EP18-P2
Vol. 27 No. 23
Replaces EP18-A
Vol. 22 No. 28

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

PLEASE

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This proposed document is published for wide and thorough review in the new, accelerated Clinical and Laboratory Standards Institute (CLSI) consensus-review process. The document will undergo concurrent consensus review, Board review, and delegate voting (ie, candidate for advancement) for 60 days.

Please send your comments on scope, approach, and technical and editorial content to CLSI.

Comment period ends

29 October 2007

The subcommittee responsible for this document will assess all comments received by the end of the comment period. Based on this assessment, a new version of the document will be issued. Readers are encouraged to send their comments to Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; Fax: +610.688.0700, or to the following e-mail address: customerservice@clsi.org

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COMMENT

This guideline recommends risk management techniques that will aid in identifying, understanding, and managing sources of error (potential failure modes) and help to ensure correct results. It is targeted for those involved in supervision of laboratory-testing quality management, and it addresses issues related to specimen collection through reporting of results.

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

(Formerly NCCLS)

Clinical and Laboratory Standards Institute

Advancing Quality in Health Care Testing

Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) is an international, interdisciplinary, nonprofit, standards-developing, and educational organization that promotes the development and use of voluntary consensus standards and guidelines within the health care community. It is recognized worldwide for the application of its unique consensus process in the development of standards and guidelines for patient testing and related health care issues. Our process is based on the principle that consensus is an effective and cost-effective way to improve patient testing and health care services.

In addition to developing and promoting the use of voluntary consensus standards and guidelines, we provide an open and unbiased forum to address critical issues affecting the quality of patient testing and health care.

PUBLICATIONS

A document is published as a standard, guideline, or committee report.

Standard A document developed through the consensus process that clearly identifies specific, essential requirements for materials, methods, or practices for use in an unmodified form. A standard may, in addition, contain discretionary elements, which are clearly identified.

Guideline A document developed through the consensus process describing criteria for a general operating practice, procedure, or material for voluntary use. A guideline may be used as written or modified by the user to fit specific needs.

Report A document that has not been subjected to consensus review and is released by the Board of Directors.

CONSENSUS PROCESS

The CLSI voluntary consensus process is a protocol establishing formal criteria for:

- the authorization of a project
- the development and open review of documents
- the revision of documents in response to comments by users
- the acceptance of a document as a consensus standard or guideline.

Most documents are subject to two levels of consensus—"proposed" and "approved." Depending on the need for field evaluation or data collection, documents may also be made available for review at an intermediate consensus level.

Proposed A consensus document undergoes the first stage of review by the health care community as a proposed standard or guideline. The document should receive a wide and thorough technical review, including an overall review of its scope, approach, and utility, and a line-by-line review of its technical and editorial content.

Approved An approved standard or guideline has achieved consensus within the health care community. It should be reviewed to assess the utility of the final document, to ensure attainment of consensus (ie, that comments on earlier versions have been satisfactorily addressed), and to identify the need for additional consensus documents.

Our standards and guidelines represent a consensus opinion on good practices and reflect the substantial agreement by materially affected, competent, and interested parties obtained by following CLSI's established consensus procedures. Provisions in CLSI standards and guidelines may be more or less stringent than applicable regulations. Consequently, conformance to this voluntary consensus document does not relieve the user of responsibility for compliance with applicable regulations.

COMMENTS

The comments of users are essential to the consensus process. Anyone may submit a comment, and all comments are addressed, according to the consensus process, by the committee that wrote the document. All comments, including those that result in a change to the document when published at the next consensus level and those that do not result in a change, are responded to by the committee in an appendix to the document. Readers are strongly encouraged to comment in any form and at any time on any document. Address comments to Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.

VOLUNTEER PARTICIPATION

Health care professionals in all specialties are urged to volunteer for participation in CLSI projects. Please contact us at customerservice@clsi.org or +610.688.0100 for additional information on committee participation.

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

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Abstract

Clinical and Laboratory Standards Institute document EP18-P2—*Risk Management Techniques to Identify and Control Laboratory Error Sources; Proposed 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 error (potential failure modes) are identified, understood, and managed. This system will assist device manufacturers, users, regulators, and accrediting agencies in assuring correct results. It addresses regulatory considerations (eg, principles and accountability), recommends the development of a partnership between users and manufacturers, provides a source-of-errors matrix, and suggests approaches to quality monitoring/identification of the problems.

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Foreword

In vitro diagnostic devices (IVDs) 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 error. The relative importance and probability (ie, the risk) of a specific error condition will vary with the device design, the user, the medical application, and the operating environment. A single quality assurance and 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 (POC), there is a pressing need to assure and control quality in the most effective and efficient manner. 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. 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).

