C51-P
Vol. 30 No. 27

Expression of Measurement Uncertainty in Laboratory Medicine; Proposed Guideline

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

28 February 2011

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: standard@clsi.org.

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COMMENT

This document describes a practical approach to developing relevant and useful estimates of measurement uncertainty and for using the information to maintain and improve the quality and application of clinical laboratory measurements.

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

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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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 addressed 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.

C51-P
ISBN 1-56238-741-3
Volume 30 Number 27
ISSN 0273-3099

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Abstract

Clinical and Laboratory Standards Institute document C51-P—*Expression of Measurement Uncertainty in Laboratory Medicine; Proposed Guideline* describes the principles of estimating measurement uncertainty and provides guidance to clinical laboratories and *in vitro* diagnostic (IVD) device manufacturers on the specific issues to be considered for implementation of the concept in laboratory medicine. This document illustrates the assessment of uncertainty of measurement with both bottom-up and top-down approaches. The bottom-up approach suggests that all possible sources of uncertainty are identified and quantified in an uncertainty budget. A combined uncertainty is calculated using statistical propagation rules. The top-down approach directly estimates the uncertainty of measurement results produced by a measuring system. Methods to estimate the imprecision and bias are presented theoretically and in worked examples.

Clinical and Laboratory Standards Institute (CLSI). *Expression of Measurement Uncertainty in Laboratory Medicine; Proposed Guideline*. CLSI document C51-P (ISBN 1-56238-741-3). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2010.

Suggested Citation

CLSI. *Expression of Measurement Uncertainty in Laboratory Medicine; Proposed Guideline.* CLSI document C51-P. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.

Proposed Guideline
December 2010

ISBN 1-56238-741-3
ISSN 0273-3099

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Acknowledgments

This guideline was prepared by the Clinical and Laboratory Standards Institute (CLSI) as part of a cooperative effort with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) to work toward the advancement and dissemination of laboratory standards on a worldwide basis. CLSI gratefully acknowledges the participation of IFCC expert Graham H. White, PhD, on this project.

CLSI, the Area Committee on Clinical Chemistry and Toxicology, and the Subcommittee on Measurement Uncertainty in Laboratory Medicine gratefully acknowledge Aristides Hatjimihail, MD, PhD, Hellenic Complex Systems Laboratory, Drama, Greece, for important contributions made during the development of this document.

Acknowledgment in Memoriam of Richard R. Miller, Jr., Subcommittee Chairholder

CLSI, the Area Committee on Clinical Chemistry and Toxicology, and the Subcommittee on Measurement Uncertainty in Laboratory Medicine also wish to recognize the contributions of Richard R. Miller, Jr., champion of measurement excellence within the clinical laboratory communities. Rick was instrumental in the development of this document and served as chairholder until his untimely passing in July 2007. Rick’s clear vision, deep wisdom, gentle wit, and above all his spirit of collegiality guided the document’s evolution and continue to inspire the subcommittee’s efforts to bring it to fruition.

Contents

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Foreword

When measurements are repeated, some variation of the results will be observed due to random variation of the measurement conditions. The differences will be noticeable if the sensitivity and resolution of the measuring system is sufficient. Therefore, for measurement results to be useful, such result variability (uncertainty) needs to be quantified so that users have an objective estimate of the quality (reliability) of the results produced. Quantification of the variability of measurement results also allows a result to be meaningfully compared with the results of other similar measurements that may have been made at different times using the same measurement system. The concept of measurement uncertainty provides a theoretical and practical framework for objectively estimating the reliability of results produced by any given measurement system.

Knowledge of the sources of uncertainty and their relative magnitude may also provide opportunities for modifying a measurement system to improve the quality of results. Uncertainty estimates at various analyte concentrations also contribute to determining uncertainty profiles, which can be important in defining the measuring interval of measurement systems to ensure that the quality of results issued meets clinical requirements.

This document describes the principles of estimating measurement uncertainty and gives guidance on the specific issues to be considered for implementation of the concept in laboratory medicine. The concept of measurement uncertainty and its use in measuring quantities in laboratory medicine is provided for clinical laboratories and *in vitro* diagnostic (IVD) device manufacturers.

Invitation for Participation in the Consensus Process

An important aspect of the development of this and all CLSI documents is the consensus process. Within the consensus process, CLSI members and other interested parties (1) have the opportunity to review and comment on CLSI publications in development; and (2) are assured that their comments will be given serious consideration. All CLSI documents evolve, as does the technology affecting laboratory or health care procedures, methods, and protocols; and therefore, through the operation of the consensus process, CLSI documents are expected to undergo cycles of evaluation and modification.

