CLINICAL AND LABORATORY STANDARDS INSTITUTE®

1st Edition

CLSI EP46™

Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures

CLSI EP46 provides developers and end users with an understanding of concepts related to setting allowable total error (ATE) goals and limits for quantitative measurement procedures. CLSI EP46 provides an overview of concepts related to total error, considerations for applying total error concepts (such as setting acceptance criteria for analytical performance characteristics), and models to inform the determination of ATE goals and limits.

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

CLSI EP46-Ed1
June 2025

Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures

Michelle R. Campbell, MS, MLS(ASCP)[CM], MB[CM], SC[CM]
J. Rex Astles, PhD, FADLM
Miranda Brun, PhD, FCACB
Janetta Bryksin, PhD, DABCC, FADLM
Kornelia Galior, PhD, DABCC
Mark Holland, PhD
Bill Jennings, MSc
Jesper Johansen, PhD
Marina Kondratovich, PhD
Paula Ladwig, MS, MLS(ASCP)
Leslie Landree, PhD
Ruediger Laubender, PhD
Sara Love, PhD, DABCC
Paulo Pereira, PhD
Victoria Petrides, MS
John Yundt-Pacheco, MS

Abstract

Clinical and Laboratory Standards Institute EP46—*Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures* provides developers (both commercial manufacturers and laboratories that create laboratory-developed tests) and medical laboratory end users with models to inform the determination of allowable total error (ATE) goals and limits. ATE goals and limits are useful during both the Establishment and Implementation Stages of the Test Life Phases Model (see CLSI EP19[1]) to assist in determining acceptance criteria for Validation and Verification Phase performance evaluations.

Approaches for determining ATE goals and limits are described based on the effect of analytical performance on clinical outcomes, the comparison with biological variation of the measurand, and the state of the art based on analytical performance similar to that of a peer group. Considerations to the phases of a measurement procedure (preanalytical, analytical, and postanalytical) in setting ATE goals or limits and sources of error contributing to the estimate of total error for which ATE is to be determined are also described.

CLSI EP46 is a resource for many CLSI method evaluation documents. Before performing a study to estimate an analytical performance characteristic of a quantitative measurement procedure (accuracy, precision, linearity, etc.), acceptance criteria should be set. These acceptance criteria should be linked to the ATE goals or limits for the measurand. CLSI EP46 provides approaches for determining ATE goals or limits and describes their application. CLSI EP46 can be used to set the ATE limits for the study protocol presented in CLSI EP21[2] for determining the total analytical error for a quantitative measurement procedure.

Clinical and Laboratory Standards Institute (CLSI). *Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures.* 1st ed. CLSI guideline EP46 (ISBN 978-1-68440-282-3 [Print]; ISBN 978-1-68440-283-0 [Electronic]). Clinical and Laboratory Standards Institute, USA, 2025.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Suggested Citation

CLSI. *Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures.* 1st ed. CLSI guideline EP46. Clinical and Laboratory Standards Institute; 2025.

CLSI EP46-Ed1

ISBN 978-1-68440-282-3 (Print)

ISBN 978-1-68440-283-0 (Electronic)

ISSN 1558-6502 (Print)

ISSN 2162-2914 (Electronic) Volume 45, Number 8

Committee Membership

Consensus Council

The Consensus Council sets priorities for CLSI standards development and votes on Final Draft documents to confirm that process requirements have been met. Consensus Council members are listed on the CLSI website: https://clsi.org/standards-development/consensus-council/

Document Development Committee on Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures

Michelle R. Campbell, MS, MLS(ASCP)^{CM}, MB^{CM}, SC^{CM}
Chairholder
Mayo Clinic
USA

J. Rex Astles, PhD, FADLM
Vice-Chairholder
Centers for Disease Control and Prevention
USA

Lorin Bachmann, PhD, DABCC, MLS(ASCP)
Virginia Commonwealth University Health System
USA

Miranda Brun, PhD, FCACB
Alberta Precision Laboratories, University of Alberta
Canada

Kornelia Galior, PhD, DABCC
Emory University
USA

Bill Jennings, MSc
Canadian Intellectual Property Office
Canada

Leslie Landree, PhD
FDA Center for Devices and Radiological Health
USA

Sara Love, PhD, DABCC
Siemens Healthcare Diagnostics, Inc.
USA

John Yundt-Pacheco, MS
Bio-Rad Laboratories, Inc.
USA

Expert Panel on Evaluation Protocols

Expert panel volunteers support the development of CLSI documents by providing technical expertise in specialty areas. Expert panel members are listed by area of expertise on the CLSI website: https://clsi.org/standards-development/expert-panels/

Acknowledgment

CLSI, the Consensus Council, and the Document Development Committee on Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures gratefully acknowledge the following volunteers for their important contributions to the development of CLSI EP46:

Janetta Bryksin, PhD, DABCC, FADLM
Emory University Hospital
USA

Miklos Erdosy, PhD
Werfen
USA

Mark Holland, PhD
Beckman Coulter
USA

Jesper Johansen, PhD
Radiometer Medical ApS
Denmark

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

Paula Ladwig, MS, MLS(ASCP)
Mayo Clinic
USA

Ruediger Laubender, PhD
Roche Diagnostics GmbH
Germany

Paulo Pereira, PhD
Portuguese Institute of Blood and Transplantation
Portugal

Victoria Petrides, MS
Abbott
USA

Contents

Foreword

The determination of analytical quality goals or limits, referred to as allowable total error (ATE), is an essential step in deciding whether a measurement procedure's total analytical error (TAE) is acceptable. In CLSI EP46, the term "goal" is used to describe an aspirational performance that is desirable for optimal clinical utility. In some cases, a goal may not currently be technically achievable or only achieved by a minority of measurement procedures. A performance "limit" focuses on the minimally acceptable performance for clinical use. Hence, a limit is a specification. Measurement procedures that cannot achieve the limit for the minimally acceptable analytical performance for ATE are not considered suitable for use.

Estimating TAE for comparison with an ATE limit can be accomplished using the approach described in CLSI EP21,[2] as well as by other approaches. Without the *a priori* establishment of acceptance criteria for ATE, it is not possible to objectively evaluate whether a measurement procedure demonstrates accuracy that meets clinical performance goals for a given intended use and patient population. A variety of sources and methods can inform goals and limits; however, the selection of the approach taken is of critical importance.

Setting ATE goals and limits should include consideration of the preanalytical, analytical, and postanalytical (sometimes referred to as preexamination, examination, and postexamination, respectively) phases of the measurement procedure under evaluation to identify when and where error(s) occur and whether their underlying causes are random or systematic. Experts have made recommendations for approaches to use for selecting criteria for informing ATE goals and limits.[3] CLSI EP46 recommends that all available relevant sources of information should be taken into consideration when determining ATE goals and limits. When available, studies on the effect of TAE on clinical outcomes should inform ATE goals and limits. For example, surveys of clinicians who use the measurand results in practice can also be helpful. For many analytes, it is also relevant to assess available information about biological variation of the measurand. For analytes that do not have a homeostatic set point, such as cardiac markers and toxins, this might not be possible. Finally, generally available information on analytical capabilities based on peer-group performance can be used as a practical and accessible source for informing ATE limits. "State of the art," when defined as the highest technically achievable performance, might be most appropriate for use to set aspirational performance goals. For some measurands, it is possible that no measurement procedures are currently able to meet requirements for optimal clinical performance.

Overview of Changes

CLSI EP46 replaces and expands on Chapter 2 (Establishing Total Analytical Error and Allowable Total Error Limits) of CLSI EP21-Ed2, published in 2016. Several changes were made in the writing of this new guideline, including:

- Differentiating the terms "goals" and "limits" as they relate to ATE.
- Discussing the functional components of error and their classification as random or systematic in nature.
- Updating the list of approaches used to determine ATE.
- Comparing TAE with measurement uncertainty and Sigma metric.
- Adding content on error budgeting.
- Describing the use of error grid analysis to determine the acceptability of a candidate measurement procedure.

NOTE: The content of CLSI EP46 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

allowable total error
biological variation
clinical outcomes
error
error budgeting
error grids
Sigma metric
total analytical error

Chapter 1

Introduction

Determining Allowable Total Error Goals and Limits for Quantitative Medical Laboratory Measurement Procedures

1 Introduction

1.1 Scope

CLSI EP46 provides guidance for selecting the relevant sources for establishing allowable total error (ATE) goals and/or limits for quantitative medical laboratory measurement procedures. This guidance is suitable for both commercial products as well as laboratory-developed tests (LDTs). It is particularly useful for end-user medical laboratories to set acceptance criteria (ie, limits) for total analytical error (TAE) before performing studies described in CLSI EP21[2] and can be used to determine acceptability of a measurement procedure for use to inform clinical decisions.

The intended users of CLSI EP46 are developers of measurement procedures (both commercial manufacturers and laboratories that create LDTs), regulatory authorities, and medical laboratory personnel.

Users should learn how to:

- Describe error and classifications of error as preanalytical, analytical, or postanalytical; random or systematic.
- Compare frameworks for applying total error concepts.
- Consider the multiple sources of error contributing to bias and imprecision in a measurement procedure.
- Determine ATE limits using models based on clinical outcome studies, biological variation of the measurand, and/or the state of the art of the measurand, dependent on the availability of data.

CLSI EP46 is not intended to provide recommendations or endorsement for specific sources of ATE limits. It does not provide guidance on estimating and evaluating TAE for quantitative measurement procedures, but instead directs users to CLSI EP21[2] for information on this topic.

1.2 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.[4] 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 M29.[5]

1.3 Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization whenever 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 different countries and regions and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. CLSI recognizes