CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

EP21

Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures

This guideline provides manufacturers and end users with an understanding of concepts related to total analytical error (TAE) for quantitative measurement procedures. An experimental protocol and data analysis method are provided to estimate TAE based upon a comparison of methods experiment with patient specimens, and to assess it relative to a pre-established goal for clinical acceptability.

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

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Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures

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Abstract

Clinical and Laboratory Standards Institute guideline EP21—*Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures* provides manufacturers and end users with a means to estimate total analytical error (TAE) for a quantitative measurement procedure and to assess if it meets pre-established specifications. Error is defined in terms of observed bias, using patient specimens tested with either a reference or comparative measurement procedure as described in CLSI document EP09.[1] This assessment incorporates multiple analytical error sources, including imprecision, bias, nonlinearity, interferences, specimen-to-specimen matrix differences, and others. EP21 can be used to judge acceptability of candidate measurement procedures relative to performance goals reflective of clinical utility.

Before an evaluation with EP21, the user selects the appropriate limits for allowable total error relative to a performance goal for clinical utility. Users also decide whether to measure TAE over the entire measuring interval, and/or at specific subintervals.

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Foreword

The concept of total analytical error (TAE) is central to the medical laboratory. When comparing laboratory results to medical decision levels, deciding if differences in serial results from a patient are meaningful, or when making other patient care decisions, clinicians seek to answer the question, "How accurate are these results?" Similarly, laboratorians want to know, "Does my measurement procedure—or one that I am considering bringing into my laboratory—meet relevant clinical performance accuracy goals?"

Although bias and precision are important performance attributes of quantitative measurement procedures, it is their integrated influence with other sources of variability—accuracy—that is most meaningful. An erroneous laboratory result is a failure, with the potential for subsequent inappropriate medical decisions and unwarranted patient care costs, regardless if due to uncorrected bias, poor precision, or both. Even in cases in which acceptable results are obtained for bias and precision through separate studies, their combined effect may be unacceptable.

The approach to estimation of TAE adopted in this guideline is based upon evaluation of the differences in patient specimen results between the candidate and a comparative measurement procedure. As such, the resulting TAE estimate incorporates multiple sources of testing errors that commonly arise in a medical laboratory. A strength of this approach is that the analyst may choose to broaden the experimental design to incorporate additional sources of variability as desired, eg, reagent and/or calibrator lot-to-lot changes, recalibrations, and extremes of reagent in-use stability.

In many cases, for various reasons, it is not possible to use a true reference measurement procedure as the comparative measurement procedure. When possible, however, the comparative measurement procedure needs to be traceable.

Chapter 1

Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline

Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures

1 Introduction

1.1 Scope

EP21 provides guidance for understanding, estimating, and evaluating total analytical error (TAE) 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 medical laboratories to assess the performance of measurement procedures intended to be put into service, relative to goals for allowable measurement error.

Through EP21, users will learn the limitations of traditional estimates of TAE that added independent point estimates of bias and imprecision, accounting for all sources of error including those due to nonlinearity, nonspecificities, lot-to-lot variations in reagent performance, etc. Users will learn how to:

- Describe the difference between TAE and total error, which includes pre- and postexamination (pre- and postanalytical) components, and why EP21 focuses only on the former.
- Explain the various available sources for establishing allowable total error (ATE) goals, also called total error allowable.
- Discuss considerations for setting ATE limits, including selection of appropriate subintervals.
- Design an experiment to measure TAE and determine if performance goals were met.

The intended users of this guideline are developers of *in vitro* diagnostic (IVD) reagents, regulatory authorities, and medical laboratory personnel.

1.2 Background

Performance characterization of medical laboratory measurement procedures was historically conducted as a set of separate studies for individual bias and precision components—a paradigm that largely continues today. It was not until 1974, when Westgard et al.[2] introduced the concept of TAE, that a useful tool for accuracy estimation was introduced to the medical laboratory.

Westgard's TAE model integrated components of systematic error (bias) and random error (within-laboratory precision, expressed as SD_{WL}) into an

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) approach in the development of standards and guidelines, which facilitates project management; defines a document structure using a template; and provides a process to identify needed documents. The QMS 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:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

EP21 covers 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 page 56.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
					X	X					
						C24					
						EP05					
						EP09					
						EP15					
						EP28					
						EP30					
		M29									
			POCT12			POCT12	POCT12				

Related CLSI Reference Materials*

C24 **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions. 3rd ed., 2006.** This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.

EP05 **Evaluation of Precision of Quantitative Measurement Procedures. 3rd ed., 2014.** This document provides guidance for evaluating the precision performance of quantitative measurement procedures. It is intended for manufacturers of quantitative measurement procedures and for laboratories that develop or modify such procedures.

