CLINICAL AND LABORATORY STANDARDS INSTITUTE®

EP18-A2

Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition

This guideline describes risk management techniques that will aid in identifying, understanding, and managing sources of failure (potential failure modes) and help to ensure correct results. Although intended primarily for *in vitro* diagnostics, this document will also serve as a reference for clinical laboratory managers and supervisors who wish to learn about risk management techniques and processes.

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 advances 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.

Appeal Process

When it is believed that an objection has not been adequately considered and responded to, the process for appeal, 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
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@clsi.org

Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition

Volume 29 Number 26

Jan S. Krouwer, PhD
Abdel-Baset Halim, DPharm, PhD, DABCC
Aristides T. Hatjimihail, MD, PhD
Ellis Jacobs, PhD, DABCC, FACB
Adam Manasterski, PhD
James H. Nichols, PhD, DABCC, FACB

Abstract

Clinical and Laboratory Standards Institute document EP18-A2—*Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition* recommends a quality management system for *in vitro* diagnostic test systems that is based on expert opinion, is practical to implement, and is applicable to various devices and settings, so sources of failure (potential failure modes) are identified, understood, and managed. This system will assist device manufacturers, regulators, accrediting agencies, and laboratory directors in ensuring correct results. It addresses regulatory considerations (eg, principles and accountability), recommends the development of a partnership between users and manufacturers, provides a source-of-failures matrix, and suggests approaches to quality monitoring/identification of the problems.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Suggested Citation

CLSI. *Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition.* CLSI document EP18-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.

Contents

Contents (Continued)

Foreword

In vitro diagnostic (IVD) devices play a crucial role in patient care, and the quality and reliability of IVD results are paramount. However, all devices and methods may be subject to preanalytical, analytical, and postanalytical (preexamination, examination, and postexamination) failure. The relative importance and probability (ie, the risk) of a specific failure condition may vary with the device design, the user, the medical application, and the operating environment. A single quality assurance and quality control (QA/QC) regimen that optimally mitigates risk for all devices does not exist. As a greater variety of devices and tests become available to meet clinical demands in various environments, including outside the traditional laboratory at the point of patient care, a pressing need to ensure and control quality in the most effective and efficient manner has been noted. Such QA/QC regimens should be based on the characteristics of the device in use, taking into consideration local variables, such as the intended use of the test and the testing environment and users. Furthermore, QA/QC procedures should be developed systematically using established quality management tools, such as Failure Modes and Effects Analysis (FMEA) and Failure Reporting, Analysis, and Corrective Action Systems (FRACAS).

The original version of this document, EP18-A—*Quality Management for Unit-Use Testing*, was limited to unit-use devices (see Appendix E). The impetus for the original document was that

"Conventional quality assurance and quality control methods in and of themselves do not assure quality. A one-size-fits-all or prescribed quality control testing protocol such as 'two levels per day of use' may not be appropriate for all testing systems. The diversity among regulatory requirements, accreditation practices, and user needs, coupled with the financial aspects of this QC method, led to the formation of the CLSI Subcommittee on Unit-Use Testing.

It is the subcommittee's intent to provide a comprehensive and flexible guideline that will enable users, manufacturers, and regulators to identify potential sources of failures in unit-use test systems and implement processes to manage these failures using new quality management models."

The original subcommittee anticipated that a broader based guideline could be created that would address both unit-use and multiuse systems. Accordingly, this revision of EP18 is applicable to all IVDs.

As represented in the table below, this document is intended to provide guidance to manufacturers of IVD devices and laboratory directors to assist in identifying potential risks and developing a strategy to control quality and mitigate potential failures.