The Area Committee on Clinical Chemistry and Toxicology 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 depends on 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 that are substantive. Where appropriate, modifications will be made to the document, and all comments, along with the subcommittee’s responses, will be retained on file at CLSI and will be available upon request.

Key Words

Bias, bottom-up, measurement uncertainty, precision, top-down, trueness

Minority Opinion

Please note that during area committee voting, the following unresolved concern was raised:

Recommended revision:

Deletion of 4th bullet in Section 4.3.2, "Uncertainty Model," which reads as follows:

- Allows the laboratory to report the bias (and its associated uncertainty, if known), along with any uncorrected result, if a laboratory cannot correct for known bias.*

Justification for recommended revision:

Bias correction may or may not be appropriate depending on the analyte measured and the situations. There are many simple well-characterized assays and some complex, not well-characterized assays being used in the laboratory. In some places, it may create more problems if we allow bias correction.

A number of analytes are not interchangeable if they come from different manufacturers and different instruments (eg, CA125, total PSA, free PSA). It will create many problems if laboratories start to check biases of these assays on different instruments and, therefore, this is not a good practice to follow.

Subcommittee's position:

The key feature of the uncertainty approach is to reduce or eliminate the bias inherent in a measurement procedure, regardless of its cause, although the bottom-up procedure as described in this document assumes that reasonable efforts are made to identify and minimize the sources of uncertainty.

Since it is stated that the first step in an uncertainty evaluation is to define the measurand and the measured quantity (see Section 5), it is unlikely that inappropriate comparisons will be performed. Moreover, it is a long-standing practice in clinical laboratories worldwide to ascertain, as far as possible, that results of measurements of patient samples are the same irrespective of where or when the defined measurand is measured.

See statement below from *Contemporary Practice in Clinical Chemistry*, edited by William Clarke and D. Robert Dufour (AACC Press, 2006).

> "It is good laboratory practice (and consistent with CLIA Regulations Section 493.1281) to adjust the calibration of different methods for the same analyte, used within a health delivery system, so the results for patient samples are the same irrespective of which method was used."

We invite further comments on this opinion, for committee consideration in advancing C51-P to the approved level in the CLSI consensus process.

*Laboratories that correct for perceived bias should understand and comply with applicable local, regional, and national regulations.

Expression of Measurement Uncertainty in Laboratory Medicine; Proposed Guideline

1 Scope

This guideline explains the concept, estimation, and application of measurement uncertainty in the field of clinical laboratory medicine. The recommendations provided are consistent with the *Guide to the Expression of Uncertainty in Measurement* (GUM)[1] and with the International Organization for Standardization (ISO) standards concerned with laboratory accreditation.

This guideline briefly discusses, but does not fully address, the following nonmeasurement sources of uncertainty of a measurement result:

- Biological variation of the measurand
- Pre- and postmeasurement processes

The guideline discusses the definition of what is intended to be measured, lists sources of measurement uncertainty, describes the generation of statistical estimates of uncertainties and their combination, and discusses the use of uncertainty estimates. The guideline applies only to quantitative measurements. In measurement procedures that are reported in qualitative terms based on a quantitative measurement, the uncertainty at the threshold(s) for a qualitative interpretation should be considered when making the qualitative assessment.

This guideline is intended for clinical laboratories and *in vitro* diagnostic (IVD) device manufacturers.

2 Introduction

Regardless of method, repeated measurements produce different results due to inherent variations within the measuring system. Some knowledge of the result variability expected from a given measurement system is required if results are to be meaningfully compared with previous results from the same patient or important clinical set-points. In addition, evaluation and elimination of bias in a measuring system relative to the relevant reference material or reference procedure is essential if results from different laboratories using the same or different measuring systems are to be compared for the same patient.

Characterization of the variability of repeated measurement results and identification of the factors that contributed to that variability can provide useful insights into the reliability of results and potential means for improvement. Existing quality control (QC) and method validation data can be used to define the performance characteristics of routine measuring systems. This document provides guidance on how measurement uncertainty can be estimated and used in the field of laboratory medicine. The principles for expression of measurement uncertainty provided in this document illustrate how the components of measurement uncertainty can be combined to estimate the performance characteristics that can be reliably achieved by the measuring system.

The objectives of this document are to:

- Familiarize the reader with the concept of measurement uncertainty.
- Describe the processes of implementing the concept in laboratory medicine.
- Describe practical approaches to developing relevant and useful estimates of measurement uncertainty.
- Discuss uses of the information obtained.