This document is one in a series of three CLSI documents concurrently undergoing revision or development that address risk assessment and implementation of quality control strategies to mitigate risks of error. This series of documents includes the current revision of this guideline, EP18—*Risk Management Techniques to Identify and Control Laboratory Error Sources*, and two new guidelines under development, EP22-P—*Presentation of Manufacturers' Risk Mitigation Information for Users of* In Vitro *Diagnostic Devices*, and EP23-P—*User-Defined QC Protocols for* In Vitro *Diagnostic Devices Based on Manufacturer's Risk Mitigation Information and the User's Environment.* One common example ties together the three documents and highlights the key features of each document. The interrelationship of the three documents is summarized below.

*EP18—*Risk Management Techniques to Identify and Control Laboratory Error Sources* is intended to provide manufacturers and laboratory professionals with systematic tools for risk management, particularly FMEA and FRACAS. (The components of FRACAS are sometimes known by other names, such as *complaint monitoring* and *corrective and preventative action* (CAPA) systems.) EP18 will discuss the use of FMEA by manufacturers to identify potential sources of error and impose all applicable measures to control those errors. A laboratory should use the information provided by a manufacturer, apply FMEA and FRACAS to identify residual errors, and apply control measures.

*EP22-P—*Presentation of Manufacturers' Risk Mitigation Information for Users of* In Vitro *Diagnostic Devices* provides guidance to manufacturers on the establishment and disclosure of information to users regarding the scope and effectiveness of design features intended to mitigate risk of potential device failures. This information includes the risk associated with such failures, how the QC design features operate, and the studies done to verify the effectiveness of those features.

*EP23-P—*User-Defined QC Protocols for* In Vitro *Diagnostic Devices Based on Manufacturer's Risk Mitigation Information and the User's Environment* describes how a user can integrate manufacturer's risk mitigation information with the unique characteristics of their environment to develop effective quality control protocols for *in vitro* diagnostic devices. Environmental characteristics can include unique factors, such as personnel competency, testing location, temperature, etc., that can impact test results.

* **NOTE:** Recommended revised Titles and Scopes have not yet been approved by the respective committees and will be modified if required in future drafts.

The previous version of this document, EP18-A—*Quality Management for Unit-Use Testing*, was limited to unit-use devices (see Appendix E on Unit-Use Devices). 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 errors in unit-use test systems and implement processes to manage these errors using new quality management models."

-Reference EP18-A

The original subcommittee anticipated that a broader-based guideline could be created that would address both unit-use and multiuse systems. Accordingly, the current revision of EP18, *Quality Management for Unit-Use Testing*, is applicable to all IVD devices.

Invitation for Participation in the Consensus Process

An important aspect of the development of this and all CLSI documents should be emphasized, and that is the consensus process. Within the context and operation of CLSI, the term "consensus" means more than agreement. In the context of document development, "consensus" is a process by which CLSI, its members, and interested parties (1) have the opportunity to review and to comment on any CLSI publication; and (2) are assured that their comments will be given serious, competent consideration. Any CLSI document will evolve as will technology affecting laboratory or health care procedures, methods, and protocols; and therefore, is expected to undergo cycles of evaluation and modification.

The Area Committee on Evaluation Protocols has attempted to engage the broadest possible worldwide representation in committee deliberations. Consequently, it is reasonable to expect that issues remain unresolved at the time of publication at the proposed level. The review and comment process is the mechanism for resolving such issues.

The CLSI voluntary consensus process is dependent upon the expertise of worldwide reviewers whose comments add value to the effort. At the end of a 60-day comment period, each subcommittee is obligated to review all comments and to respond in writing to all which are substantive. Where appropriate, modifications will be made to the document, and all comments along with the subcommittee's responses will be included as an appendix to the document when it is published at the next consensus level.

A Note on Terminology

CLSI, as a global leader in standardization and harmonization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all challenges to harmonization. In light of this, CLSI recognizes that harmonization of terms facilitates the global application of standards and is an area of immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In the context of this guideline, it is necessary to point out that several terms are used differently in the USA and other countries, notably those in Europe.

