HEALTH HOLDING

HAFER ALBATIN HEALTH CLUSTER
MATERNITY AND CHILDREN HOSPITAL

Department:	Laboratory and Blood Bank		
Document:	Departmental Policy and Procedure		
Title:	Verification and Evaluation of Reference Ranges/Intervals and Cut off Values		
Applies To:	All Laboratory and Blood Bank Staff		
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1. PURPOSE:

1.1 Reference ranges are sets of values used by the health professionals to interpret the results and are considered the most authoritative tools in laboratory science to assist in the decision-making phase, hence useful for patient care.

2. DEFINITONS:

2.1 Reference range: Is the prediction interval between which 95% of values of a reference group fall into, in such a way that 2.5% of the time a sample value will be less than the lower limit of this interval, and 2.5% of the time it will be larger than the upper limit of this interval. They are sometimes termed normal ranges or normal values. However, using the term normal may not be appropriate as not everyone outside the interval is abnormal, and people who have a condition may still fall within this interval.

2.2 Reference group: They are individuals selected for comparison using defined criteria

2.3 Reference value: value obtained by observation or measurement of quantity on an individual belonging to reference group.

2.4 Reference distribution: statistical distribution of reference values.

2.5 Reference limit: derived from reference distribution.

2.6 Reference Interval: interval between and including two reference limits.

3. POLICY:

3.1 This policy describes the process of adopting reference ranges from already established reference range guides.

4. PROCEDURE:

4.1 **The laboratory implements policies and procedures that define:**

4.1.1 Circumstances and method for establishing reference ranges:

4.1.1.1 Reference ranges should be established locally whenever a new test is introduced, or an existing method is changed due to difference in the operating conditions, criteria for selection of healthy subjects, the patient population, temperature, humidity, subject preparation and sample collection circumstances.

4.1.1.2 The reference ranges are established by testing the considerable number of healthy population (about 120 samples) and figuring out what appears to be "Normal" for them. However, it is critical to define the reference population. Demographically, it should match the population whose laboratory results will be compared to this reference range.

4.1.1.3 However, it seems to be a difficult option for a laboratory, so they can alternatively be verifying the adopted reference ranges from international sources.

4.2 **Circumstances and method for verifying published reference ranges:**

4.2.1 Circumstances for verification:

4.2.1.1 The adopted reference ranges should be verified or reviewed periodically.

4.2.1.2 Verification should also be done whenever an interval is thought to be no longer appropriate.

4.2.1.3 Verification should be done when a pre-examination or examination (analytical) procedure is changed.

4.2.1.4 Verification should be done when physicians raise questions about the existing normal values if they notice too many normal individuals being flagged abnormal.

4.2.2 Method of verification:

4.2.2.1 Select the analyse for which the reference range is to be established, and the methodology and instrumentation which will be used for testing. Study what is already known about the analyte, including variables which are already known to cause variation within and between individuals.

4.2.2.2 Review the methodology with attention to the impact of variables known to be associated with sample procurement, transport, processing, and storage.

4.2.2.3 Define the reference population using specific criteria, including exclusion criteria (which might include recent surgery, tobacco use, over-the-counter medications, etc.) and partitioning criteria (which might include age, gender, race, etc.). Note that a condition such as pregnancy might be an exclusion criterion for one study but a partitioning criterion for another study.

4.2.2.4 Once reference individuals have been identified, it is important that pre-analytical factors be addressed carefully before samples are collected and analysed. Subject preparation (e.g., fasting, physical activity, medication), sample collection (e.g., time of day, tourniquet time, tube type), and sample handling (e.g., clotting time, centrifugation, storage) should all be standardized.

4.2.2.5 Choose a sampling method. Ideally, this method should yield a random sample of individuals representing the reference population.

4.2.2.6 The reference range can be verified by running 20 samples from reference individuals using standardized methods. It is important to treat these specimens exactly as patient specimens are treated; if no more than 2 results fall outside the manufacturer/published range that reference range can be verified. (CLSI guidelineC28-A3c)

4.2.2.7 Analyse the results using the following approaches:

4.2.2.7.1 In cases, where the reference distribution of analyse shows Gaussian distribution (symmetrical), parametric methods are used. According to this, the determination of reference limits would be calculated as values two standard deviations below and above the mean.

4.2.2.7.2 Many parameters displayed non-Gaussian distributions, non-parametric methods were used which involves establishing the values falling at the 2.5 and 97.5 percentiles of the population as the lower and upper reference limits. and the reference interval can be defined as the central 95% interval bounded by the 2.5 and 97.5 percentiles the percentiles were calculated and the reference intervals reported as values corresponding to 2.5 percentile (r1) and 97.5 percentile (r2):

4.2.2.7.2.1 $r1 = 0.025 \times n$ (number of values)

4.2.2.7.2.2 $r2 = 0.975 \times n$

4.3 **Circumstances and method for the re-evaluation of reference ranges:**

4.3.1 Reference intervals must be evaluated at the following times: Upon introduction of a new analyse by a laboratory.

4.3.1.1 With a change of analytical methodology.

4.3.1.2 With a change in study participant population (e.g., a method typically used for determining test results for adults is to be used for a primarily paediatric population).

5. MATERIALS AND EQUIPMENT:

N/A

6. RESPONSIBILITIES:

6.1 Adopting reference ranges: Heads of respective sections
6.2 Verifying reference ranges: Section supervisor/Head of section/Lab Quality Head
6.3 Approval and monitoring: Lab Director

7. APPENDICES:

N/A

8. REFERENCES:

8.1 Haggstrom M.: Establishment and clinical use of reference ranges.
8.2 DAIDS Guidelines for Good Clinical Laboratory Practice Standards.
8.3 Gary L. Horowitz M.D, Reference interval: Practical aspects.

9. APPROVALS:

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