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Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition

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.

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

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Clinical and Laboratory Standards Institute
950 West Valley Road, Suite 2500
Wayne, PA 19087 USA
P: 610.688.0100
F: 610.688.0700
www.clsi.org
standard@clsi.org

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Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition

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Jeffrey R. Budd, PhD
A. Paul Durham, MA
Thomas E. Gwise, PhD
Beimar Iriarte, MS
Anders Kallner, MD, PhD
Kristian Linnet, MD, PhD
Robert Magari, PhD
Jeffrey E. Vaks, PhD

Abstract

Clinical and Laboratory Standards Institute document EP09-A3—*Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition* is written for laboratorians and manufacturers. It describes procedures for determining the bias between two measurement procedures, and it identifies factors for consideration when designing and analyzing a measurement procedure comparison experiment using split patient samples. An overview of the measurement procedure comparison experiment includes considerations for both manufacturers and laboratorians. Details on how to create difference and scatter plots for visual inspection of the data are provided. Once the data are characterized, various methods are introduced for quantifying the relationship between two measurement procedures, including bias estimates and regression techniques. The final section contains recommendations for manufacturers' evaluation of bias and statement format for bias claims.

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Committee Membership

Consensus Committee on Evaluation Protocols

James F. Pierson-Perry
Chairholder
Siemens Healthcare Diagnostics
Newark, Delaware, USA

Mitchell G. Scott, PhD
Vice-Chairholder
Barnes-Jewish Hospital
Washington University
School of Medicine
St. Louis, Missouri, USA

Rex Astles, PhD, FACB, DABCC
Centers for Disease Control and Prevention
Atlanta, Georgia, USA

Jeffrey R. Budd, PhD
Beckman Coulter
Chaska, Minnesota, USA

Karl De Vore
Bio-Rad Laboratories, Inc.
Irvine, California, USA

Jonathan Guy Middle, PhD
University Hospital Birmingham NHS Trust
Birmingham, United Kingdom

James H. Nichols, PhD, DABCC, FACB
Vanderbilt University
School of Medicine
Nashville, Tennessee, USA

Gene Pennello, PhD
FDA Center for Devices and Radiological Health
Silver Spring, Maryland, USA

Document Development Committee on Method Comparison and Bias Estimation Using Patient Samples

Jeffrey R. Budd, PhD
Chairholder
Beckman Coulter
Chaska, Minnesota, USA

A. Paul Durham, MA
Culver City, California, USA

Thomas E. Gwise, PhD
FDA Center for Drug Evaluation and Research
Silver Spring, Maryland, USA

Anders Kallner, MD, PhD
Karolinska Hospital
Stockholm, Sweden

Kristian Linnet, MD, PhD
University of Copenhagen
Copenhagen, Denmark

Staff

Clinical and Laboratory Standards Institute
Wayne, Pennsylvania, USA

Luann Ochs, MS
Senior Vice President – Operations

Ron S. Quicho
Staff Liaison

Patrice E. Polgar
Project Manager

Megan L. Tertel, MA
Editor

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Beimar Iriarte, MS
Abbott Diagnostics
Abbott Park, Illinois, USA

Robert Magari, PhD
Beckman Coulter
Miami, Florida, USA

Jeffrey E. Vaks, PhD
Roche Molecular Diagnostics
Pleasanton, California, USA

Contents

Contents (Continued)

Foreword

Measurement procedure comparison is one of the most common techniques used by both manufacturers and clinical laboratorians to estimate the bias of an *in vitro* diagnostic (IVD) measurement procedure relative to a comparator. It involves the comparison of results from patient samples from two measurement procedures intended to measure the same component (eg, concentration of a measurand) with the key determination being the estimate of bias between them.

A number of different scenarios exist in which measurement procedure comparison studies are indicated. For both the manufacturer and the clinical laboratorian, the ideal scenario is the comparison of a candidate measurement procedure to a generally accepted standard or reference measurement procedure. In the case of a manufacturer, this involves the establishment and perhaps verification of performance claims for bias, while in the case of a laboratorian, it involves introducing a measurement procedure into the laboratory, including verification of such manufacturer claims (specifications). The scope of the experimental and data-handling procedures for these two purposes will differ. In either case the assumption that the reference measurement procedure provides "true" values means that bias (systematic measurement error) is estimated.