	Prevention	Detection
Manufacturer	Risk assessment and risk mitigation for manufacturers References: • International Organization for Standardization (ISO) 14971[1] • CLSI document EP18	Embedded instrument checks and controls Information regarding design features intended to mitigate risk of potential device failures that can affect the accuracy of test results
Laboratory	Techniques (FMEA and FRACAS) to identify and control laboratory failure sources Reference: • CLSI document EP18	Laboratory implemented quality control procedures Reference: • ISO 15189[2]

Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition

1   Scope

This document provides guidance for risk management activities that include risk analysis (Failure Modes and Effects Analysis [FMEA]), fault trees, and risk monitoring (Failure Reporting, Analysis, and Corrective Action Systems [FRACAS]). These approaches are based on best practices; practical to implement; applicable to all diagnostics assays; and scientifically based, so sources of failure are identified, understood, and managed.

This guideline applies to *in vitro* diagnostic device (IVD) test systems used by providers of health care services in any setting. The scope of this guideline comprises testing components, locations, and users. Specifically, the testing components include preanalytical, analytical, and postanalytical (preexamination, examination, and postexamination) processes.

This document is intended primarily for IVD manufacturers. However, it is also intended as an important reference for clinical laboratory directors and supervisors who wish to learn about risk management techniques and processes. Although the concept of risk reduction is not new in the laboratory, the risk management tools in this guideline may be new to laboratorians, and will create a need for laboratory directors and supervisors to gain an understanding of these techniques so they can apply these principles and processes in development of their customized quality plan. EP18 is intended to help in that effort.

2   Introduction

Diagnostic testing presents unique challenges to manufacturers, users, regulators, and accrediting agencies. Manufacturers and the clinical laboratory are faced with the task of keeping systems operational and producing results (reliability), as well as ensuring that the results meet minimum performance standards. Examples include accuracy and those elements that affect accuracy such as precision, bias, and limit of detection. *Any* failure source (see Appendix B for some examples of failures) can affect the accuracy and/or reliability of a result.

Risk management attempts to answer four questions:

1.   What can go wrong? (process mapping, brainstorming)

2.   How bad is it? (severity of harm, especially with downstream events)

3.   How often? (probability of occurrence for potential errors, frequency of occurrence for observed errors)

4.   What should be done to mitigate/reduce the risk? (prioritization of risks)

Many evaluation protocols documents have focused on evaluating parameters that affect accuracy, such as linearity (see CLSI document EP06),[4] precision (see CLSI document EP05),[5] and bias (see CLSI document EP09).[6] EP18 takes a more global approach regarding accuracy and reliability by using risk analysis methods to ensure that

•   The risk of potentially hazardous situations has been lowered to an acceptable level.

•   The rate of hazardous situations that have occurred has been lowered to an acceptable level where an acceptable level can be an as low as reasonably practicable (ALARP) level.

1

These risk analysis methods are part of a quality assurance (QA) program.

The following basic concepts directed the development of this guideline:

Diagnostic devices are extremely diverse in their technology, design, and function. Every test system is subject to hazards or hazardous situations during the preanalytical (preexamination), analytical (examination), and postanalytical (postexamination) stages of testing. The relative importance and likelihood of these failures varies with the device, the sample, the user, and the environment. In addition, a high level of variability exists in terms of skill and knowledge level among end users. For example, the hospital or commercial laboratory IVD user is often more skilled and knowledgeable in laboratory techniques than the average user of a point-of-care (POC) device.

Based on the concepts outlined earlier, the guideline follows a systems approach to quality management.[7] The phases of the testing process are defined, and the potential as well as any observed sources of failure within each phase are identified.

The number of potential and observed failures is large; this makes it important to prioritize efforts to reduce risk, because resources are limited. For example, some failures are almost certain to cause patient harm (eg, a hyperglycemic glucose result when the patient is hypoglycemic), whereas a result that must be repeated but is not time sensitive only raises cost. The effect of patient harm is usually more severe than the effect of increased cost. With the classification of severity of harm and probability (or frequency) of occurrence, one can prioritize the importance of events with Pareto analysis (see Section 6.11). It is also likely—although not certain—that the most severe events are potential events (eg, they have not been observed), whereas less severe events are often observed. It is important to conduct both FMEA (to reduce the risk of potential failure events) and FRACAS (to reduce the rate of observed failure events), because each risk analysis process has a different focus.

