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CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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EP21-A

Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline

This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method which can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay's total analytical error by using quality control samples.

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

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Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline

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Abstract

CLSI document EP21-A—*Estimation of Total Analytical Error for Clinical Laboratory Methods*; *Approved Guideline* provides manufacturers and end users with a means to estimate total analytical error for an assay. The procedure includes a data collection protocol and analysis method, which is largely graphical. The result is compared to a total analytical error goal.

The procedure described herein relies on a method comparison data collection procedure such as that described in NCCLS document EP9—*Method Comparison and Bias Estimation Using Patient Samples*. Two calculation methods are used: parametric and nonparametric. CLSI document EP21 can be used to judge the clinical laboratory acceptability of new methods by using patient specimens, or to monitor an assay's total analytical error by using quality control samples.

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Foreword

NCCLS document EP21—*Estimation of Total Analytical Error for Clinical Laboratory Methods* provides manufacturers and end users a means to estimate total analytical error for an assay. The procedure includes a data collection protocol and analysis method, which is largely graphical. The result is compared to a total analytical error goal.

Total analytical error (or measurement error) refers to assay errors from all sources arising from the data collection experiment. If the data collection protocol is representative of routine assay use, then estimation of total analytical error will provide a snapshot of the distribution of differences between a candidate assay and its comparison method. If the comparison method is a reference method and the reference method imprecision is minimized through replication, then except for the small imprecision left in the reference method, these differences estimate differences between the candidate method's result and the true assay concentration. When the candidate method is a comparison method, these differences cannot all be attributed to the candidate method, yet they are nevertheless important to estimate, since they will be observed by clinicians.

Whereas total analytical error is of paramount importance in judging the acceptability of a candidate method, it is surprising how infrequently it has been used. Alternatives to total analytical error have been the calculation of total error sources and their combinations ("estimation of measurement uncertainty"). This is a complex procedure which requires correctly specifying a model that describes how the error sources should be combined. Another frequent alternative has been estimation of some of the total analytical error sources without any attempt to combine them.

The procedure described in this guideline relies on a method comparison data collection procedure such as that described in NCCLS document EP9—*Method Comparison and Bias Estimation Using Patient Samples*. Two calculation methods are used: parametric and nonparametric. Whereas the parametric method is more efficient statistically, it requires normally distributed differences. This can be achieved by transformation; however, the committee decided that the transformation process and its associated tests would be too complicated for many users. The nonparametric method has no assumptions about the distribution. Two plots are produced to help users assess the distribution of differences.

This guideline can be used to judge the clinical laboratory acceptability of new methods by using patient specimens, or to monitor an assay's total analytical error by using quality control samples.

A Note on Terminology

NCCLS, as a global leader in standardization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. NCCLS recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in NCCLS, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all obstacles to harmonization. In light of this, NCCLS recognizes that harmonization of terms facilitates the global application of standards and is an area of immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In the context of this document, it is necessary to point out that the term *"Total analytical error*" is used differently in the U.S. than in other countries, notably those in Europe. *"Total analytical error"* is an accepted U.S. term and is used in EP21-A the way *"Total analytical error interval"* would be conceptualized in Europe, due to its description of a distribution of errors. At this time, the subcommittee has chosen *not* to replace the term due to U.S. nonfamiliarity and for the sake of the practicability of the guideline.

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There are several cases in this guideline, however, where *"Total analytical error"* corresponds to the ISO term *"Error of measurement,"* i.e., the "result of a measurement minus a true value of the measurand." (VIM93-3.10). Both expressions contain both random and systematic effects. Users of EP21-A should understand that the fundamental meanings of these terms are similar, and where appropriate, the ISO term has been inserted parenthetically throughout the text. All terms are also defined along with explanatory notes in the guideline's Definitions section.

All terms and definitions will be reviewed for consistency with international use, and revised appropriately during the next scheduled revision of this document.

Key Words

Error, error of measurement, measurement error, total analytical error, total analytical error interval

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Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline

1 Scope

This document presents protocols and procedures to estimate and report analytical error for clinical laboratory assays. These protocols and procedures are applicable to all quantitative analytical clinical laboratory methods. The target audience includes both manufacturers and end users in laboratories. The prime procedural difference between these two groups is the amount of data collected.

This guideline will be useful to users in settings with only one instrument as well as to those with multiple laboratories and multiple instruments.

2 Introduction

Total analytical error as a concept has been around for many years.[1,2] However, the use of total analytical error as an evaluation method for diagnostic assays is more recent.[3,4] As Westgard pointed out in his 1974 article, physicians, prime consumers of diagnostic test data, think in terms of total analytical error, not random or systematic error. Yet for many years, the estimation of random and systematic error was often performed without an attempt to combine them to estimate total analytical error, the real metric of interest.

This document addresses this deficiency by providing a method to directly estimate total analytical error, both for manufacturers and end users in laboratories. To facilitate understanding of the interrelationship of all error sources, a hierarchical, graphical chart known as a "cause and effect diagram" is used. It is recommended that for most cases, if one has knowledge of total analytical error and outliers, then one has sufficient information to judge the acceptability of a diagnostic assay.

A data collection protocol is presented for patient samples that leverages existing NCCLS document EP9—*Method Comparison and Bias Estimation Using Patient Samples*. Quality control data can be used to monitor total analytical error, after estimation of total analytical error with patient specimens.

Two calculation methods are presented: a parametric method which requires certain assumptions, and a nonparametric method which requires fewer assumptions. Both methods are supported by graphical analyses that can be performed independently of any calculations. Estimation requires total analytical error specifications. This document assumes these specifications exist and does not address their generation.

Finally, this guideline briefly reviews modeling methods and outlines a simulation approach. The simulation method is more suitable for manufacturers due to its complexity.

Examples illustrate these concepts with actual data.

3 Definitions

Accuracy - Closeness of the agreement between the result of a measurement and a true value of the measurand (*VIM93-3.5.*)

Assay - A quantitative determination or measurement of the amount, activity, or potency of a constituent or characteristic.

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