Quite commonly, however, there is no standard or reference measurement procedure. The manufacturer instead compares a candidate measurement procedure to the best measurement procedure currently available. The laboratorian usually compares the candidate and an available procedure. Then, there may not be a "true" value and the "difference," rather than the "bias," is estimated.

Given the variety of performance characteristics of IVD measurement procedures, a single experimental design is not appropriate for all types of laboratorian and manufacturer measurement procedure comparisons. Therefore, performance characteristics such as measuring interval and precision profile are taken into account in structuring an experiment for comparing two measurement procedures. Multiple worked examples are presented.

This document is intended to promote effective and correct data analysis and reporting using standard experimental and statistical methods.

It is recommended that manufacturers of clinical laboratory measurement procedures and/or devices use this document to establish and standardize their bias performance claims. Many different forms have been used for such claims, and they have not always been sufficiently specific to allow user verification.

A number of changes and additions are included in this revision of the document, including:

- Broader coverage of method comparison applications
- More reasons for comparisons based on patient samples (factor comparisons [eg, sample tube types])
- Visualization/exploration of data using difference plots
- Regression descriptions including weighted options, Deming, and Passing-Bablok techniques
- Measurement of bias using difference plots
- Measurement of bias at clinical decision points
- Computation of confidence intervals for all parameters

- Outlier detection using extreme studentized deviate
- Relocation of most of the detailed mathematical descriptions to the appendixes

> **NOTE:** Due to the complex nature of the calculations in this guideline, it is recommended that the user have access to a computer and statistical software, such as StatisPro™ method evaluation software from CLSI.

Key Words

Alternative regression methods, bias, evaluation protocol, experimental design, linear regression, measurement procedure comparison, outliers, quality control, residuals

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1 Scope

This document provides guidance for designing an experiment and selecting methods to quantify systematic measurement error (bias or difference) between measurement procedures based on comparing patient samples. It provides procedures to determine the average bias between two measurement procedures either across their measuring intervals or at selected concentrations. Intended users of this guideline are manufacturers of *in vitro* diagnostic (IVD) reagents—which includes those who create laboratory-developed tests—as well as regulatory bodies and clinical laboratory personnel.

This document is for use with measurement procedures that provide quantitative numerical results. This document is not intended for use with ordinal IVD measurement procedures, commonly referred to as qualitative procedures (see CLSI document EP12[1]). This document is not intended to address evaluation of random error (see CLSI documents EP05[2] and EP15[3]) or to determine the total error inherent in a comparison of measurement procedures (see CLSI document EP21[4]). It is not intended to measure the variability of multiple replicates collected during the measurement of a sample, nor is it intended to measure the bias of individual measurements such as those resulting from sample interference (as covered in CLSI document EP07[5]).

2 Introduction

The purpose of this document is to establish good practices at measuring average bias over the measuring interval in a population of patient samples, relative to a comparative or reference method. Difference plots are used to visually portray the relationship between measurement procedures to evaluate if the relationship is consistent with a constant difference or as a constant percentage difference (constant CV) over the measuring interval. The plots are also used to determine the bias estimate from such plots through either an average or a median. Given the knowledge gained from the difference plots, users are provided with regression fit options to characterize bias in terms of slope and intercept and bias estimates at selected concentrations.

This document describes multiple situations in which measurement procedures are compared, each of which has its own experimental requirements. These requirements dictate differences in the number of factors to incorporate into the experimental design, the number of samples, and the number of replicates for each sample. The situations covered in this document assume a study is comparing two procedures that measure the same quantity by using measurement procedure results from study samples.

In selecting an analysis technique for a set of data, a stepwise process is described that starts with visual data inspection using difference and scatter plots. The data from difference plots can then be used to estimate the bias (or percent bias) between measurement procedures. Clinical laboratorians may require no further analysis. The document continues, however, by describing various regression techniques and their underlying assumptions that help determine which one should be used in each situation. Such techniques can, in many cases, provide more robust estimates of bias, so clinical laboratories may wish to use them. Manufacturers will use them in almost all cases. The goal throughout the document is to propose a set of techniques for determining bias between measurement procedures and to detail the strengths and weaknesses of these techniques for given situations.

A brief description of measurement procedure comparison scenarios is provided in the following sections. Section 2.1 is a general overview common to all scenarios. Sections 2.2.1 and 2.2.2 are intended for