EP27-P
Vol. 29 No. 16

How to Construct and Interpret an Error Grid for Diagnostic Assays; 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

31 August 2009

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 guideline describes what an error grid is, why it is useful, and how to construct and interpret the information. Guidance is provided for manufacturers and for the clinical laboratory.

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

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.

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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; and
- 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.

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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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How to Construct and Interpret an Error Grid for Diagnostic Assays; Proposed Guideline

Jan S. Krouwer, PhD
Anders Kallner, MD, PhD
Anthony Killeen, MD, PhD
Marina Kondratovich, PhD
Stellan Lindberg, MSc
S Nandagopalan, PhD
Thomas Smith
Ann F. Stankiewicz, PhD

Abstract

Clinical and Laboratory Standards Institute document EP27-P—*How to Construct and Interpret an Error Grid for Diagnostic Assays; Proposed Guideline* describes what an error grid is, why it is useful, and how to go about constructing it. Error grids inform users about the performance required to prevent potential patient harm. Once constructed, error grids can be populated with data from a method comparison experiment. Then one can calculate the proportion of data in each error grid zone as well as confidence intervals. Three examples are provided.

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Proposed Guideline

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Committee Membership

Area Committee on Evaluation Protocols

Greg Cooper, CLS, MHA
Chairholder
Bio-Rad Laboratories, Inc.,
QSD Division
Plano, Texas, USA

R. Neill Carey, PhD
Vice-Chairholder
Peninsula Regional Medical Center
Salisbury, Maryland, USA

John Rex Astles, PhD, FACB
Centers for Disease Control and Prevention
Atlanta, Georgia, USA

Jeffrey R. Budd, PhD
Beckman Coulter, Inc.
Chaska, Minnesota, USA

George S. Cembrowski, MD, PhD
University of Alberta Hospital
Edmonton, Alberta, Canada

David L. Duewer, PhD
National Institute of Standards and Technology
Gaithersburg, Maryland, USA

Anders Kallner, MD, PhD
Karolinska Hospital
Stockholm, Sweden

James F. Pierson-Perry
Siemens Healthcare Diagnostics
Newark, Delaware, USA

Mitchell G. Scott, PhD
Washington University School of Medicine
St. Louis, Missouri, USA

Lakshmi Vishnuvajjala, PhD
FDA Center for Devices and Radiological Health
Rockville, Maryland, USA

Advisors

David A. Armbruster, PhD, DABCC, FACB
Abbott Diagnostics
Abbott Park, Illinois, USA

Carl C. Garber, PhD, FACB
Quest Diagnostics, Incorporated
Madison, New Jersey, USA

Patricia E. Garrett, PhD
SeraCare Life Sciences, Inc.
Portland, Maine, USA

Claude Giroud, PhD
Bio-Rad Laboratories, Inc.
Marnes-La-Coquette, France

Martin H. Kroll, MD
Boston Medical Center
Boston, Massachusetts, USA

Jan S. Krouwer, PhD
Krouwer Consulting
Sherborn, Massachusetts, USA

Jacob (Jack) B. Levine, MBA
Siemens Healthcare Diagnostics
Tarrytown, New York, USA

Kristian Linnet, MD, PhD
University of Copenhagen
Copenhagen, Denmark

Robert J. McEnroe, PhD
Roche Diagnostics Operations, Inc.
Indianapolis, Indiana, USA

James H. Nichols, PhD, DABCC, FACB
Baystate Medical Center
Springfield, Massachusetts, USA

Luann Ochs, MS
BD Diagnostics-TriPath
Durham, North Carolina, USA

Donald R. Parker, PhD
Bayer HealthCare, LLC
Elkhart, Indiana, USA

Nils B. Person, PhD, FACB
Siemens Healthcare Diagnostics
Flanders, New Jersey, USA

Donald M. Powers, PhD
Powers Consulting Services
Pittsford, New York, USA

Max Robinowitz, MD
FDA Center for Devices and Radiological Health
Rockville, Maryland, USA

Michele M. Schoonmaker, PhD
Cepheid
Sunnyvale, California, USA

Daniel W. Tholen, MS
American Association for Laboratory Accreditation
Traverse City, Michigan, USA

Jack Zakowski, PhD, FACB
Beckman Coulter, Inc.
Brea, California, USA

Subcommittee on How to Construct and Interpret an Error Grid for Diagnostic Assays

Jan S. Krouwer, PhD
Chairholder
Krouwer Consulting
Sherborn, Massachusetts, USA

Anders Kallner, MD, PhD
Karolinska Hospital
Stockholm, Sweden

Anthony Killeen, MD, PhD
University of MN Medical Center-Fairview
Minneapolis, Minnesota, USA

Marina Kondratovich, PhD
FDA Center for Devices and Radiological Health
Rockville, Maryland, USA