See CLSI document GP26[8] for a detailed account of the components of a quality management system. These components provide examples of types of control measures (mitigations) that can be used to prevent failures.

This guideline illustrates the following concepts with examples of each in the appendixes:

- The generic sources-of-failures matrix is presented for manufacturers to consider when designing systems and using FMEA as a design review aid

- The use of FMEA is explained as a way to reduce the risk of potential failures and includes
  – an example of a completed FMEA by a manufacturer
  – an example of a completed FMEA by a clinical laboratory

- The use of FRACAS is explained as a way to reduce the rate of observed failures and includes
  – an example of a completed FRACAS by a clinical laboratory

The key to the success of this approach is cooperation and appropriate exchange of information among manufacturers and IVD users. In this way, high-quality patient care can be delivered through the competent use of accurate and reliable testing systems.

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 infectious agents and thus are

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in CLSI document HS01—*A Quality Management System Model for Health Care.* The quality management system 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:

Documents and Records	Equipment	Information Management	Process Improvement
Organization	Purchasing and Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessment—External and Internal	Facilities and Safety

EP18-A2 addresses 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 on the following page.

Documents and Records	Organization	Personnel	Equipment	Purchasing and Inventory	Process Control	Information Management	Occurrence Management	Assessment —External and Internal	Process Improvement	Customer Service	Facilities and Safety
					X EP05 EP06 EP07 EP09 EP10 EP12 EP14 EP15 EP17 EP19 EP21 GP10		X	X EP10	X EP07		
GP26	GP26	GP26	GP26	GP26 HS11	GP26 M29	GP26	GP26	GP26	GP26	GP26	GP26 M29

Adapted from CLSI document HS01—*A Quality Management System Model for Health Care.*

Related CLSI Reference Materials[*]

EP05-A2   **Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (2004).** This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers' precision performance claims and determining when such comparisons are valid; as well as manufacturers' guidelines for establishing claims.

EP06-A   **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (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.

EP07-A2   **Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition (2005).** This document provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interfering substances on clinical chemistry test results.

EP09-A2   **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (2002).** This document addresses procedures for determining the bias between two clinical methods, and the design of a method comparison experiment using split patient samples and data analysis.

EP10-A3   **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2006).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

EP12-A2   **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition (2008).** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.

EP14-A2   **Evaluation of Matrix Effects; Approved Guideline—Second Edition (2005).** This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two measurement procedures are compared.

EP15-A2   **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2005).** This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods using a protocol designed to be completed within five working days or less.

EP17-A   **Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004).** This document provides guidance for determining the lower limit of detection of clinical laboratory methods, for verifying claimed limits, and for the proper use and interpretation of the limits.

EP19-R   **A Framework for NCCLS Evaluation Protocols; A Report (2002).** This report describes the different types of performance studies that are conducted to evaluate clinical assays.

EP21-A   **Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline (2003).** This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method that can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay's total analytical error by using quality control samples.

GP10-A   **Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Approved Guideline (1995).** This document provides a protocol for evaluating the accuracy of a test to discriminate between two subclasses of subjects when there is some clinically relevant reason to separate them. In addition to the use of ROC plots, the importance of defining the question, selecting the sample group, and determining the "true" clinical state are emphasized.

GP26-A3   **Application of a Quality Management System Model for Laboratory Services; Approved Guideline—Third Edition (2004).** This guideline describes the clinical laboratory's path of workflow and provides information for laboratory operations that will assist the laboratory in improving its processes and meeting government and accreditation requirements.

---

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

Related CLSI Reference Materials (Continued)

HS11-A   **A Model for Managing Medical Device Alerts (Hazards and Recalls) for Healthcare Organizations; Approved Guideline (2005).** This document provides a framework for health care delivery organizations to respond to externally generated notifications of medical device hazards and recalls while focusing on the quality constructs of process control, occurrence management, and process improvement.

M29-A3   **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline— Third Edition (2005).** 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.

Sample

CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®