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.

Overview of Changes

This revision of EP21 is based upon extensive discussions with its current and potential users. It follows the same basic testing protocol as the previous edition, and incorporates updates designed to promote its relevance and use by both manufacturers and laboratorians. These updates include:

- Greater clarity in developing the concepts of total error and TAE
- Expanded guidance on selection of suitable acceptance criteria
- Overview of the relationship between TAE and the Sigma metric
- Simplified data analysis

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

KEY WORDS

Error
Error of measurement
Measurement error
Sigma metric
Total allowable error
Total analytical error
Total error

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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