S Nandagopalan, PhD
LifeScan, Inc.
Milpitas, California, USA

Thomas Smith
Ortho-Clinical Diagnostics, Inc.
Rochester, New York, USA

Ann F. Stankiewicz, PhD
Roche Diagnostics Operations
Indianapolis, Indiana, USA

Advisors

Stellan Lindberg, MSc
HemoCue AB
Angelholm, Sweden

Peter Osella
Sysmex America, Inc.
Mundelein, Illinois, USA

Staff

Clinical and Laboratory Standards Institute
Wayne, Pennsylvania, USA

Lois M. Schmidt, DA
Vice President, Standards Development and Marketing

Jane M. Oates, MT(ASCP)
Staff Liaison

Melissa A. Lewis
Editorial Manager

Carol DiBerardino, MLA, ELS
Assistant Editor

Contents

Foreword

Error grids are well known for glucose assays, but otherwise are used little. This guideline attempts to change this by discussing why error grids are important. Guidance is provided about how to construct an error grid both for manufacturers and end users. The purpose of an error grid is to inform users about the likelihood of potential patient harm. Typically, at least three zones are constructed. The allowable total error zone (ATE or Zone A) is specified to contain a large proportion of the data (95%) and is unlikely to cause patient harm. The limits of erroneous results (LER or Zone C) are specified to contain little or no data, because results in this zone have a high potential to cause patient harm. Zone B contains the remainder of the results.

Guidance is provided on how one locates the three zones, based on the clinical implications of errors. Guidance is also given on how to graph the error grids and how to estimate the proportions in each zone with confidence intervals. Examples are provided for three different assays.

Note that the trade name Microsoft Excel is included in Section 7.1, Section 8.1.6, Appendix A, and Appendix B, and the trade name Microsoft Word is included in Appendix A of this document. It is the Clinical and Laboratory Standards Institute's policy to avoid using a trade name unless the product identified is the only one available, or it serves solely as an illustrative example of the procedure, practice, or material described. In this case, the subcommittee and area committee believe the trade names are used as illustrative examples in Appendixes A and B of the document. Users of this document can construct error grids using any equivalent software. It should be understood that information on these products in this guideline also applies to any equivalent products. Please include in your comments any information that relates to this aspect of EP27-P.

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 and 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.

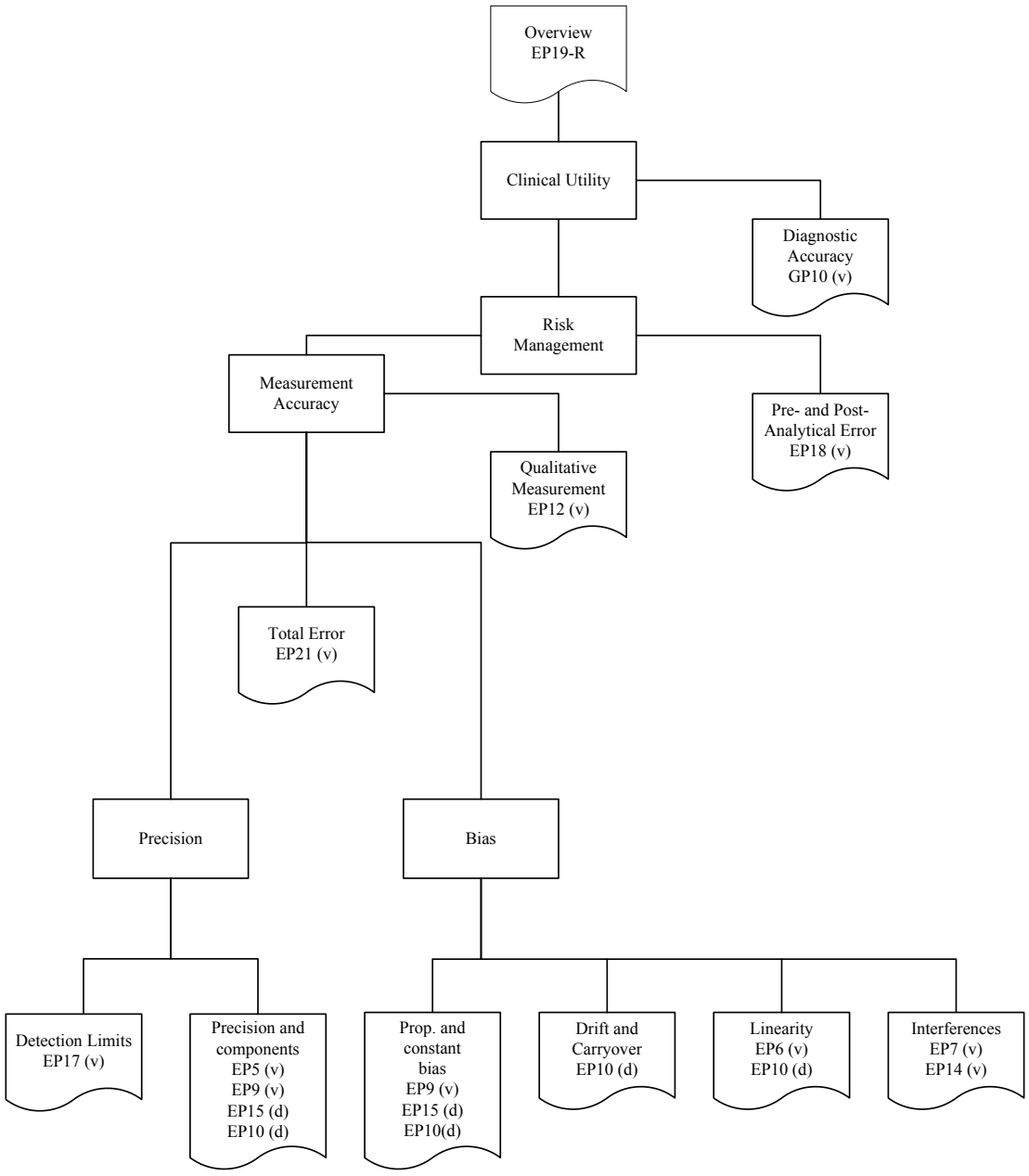
The Area Committee on Evaluation Protocols has attempted to engage the broadest worldwide representation in the committee deliberations to develop this document. Consequently, it is expected that issues may still remain unresolved when the proposed-level document is published. Review and comment within the CLSI 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 final document. At the end of a 60-day comment period, each subcommittee is obligated to review all comments and to respond in writing to all substantive comments. Where appropriate, modifications will be made to improve the document, and all comments along with the subcommittee's responses will be included in an appendix when the document is published at the next consensus level.

