CLINICAL AND LABORATORY STANDARDS INSTITUTE®

3rd Edition

CLSI EP21™

Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures

CLSI EP21 provides developers and end users with an understanding of concepts related to total analytical error (TAE) for quantitative measurement procedures. An experimental protocol and analytical method are provided to estimate TAE based on a comparison of results between the candidate method and a comparator method using patient specimens. Each paired difference is compared with a pre-established specification for acceptability, ie, the allowable total error (ATE). Guidance for determining the ATE is provided in CLSI EP46.

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

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For additional information on committee participation or to submit comments, contact CLSI.

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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 EP21—*Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures* provides developers (both manufacturers and laboratories that create laboratory-developed tests) and medical laboratory end users with a means to estimate total analytical error (TAE) for a quantitative measurement procedure. Results are used to assess if the measurement procedure meets pre-established limits for allowable total error (ATE). Error is defined in terms of observed differences using patient specimens tested with either a reference or comparator measurement procedure. This assessment can incorporate multiple analytical error sources, including imprecision, bias, nonlinearity, interferences, specimen-to-specimen matrix differences, and others. CLSI EP21 can be used to evaluate acceptability of a candidate measurement procedure relative to acceptable performance for the intended clinical use of patient test results.

Before estimation of TAE with CLSI EP21, the user selects the appropriate ATE limit for clinical utility using the protocol described in CLSI EP46.[1] Users also decide whether to evaluate TAE over the entire analytical measuring interval, and/or at specific subintervals.

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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/

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Contents

Foreword

The concept of total analytical error (TAE) is central to the medical laboratory. Clinicians seek to answer the question, "How accurate are these results?" when comparing laboratory results with medical decision levels, when deciding if differences in serial results from a patient are meaningful, or when making other patient care decisions. 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 often the most meaningful. An erroneous laboratory result is a failure with the potential for subsequent inappropriate medical decisions and unwarranted patient care costs, regardless of which error component(s) contributed to the inaccuracy. Even in cases in which acceptable estimates are obtained for bias and imprecision through separate studies, their combined effect might be unacceptable.

CLSI EP21 presents 2 study approaches (termed "minimum" and "robust") for the estimation of TAE, which are tailored to the phase of the Test Life Phases Model (see CLSI EP19[2]) and user of the measurement procedure being evaluated. Both the minimum and robust approaches to the estimation of TAE adopted in CLSI EP21 are based on evaluation of the differences in patient sample results between the candidate and comparator measurement procedures. 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 the adaptability of the experimental design to incorporate additional sources of inaccuracy as desired, eg, reagent and/or calibrator lot changes, calibration cycles, and extremes of reagent in-use stability.

Overview of Changes

CLSI EP21-Ed3 replaces CLSI EP21-Ed2, published in 2016. Several changes were made in this edition, including:

- Harmonizing terminology, abbreviations, and definitions related to TAE.
- Extracting content on determining allowable total error limits from Chapter 2 of the previous edition to be included in a new CLSI EP46[1] because the setting of acceptance criteria for allowable total error is foundational to (and as such, referenced by) several CLSI method evaluation documents.
- Additional considerations for developers (both manufacturers and laboratories that create laboratory-developed tests) for a more rigorous experimental design.
- Updating and expanding worked examples in the appendix, including the addition of a worked example with subintervals.

NOTE: The content of CLSI EP21 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 **total analytical error** **total error**

error

Chapter 1

Introduction

Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures

1 Introduction

1.1 Scope

CLSI EP21 provides guidance for understanding, estimating, and evaluating the acceptability of total analytical error (TAE) for quantitative medical laboratory measurement procedures. This guidance is suitable for both commercially manufactured products as well as laboratory-developed tests (LDTs). It is also useful for medical laboratories to assess the performance of measurement procedures intended to be put into use. Allowable total error (ATE) limits should be determined before CLSI EP21 is used to estimate and assess TAE. Users should consult CLSI EP46[1] for guidance for setting limits for ATE, with consideration to how test results are used to inform patient care.

The intended users of CLSI EP21 are developers of measurement procedures (both commercial manufacturers and laboratories with LDTs), regulatory authorities, and medical laboratory personnel.

Through CLSI EP21, users learn how to:

- Describe the difference between TAE and total error, which includes pre- and postanalytical components (sometimes referred to as pre- and postexamination, respectively), and understand why CLSI EP21 focuses on the former.
- Define subintervals within a measurement procedure's analytical measuring interval (AMI) as it relates to medical decision levels affecting clinical decisions and patient management.
- Design an experiment to estimate TAE and determine if performance goals were met for the entire AMI of a measurement procedure or, when applicable, subintervals of the AMI.

The focus of CLSI EP21 is primarily on estimating errors occurring during the analytical phase of the testing process (total analytical error) and not the total testing process (total error), which encompasses the preanalytical through the postanalytical phases. The protocol provided estimates the combined impact of multiple sources of error, including but not limited to bias, imprecision, and other factors (eg, nonlinearity, interferences, specimen-to-specimen matrix differences). Although bias and imprecision both contribute to the TAE estimated using the protocol in CLSI EP21, separate estimates of these parameters are not obtained. To evaluate the bias between 2 measurement procedures, see CLSI EP09.[3] To evaluate the precision performance of quantitative measurement procedures, see CLSI EP05.[4] For user verification of precision and estimation of bias, see CLSI EP15.[5] CLSI EP21 is not intended to provide guidance on identifying the source(s) of error or mitigation of TAE that falls outside of pre-established acceptance criteria. It does not cover the considerations for or approaches to setting ATE limits, but instead directs users to CLSI EP46[1] for information on this topic. CLSI EP21 is not intended for use in evaluating qualitative medical laboratory measurement procedures.

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