

Verification of Reference Intervals in the Medical Laboratory Implementation Guide



EP28-Ed3-IG

Introduction

This implementation guide describes the minimum procedures necessary for a medical laboratory to verify that a preestablished reference interval for quantitative tests (eg, from previous studies, literature, or developer's information) is transferrable to the laboratory's similar tests.

IMPORTANT NOTE: The study outlined in this implementation guide does not include information regarding establishing or verifying reference intervals when none exist. Instead, test developers should consult CLSI document EP28¹ for guidance on establishing or verifying new reference intervals. Laboratories and commercial manufacturers are collectively referred to as “developers” in this implementation guide.

Verifying a Preestablished Reference Interval

A laboratory may have an established reference interval for a specific analyte, using a specific methodology, for its subject population. When the laboratory decides to change test methods or modify the existing test method (eg, different antibody, different calibration), it needs to conduct a method comparison study between the new and old methods. The study can be used to determine whether the existing reference interval can be transferred to the new or modified test or whether a new reference interval needs to be established. The comparison study can use fresh samples from any patients (ie, not necessarily from reference individuals) to investigate the relationship between the methods. In general, if the new test method has similar imprecision and known interferences, uses standards or calibrators traceable to the same primary standard, and provides values that are analytically or clinically comparable, then the reference interval can be transferred. However, regulators or accreditors might require verification of the reference interval with a small number of samples (eg, 20) from a reference population.

A medical laboratory may adopt a reference interval established by another laboratory or diagnostic test developer for the same or for an analytically or clinically comparable test method. In this case, the laboratory needs to ensure the comparability of the populations and other preexamination factors, eg, selection of the reference individuals and specimen type, specimen collection method, and specimen handling procedures. Verification can be accomplished by one of three methods:

- Subjective assessment
- Statistical test using samples from a small number of reference individuals (eg, 20)
- Evaluation of a larger number of reference individuals (eg, > 20 but < 120, the number needed to perform a standard reference interval study)

Verification Using Small Numbers of Reference Individuals

A preestablished reference interval can be verified by testing samples from a small number of reference individuals (eg, 20) from the laboratory's own population and comparing these values with the values from the larger original study. The preexamination and examination factors from the original study should be consistent with the laboratory's operation. In addition, the geographic location or demographic variables of the reference individuals should be substantially similar in the original study and the new study.

NOTE 1: The preestablished reference interval must have been established by testing a population of ≥ 120 reference individuals.

NOTE 2: CLSI document EP28¹ uses the term "validation." This usage of the term is outdated. It has been replaced by "verification" in this implementation guide.

Verification of the Reference Interval

The reference interval verification process is outlined in the figure below.