Key Words

Allowable total error region (ATE, Zone A), error grid, limits of erroneous result region (LER, Zone C)

Laboratory Failure Sources and CLSI Evaluation Protocols Documents



Laboratory Failure Sources and CLSI Evaluation Protocols (EP) 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 Reference Materials section at the end of this document.

How to Construct and Interpret an Error Grid for Diagnostic Assays; Proposed Guideline

1 Scope

Although there are many protocols for evaluating diagnostic assays, one can always ask the question, "is the estimated performance 'good enough'"? This is a difficult question to answer, and previous attempts from CLSI and the International Organization for Standardization Technical Committee (ISO/TC) 212 to establish analytical performance goals for assays failed to be completed. This project provides a different approach by leveraging the long-standing, existing glucose error grids.[1,2] EP27 explains how to construct error grids for any diagnostic assay, with a focus on the following:

- the region that should include most (95%) of the data – the allowable total error (ATE) region; and
- the region that should include ideally none (0%) of the data – the limits of erroneous results (LER) region.

Moreover, these grids are illustrated for different diseases and uses (eg, screening vs monitoring). This can lead to different error grids for the same assay. Regulatory practices, which can be different in different countries, can also affect error grids.

These grids are graphed in a spreadsheet so the output of existing evaluation protocol procedures can display data in the error grid.

Guidance is provided on how to quantify the amount of data and its corresponding confidence interval in each error grid region.[b]

In addition, the document is geared toward manufacturers with respect to construction of error grids. However, it is applicable also to clinical laboratories, because data from protocols such as CLSI document EP15[3] or EP09[4] can be displayed in an error grid.

This document is intended for any quantitative assay whereby both the test and comparative methods measure the same measurand using the same units.

2 Introduction

Assay quality is important because *in vitro* diagnostic (IVD) results play an ever-increasing role in medical decision making. Initial evaluations of assay quality focused on analytical performance parameters, such as average bias and imprecision.[5] In a way, this was unfortunate because even though Westgard suggested that total analytical error is important,[6] it has been common to model total analytical error by combining estimated individual analytical performance parameters rather than directly estimating total error.[7] Bland and Altman suggested a direct measure of total analytical error[8] that was an improvement because models were not needed. Shortly afterward, Clarke developed the glucose error grid.[1,2] The error grid provides more information than total error alone, because the error grid shows how much error is problematic at each glucose concentration. Moreover, the error grid separates errors into a hierarchy—small errors are allowable, whereas large undetected errors at specific concentrations must be avoided, because they are almost certain to cause patient harm.

[b] Note that error grids are required in the US Food and Drug Administration (FDA) guidance document for Clinical Laboratory Improvement Amendments (CLIA) waiver applications. Hence, this document supports this FDA requirement. Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices. OMB control number 0910-0598. Issued January 30, 2008.