HOKLAS Supplementary Criteria No. 32

'Medical Testing' Test Category – Verification of Biological Reference Intervals from Other Sources

1. INTRODUCTION

1.1 Biological reference intervals are established by assaying samples that are obtained from individuals that meet carefully defined criteria. Protocols of the International Federation of Clinical Chemistry Expert Panel on Theory of Reference Values (IFCC EPTRV) and that of the Clinical and Laboratory Standards Institute (CLSI) approved guideline EP28-A3c offer systematic processes that use carefully selected reference sample groups to establish reference intervals. These protocols typically need a minimum of 120 reference individuals for each group (or subgroup) to establish biological reference intervals which are resource intensive. Therefore, laboratories (receiving laboratories) are becoming more reliant on transference of well established biological reference interval from other laboratories or manufacturers (donor laboratories) that can be verified using less resource intensive approaches.

2. VERIFICATION CRITERIA

2.1 Before a laboratory can apply the reference intervals established by other organisations, such intervals shall be adequately verified.

2.2 This document sets out the three verification approaches acceptable to HKAS. Laboratories following the given approaches are considered as meeting cl. 5.5.2 of HOKLAS 015 (5^{th} edition).

2.3 Other verification methods may also be accepted if the laboratory can demonstrate that they can provide the same degree of assurance as the three approaches described below.

2.4 This document does not address the issue of the establishment of biological reference intervals and has no intention to recommend replacing it with the transference approaches. Instead, laboratories shall provide evidence that there are no substantial differences in the demographics or geographics between the populations of the receiving and donor laboratories to demonstrate that transference is acceptable.

2.5 There are certain analytes where reference intervals have been replaced by decision limits, for instance, for cholesterol and glycated haemoglobin. For such analytes, verification of the decision limits adopted is not expected. The laboratory shall find out from the manufacturers the traceability of their methods and with such information recorded in the laboratory's document.

3. APPROACHES TO VERIFY TRANSFERENCE OF REFERENCE INTERVALS

A laboratory shall select a suitable method out of the following three for verifying the adopted reference intervals and document all the verification processes and findings.

3.1 Reviewing pertinent factors of original study

The receiving laboratory may transfer reference intervals without doing any verification study if the laboratory reviews and considers the factors of the original study from the donor laboratory are consistent with the operation and test subject population of the laboratory. The receiving laboratory should review:

a. the demographics of the sample reference group,
b. the selection process,
c. the preanalytical and analytical procedural details,
d. the analytical performance, and
e. the method of estimating the biological reference interval.

Use this approach when there is difficulty in obtaining sufficient samples to verify the biological reference intervals, e.g. biological reference intervals for sub-population, particularly the paediatrics year-by-year intervals.

3.2 Verification with 20 samples

The receiving laboratory may transfer biological reference intervals from the donor laboratory after verification by analysing 20 reference individual samples. The receiving laboratory should:

a. consider the consistency of the preanalytical and analytical factors between the donor and receiving laboratories
b. collect and analyse samples from 20 individuals who represent the reference sample population
c. detect and exclude outliers
d. adopt the biological reference interval if two or fewer tests fall outside

the claimed reference interval

e. repeat the process if three or more tests fall outside the claimed reference interval
f. if three or more again fall outside the limits, review the analytical procedures, and consider whether the receiving laboratory should establish its own biological reference intervals

This approach is statistically sound, comparatively simple, requires a minimum of data, and provides a clear criterion for interpretation and verification of the transference. It should be suitable for common quantitative tests in medical testing.

3.3 Verification with 60 samples

The receiving laboratory may examine 60 reference individual samples and detect the statistical significance of the difference of the mean with the donor laboratory. The receiving laboratory should:

a. consider the consistency of the preanalytical and analytical factors between the donor and receiving laboratories
b. collect and analyse samples from 60 individuals who represent the reference sample population
c. detect and exclude outliers
d. check the SDs obtained by the donor and receiving laboratories,
   - the larger SD, for example S_2, should not $\geq 1.5\ S_1$
e. compare the means and SDs of the donor and receiving laboratories and calculate statistic z

$$z = \frac{\left|x_1 - x_2\right|}{\left[\left(\frac{S_1^{\,2}}{n_1}\right) + \left(\frac{S_2^{\,2}}{n_2}\right)\right]^{1/2}}$$

f. compare the calculated z with a critical value z^*

$$z^* = 3\left\{\left[\left(n_1 + n_2\right)/2\right]/120\right\}^{1/2}$$

g. adopt the biological reference interval if the calculated z does not exceed the critical value

The statistical comparison is more complicated in this approach and makes it less attractive than the 20 samples approach. However, this approach shall be used when the information from the donor laboratory is not adequate or when the method in the receiving laboratory is based on a different measurement

principle or different measurement specificity.

Notes: n_1 and n_2 are the number of samples examined by the two laboratories
x_1 and x_2 are the means of the two laboratories
S_1 and S_2 are the standard deviations of the two laboratories

4. REFERENCES

(1) CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition, Clinical and Laboratory Standards Institute, 2010.

(2) Horowitz Gary L. Establishment and use of reference values. In: *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics.* 6th Edition: Elsevier Saunders; 2018: 95 - 118.

(3) Patricia L. Barry BS, James O. Westgard. Basic method validation – reference interval transference. 2008 http://www.westgard.com/lesson30.htm (accessed on 21 March 2019).

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