CLSI consensus process, and does not necessarily reflect the views of any single individual or organization.

Key Words

Patient risk, quality control, quality control plan, quality control rules, quality control strategy, quality requirements, Sigma metric

Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline

1.1 Scope

This guideline explains the purpose of statistical QC for quantitative measurement procedures, describes an approach for planning a QC strategy for a particular measurement procedure, describes the use of QC material and QC data, and provides examples that demonstrate a practical QC planning process for medical laboratories.

The recommendations for establishing and maintaining a statistical QC strategy are applicable to quantitative laboratory measurement procedures in all fields of laboratory medicine for which stable control materials can be measured in the same manner as patient specimens. The intended users of this guideline include those responsible for designing, implementing, and using QC, ie, medical laboratory scientists.

This guideline does **not**:

- Describe built-in control mechanisms that might be part of a measuring system, or qualitative or semiquantitative measurement procedures.
- Define specific QC strategies that are appropriate for an individual device or technology.
- Describe alternatives to statistical process control, eg, real-time patient-based QC.
- Consider specific legal requirements that may impose different philosophies or procedures on QC practices (eg, a specific approach for defining quality requirements, specific values for quality requirements, a specific procedure for determining target values for control materials, or a frequency and number of QC measurements) defined by government regulation in a specific country or region.

Additionally, there are types of random errors that may affect measurements performed on individual specimens, rather than a whole group of specimens, and those errors are not detected by a statistical QC strategy. Such errors may be due to the specific design of a measuring system (eg, effect of specimen

viscosity, carryover from a previous specimen, or specimen-specific interferences) or possible operator errors that affect individual specimens, as well as preexamination errors of specimen preparation, storage, and transportation. Special QC strategies may be needed to monitor known special vulnerabilities that relate to a particular device or system design.

1.2 Background

Statistical QC strategies are implemented to monitor a measurement procedure's performance to detect any change relative to stable baseline analytical performance. When the actual performance deviates from the expected model, the QC strategy is designed to alert the laboratorian to a change that may affect medical decision making and potentially lead to incorrect treatment, delays in treatment, or patient harm. Designing an effective QC strategy entails determining the magnitude of the change in performance that compromises the usefulness of the measurement procedure results.

There is abundant literature explaining the theoretical and practical bases for initiating and maintaining QC strategies in clinical chemistry³⁻⁹; however, the routine practice of statistical QC depends on understanding how to:

- Plan QC strategies based on the performance of the measurement procedure and the performance needed to support the intended medical use of the results, including selecting appropriate control materials, establishing the expected values for those control materials, determining when to evaluate controls, and identifying the control rules to determine acceptable performance.
- Implement QC strategies to identify situations when a measurement procedure may not be providing results that are suitable for use in medical decisions.
- Respond to out-of-control situations.

The prevalence of a broad range of automated medical laboratory instruments using widely different measuring principles has complicated the terminology and the steps necessary for establishing QC strategies. There are some highly automated systems that can perform specific, built-in checks that help detect potential problems and alert the operator to instrument malfunction. However, the benefit of statistical QC using samples intended to simulate measurement of patient specimens is that it monitors the outcome of many of the variables and steps that occur in the entire measurement procedure.

1.3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of bloodborne pathogens. Published guidelines are available that discuss the daily operations of diagnostic medicine in humans and animals while encouraging a culture of safety in the laboratory.¹⁰ For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.¹¹

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) approach in the development of standards and guidelines, which facilitates project management; defines a document structure using a template; and provides a process to identify needed documents. The QMS approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are as follows:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

C24 covers the QSEs indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
		M29			X	X EP05 EP06 EP09 EP15 EP23 EP26 EP31					

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

C24 covers the medical laboratory path of workflow step indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section.

Preexamination				Examination			Postexamination	
Examination ordering	Sample collection	Sample transport	Sample receipt and processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
EP31		EP31		X EP23	EP23 EP31	EP23		

Related CLSI Reference Materials*

- EP05** **Evaluation of Precision of Quantitative Measurement Procedures. 3rd ed., 2014.** This document provides guidance for evaluating the precision performance of quantitative measurement procedures. It is intended for manufacturers of quantitative measurement procedures and for laboratories that develop or modify such procedures.
- EP06** **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach. 1st ed., 2003.** This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.
- EP09** **Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed., 2013.** This document addresses the design of measurement procedure comparison experiments using patient samples and subsequent data analysis techniques used to determine the bias between two *in vitro* diagnostic measurement procedures.
- EP15** **User Verification of Precision and Estimation of Bias. 3rd ed., 2014.** This document describes the estimation of imprecision and of bias for clinical laboratory quantitative measurement procedures using a protocol that can be completed within as few as five days.
- EP23™** **Laboratory Quality Control Based on Risk Management. 1st ed., 2011.** This document provides guidance based on risk management for laboratories to develop quality control plans tailored to the particular combination of measuring system, laboratory setting, and clinical application of the test.
- EP26** **User Evaluation of Between-Reagent Lot Variation. 1st ed., 2013.** This document provides guidance for laboratories on the evaluation of a new reagent lot, including a protocol using patient samples to detect significant changes from the current lot.
- EP31** **Verification of Comparability of Patient Results Within One Health Care System. 1st ed., 2012.** This document provides guidance on how to verify comparability of quantitative laboratory results for individual patients within a health care system.
- M29** **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

Explore the Latest Offerings From CLSI!

As we continue to set the global standard for quality in laboratory testing, we are adding products and programs to bring even more value to our members and customers.



By becoming a CLSI member, your laboratory will join 1,600+ other influential organizations all working together to further CLSI's efforts to improve health care outcomes. You can play an active role in raising global laboratory testing standards—in your laboratory, and around the world.

Find out which membership option is best for you at www.clsi.org/membership.



Find what your laboratory needs to succeed! CLSI U provides convenient, cost-effective continuing education and training resources to help you advance your professional development. We have a variety of easy-to-use, online educational resources that make eLearning stress-free and convenient for you and your staff.

See our current educational offerings at www.clsi.org/education.



When laboratory testing quality is critical, standards are needed and there is no time to waste. eCLIPSE™ Ultimate Access, our cloud-based online portal of the complete library of CLSI standards, makes it easy to quickly find the CLSI resources you need.

Learn more and purchase eCLIPSE at cli.org/eCLIPSE.

For more information, visit www.clsi.org today.

SAMPLE



CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®

950 West Valley Road, Suite 2500, Wayne, PA 19087 USA

P: +1.610.688.0100 Toll Free (US): 877.447.1888 F: +1.610.688.0700

E: customerservice@clsi.org www.clsi.org

PRINT ISBN 1-56238-946-7

ELECTRONIC ISBN 1-56238-947-5