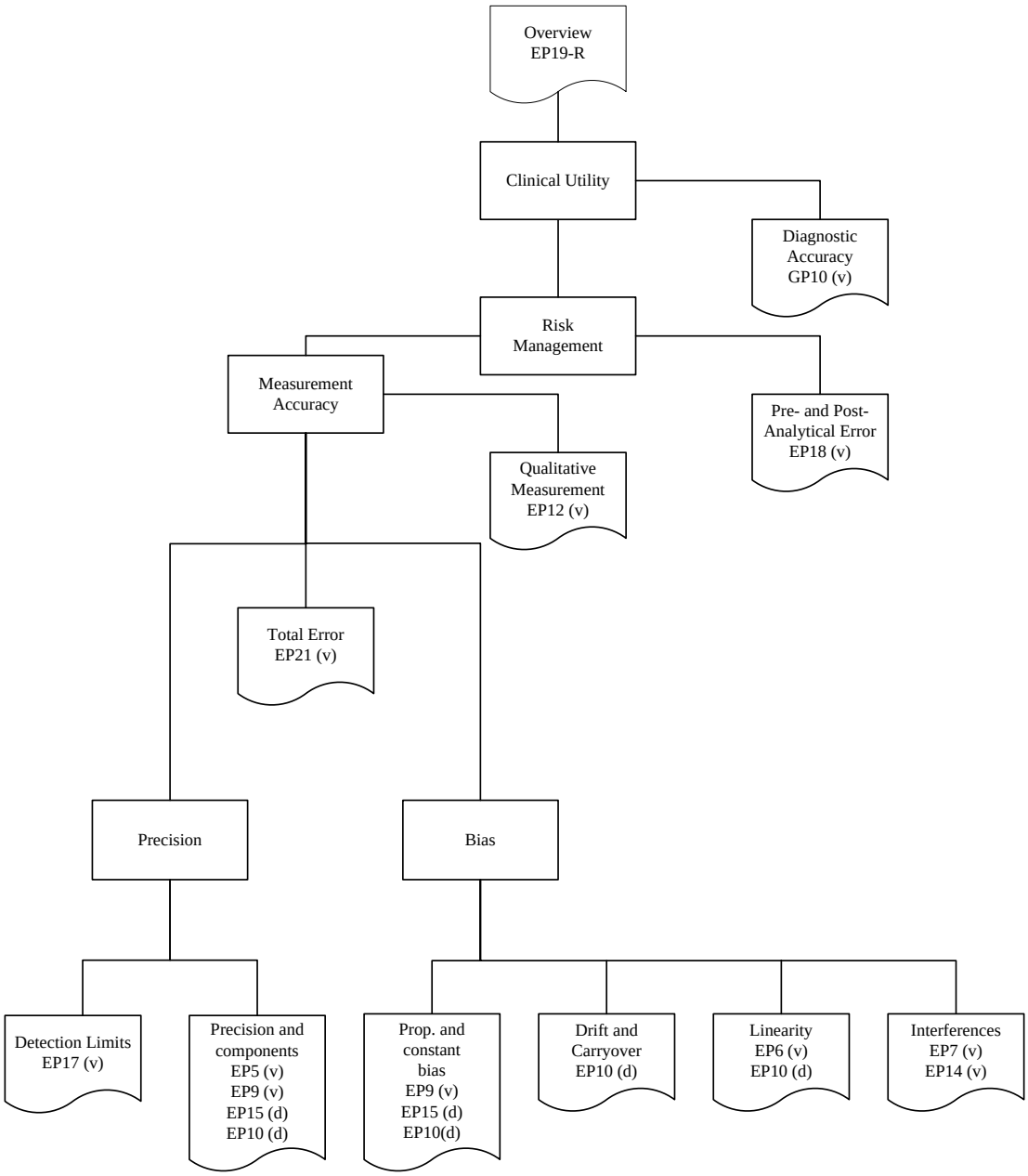
In order to align the usage of terms to ISO, the term *trueness* is used in this document when referring to the closeness of the agreement between the average value from a large series of measurements and an accepted reference value. The term *accuracy*, in its metrological sense, refers to the closeness of the

agreement between the result of a (single) measurement and a true value of a measurand, thus comprising both random and systematic effects.

Key Words

Quality assurance, quality control, quality management, quality system

Laboratory Error Sources and CLSI Evaluation Protocols Documents



Documents marked (d) provide guidance for demonstrating that a source of measurement inaccuracy is within acceptable limits. Documents marked (v) provide guidance for more rigorous evaluation of inaccuracy components.

Laboratory Error Sources and CLSI Evaluation Protocols Documents.[a] This figure illustrates the relationship among parameters estimated by EP documents. Items higher up in the figure are more comprehensive, whereas lower-level items are more specific. Overall, the figure is much like a cause-and-effect diagram. Documents marked (d) provide guidance for demonstrating that a source of measurement inaccuracy is within acceptable limits. Documents marked (v) provide guidance for more rigorous evaluation of inaccuracy components.

[a] For a description of each of the documents listed, please see the Related CLSI/NCCLS Publications section at the end of this document.

The laboratory sources of error figure on the preceding page is based on a figure that has appeared in the following publication: Krouwer JS. Estimating total analytical error and its sources: techniques to improve method evaluation. *Arch Pathol Lab Med.* 1992;116:726-731.[1] Reprinted with permission from the American Medical Association.

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

1 Scope

This document provides guidance for risk assessment procedures that are based on best practices, practical to implement; applicable to all diagnostics assays; and scientifically based so sources of error are identified, understood, and managed. This guidance will aid device manufacturers and users in ensuring correct results.

The scope of this guideline comprises testing components, locations, and users. Specifically, the testing components include:

- specimen collection;
- sample presentation;
- instrument/reagents;
- result/readout/raw data;
- preliminary review; and
- integration into the patient record.

This guideline applies to IVD test systems used by providers of health care services in any setting.

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 accuracy standards (performance). ***Any*** error source can affect the accuracy and/or reliability of a result.

Risk management attempts to answer the four questions in the following figure.