

Pediatric Reference Range Development Guidelines

Author: Kurt L. Michael and Joe Fitzgibbon

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The Medical Director of the laboratory is responsible for establishing and approving laboratory reference ranges to provide the clinician with an understanding of how to interpret assay results. During this process the Medical Director will often seek input or advice from clinicians, laboratory staff and others involved. Each laboratory is responsible for developing their own analyte reference ranges specific both to the population served and to the instruments/methods of assay used. Many times these ranges are influenced by age and gender, which are called partitions. This complicates pediatric range development as there can be frequent partition changes due to infant and child development. In the Clinical Trial setting the assay reference ranges must be developed as necessary to cover specific age and gender ranges for all scheduled visits during the trial.

Due to the possible number of partitions and the difficulty in obtaining primary data, a tiered approach may be necessary to develop workable reference ranges. The guidance offered in this document lists several options with the understanding that laboratories can begin reference range development at the tier that is most attainable and then work to refine and improve their ranges to best serve their pediatric patients.

Tier 1: Full scientific study

A complete study following Clinical Laboratory Standards Institute (CLSI) guideline C28-A3 with a minimum of 120 healthy patients per analyte per partition can be performed to establish ranges unique to the laboratory and their patient population. This study will often merit publication. These studies are often performed with healthy adults, but many sites find it particularly difficult to perform this type of study on pediatric populations, since it requires blood to be drawn from healthy infants and young children.

Tier 2: Transference study

A transference study following Clinical Laboratory Standards Institute (CLSI) guideline C28-A3 adopts an analyte range and attempts to verify it with 20 patients per analyte partition and a 90% fit. The adopted ranges are usually derived from published sources or equipment manufacturer's recommended ranges.

Tier 3: Literature and practice based adoption

A compromise approach is a thorough search of the literature and regional pediatric reference ranges combined with a clinically informed selective adoption from those ranges by the Medical Director, often in consultation with physicians (particularly pediatricians) and other interested parties. Documentation needs to include at least: 1) the source and reasons for range adoption for each analyte and 2) a written plan of review over time of the appropriateness of the adopted range. If range verification data can be collected over time, then that should be considered during the review process.

Below is an outline of the steps to consider when using the Tier 3 approach:

1. The Medical Director is charged with the approval of reference ranges. This decision is often made in conjunction with a small group of local experts (clinicians, pediatricians, clinical laboratory personnel and other invested parties).
2. Research current reference ranges in use, regional laboratory's ranges, medical decision points and literature for candidate normal reference ranges.

3. Determine analytes that need to have reference ranges (all assays performed or released by the laboratory).
4. Determine any gender and biological age groupings for each analyte for which separate range partitions need to be adopted. This should be accomplished with an understanding of the necessary age ranges to cover all current protocol study visits, known future studies and patient safety.
5. The medical director, using clinical judgment, personal experience and research, would develop working reference ranges for all identified partitions considering each analyte separately. Two examples of this are below:
 - a. In your population one source might be best for sodium, potassium and chloride, while another source might be best for liver enzymes: ALT and AST.
 - b. Analytes that depend on calculations, such calculated LDL, should be taken from the same source as the components of the calculations: Triglycerides, Cholesterol and HDL.
6. Documentation is required and needs to include at least: 1) the source and reasons for range adoption for each analyte and, 2) a written plan of review over time of the continued appropriateness of the adopted ranges.
7. If data can be collected over time for the verification of the proposed ranges, the gender, age and results would need to be carefully tracked. These would then be used during the review process. If 20 data points per partition can be collected with a 90% fit, then the data would be considered a transference study (i.e., a Tier 2 approach).
8. During the review process the ranges may be verified, adjusted with cause or left to collect more data for verification.
9. All steps should be documented and available to inspectors and regulatory agencies.

References:

1) American Association for Clinical Chemists. *Pediatric Reference Intervals*. 6th ed. Steven J. Soldin, Carlo Brugnara, and Edward C. Wong. Washington DC: AACC Press, 2007.

2) Clinical and Laboratory Standards Institute (CLSI). *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition* CLSI document C28-A3 (ISBN 1-56238-682-4). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2008.

3) College of American Pathologists (CAP), Commission on Laboratory Accreditation, Chemistry and Toxicology Checklist, REVISED 09/27/2007

CHM.15000 Phase II N/A YES NO

Are all patient/client results reported with reference (normal) intervals or interpretations as appropriate?

NOTE: The laboratory must report reference (normal) intervals or interpretations with patient/client results, where such exist. This is important to allow proper interpretation of patient/client data. In addition, the use of high and low flags (generally available with a computerized laboratory information system) is recommended. For urine testing for drugs of abuse, the cut-off value for positive results should be listed, either in the report or in a separate chart/memorandum that is available to clinicians.

4) College of American Pathologists (CAP), Commission on Laboratory Accreditation, Laboratory General Checklist

GEN.42162 Phase II N/A YES NO

Has the laboratory established or verified its reference intervals (normal values)?

NOTE: Reference intervals are important to allow a clinician to assess patient results against an appropriate population. The reference range must be established or verified for each analyte and specimen source (e.g., blood, urine, cerebrospinal fluid), when appropriate. For many analytes (e.g., therapeutic drugs and CSF total protein), literature references or a manufacturer's package insert information may be appropriate.

5) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments of 1988; final rule. *Fed Register*. 1992(Feb 28):7164 [42CFR493.1213]

6) Van der Meulen EA, et al. Use of small-sample-based reference limits on a group basis. *Clinical Chem*. 1994; 40:1698-170