EP09 **Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed., 2013.** This document addresses the design of measurement procedure comparison experiments using patient samples and subsequent data analysis techniques used to determine the bias between two *in vitro* diagnostic measurement procedures.

EP15 **User Verification of Precision and Estimation of Bias. 3rd ed., 2014.** This document describes the estimation of imprecision and of bias for clinical laboratory quantitative measurement procedures using a protocol than can be completed within as few as five days.

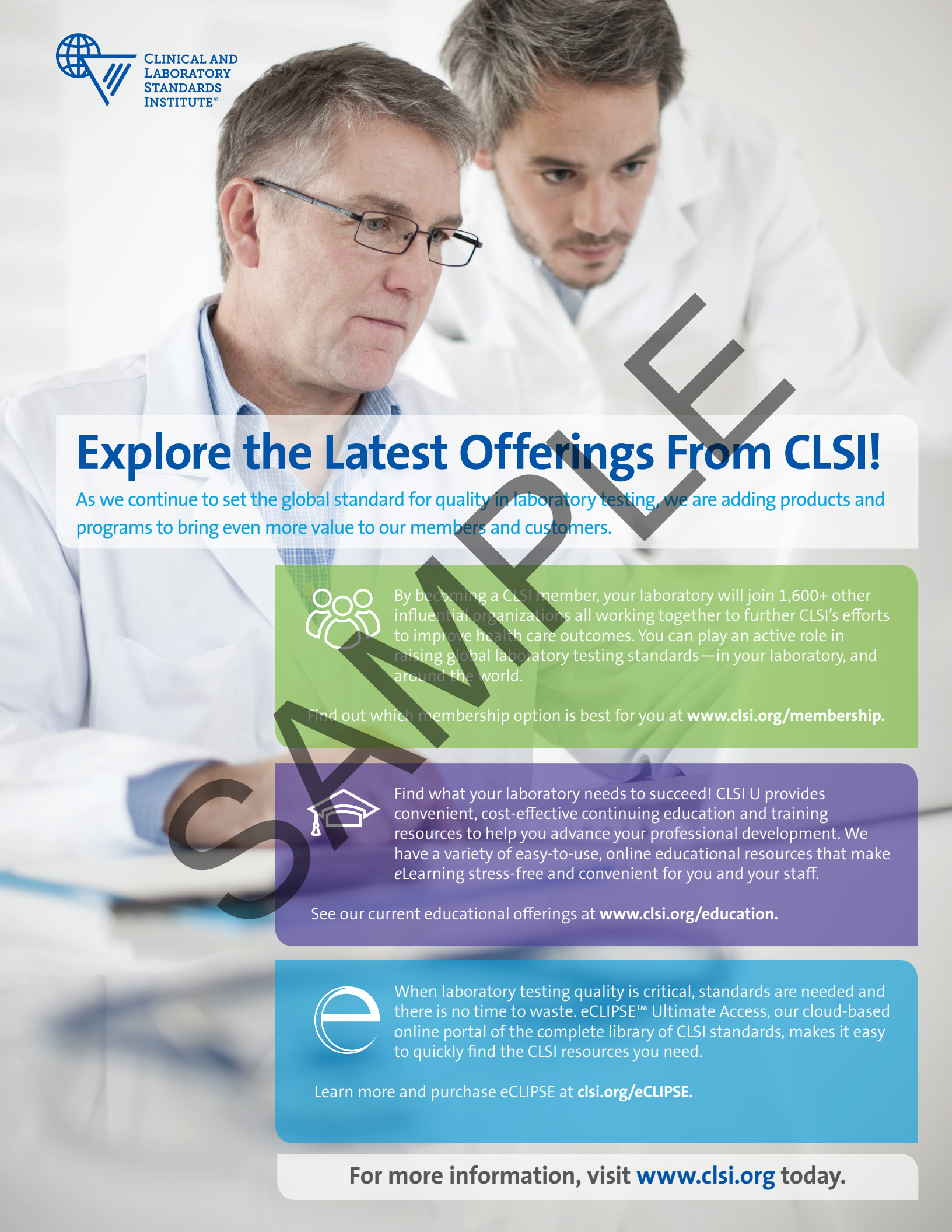
EP28 **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory. 3rd ed., 2010.** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests.

EP30 **Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine. 1st ed., 2010.** This document provides information to help material manufacturers in the production and characterization of commutable reference materials, as well as to assist assay manufacturers and laboratorians in the appropriate use of these materials for calibration and trueness assessment of *in vitro* diagnostic medical devices.

M29 **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** 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.

POCT12 **Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities. 3rd ed., 2013.** This document contains guidelines for performance of point-of-care blood glucose meter systems that stress quality control, training, and administrative responsibility.

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



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