Post-market surveillance of the implementation of result traceability in clinical enzymology

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Which criteria should the surveillance fulfill?

• Which samples?
• Which references?
• What variation is allowable?
Looking for a Grail?

Searching the Grail

1. Samples

- Commutable
- Stable
- Concentration range covering clinical range
Calibration 2000

- Commutable material proven by twin-study
- Reference values
- Covering range of clinical interest
- Stable

Holy Grail
San Greal
Sang Real
Searching the Grail

2. Reference

- Reference system IVD
- Reference method targets

IVD directive

- Traceability to reference systems
- 80 category A analytes
- JCTLM defines reference methods and reference materials
Traceability

• Reference system
  – Reference method
  – Reference materials
  – Reference laboratories
• Industry calibrate kits and reagents
• Surveillance (EQA) trueness verification
  – Commutable materials
Example Enzymes

- IFCC reference procedures for 6 enzymes
- Commercial systems should be traceable
- International study for trueness verification

International enzyme study

- Commutable material Calibration 2000
  - Calibration 2000, Weykamp
- 70 laboratories Italy, Germany Netherlands
- Reference laboratories targets
  - Panteghini, Schumann, Franck
- NEQAs organizers
  - Franzini, Kruse, Baadenhuijsen, Kuypers
Trueness verification

- Commutable material Calibration 2000
- Reference method target values
- Allowable area of deviation based on biological variance concept

Searching the Grail

3. Allowable variation

- Reference method targets
- Variance limits based on biological variance
Biological variation

- CVw within-person variation
- CVb between-person variation
- CVa desirable analytical variation
  \[ CVa = 0.5 \times CVw \]
- B maximum allowable bias
  \[ B = 0.25 \sqrt{(CVw^2 + CVb^2)} \]
- TE total allowable error
  \[ TE = 1.65 \times CVa + B \]
Statistics

- \((1.65 \times \text{SDbl} + 1X - T) < AB \) (P=95%)
- \(\text{SDbl max} = (AB - 1X - T) / 1.65\)
- \(\text{SDwl max} = (\text{TAE} - 1.96 \times \text{SDbl} - 1X - T) / 1.96\)
- \(a = [(T+1.96 \times \text{SDbl max}) - X] / \text{SDbl}\)
- \(b = [X - (T-1.96 \times \text{SDbl max})] / \text{SDbl}\)
- \(\text{ID}(a) - D(b) \times 100\% \) is perc. Labs measuring within limits

IVD Trueness verification

![IVD Trueness verification](image)

Fig. 1. Target values (TAE) with mean (SD) for each company system, and the area (shaded) of maximum allowable SD, in absence of significant bias.

November 25th 2008

Dr. Rob Jansen
### % Labs expected to measure within limits

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**Example Creatinine**

- IFCC reference method
- Commercial systems should be traceable
- International study for trueness verification
  - J. DeLanghe e.a. CCLM 2008, submitted
Creatinine Total error budget

Consequences

- EFCC/IFCC define allowable variation
- Industry: traceability
- Abandon non-specific methods
- EQA: commutable materials
  - Calibration 2000
- EQA: Biological variation concept
  - Introduced in SKML survey's
- Individual laboratories: TAE
Searching the Grail

3. Allowable variation in EQA

- Commutable materials
- Reference method targets
- Variance limits based on biological variance
- Comparison with state of the art
EQA in The Netherlands

- Commutable control sera
- Target values by reference methods
- Variance criteria based on biological variance concept
- Comparison with state of the art
Which criteria?

• Total allowable error \(1.65 \times CV_a + B\)
• Desirable SD \(CV_a = 0.5 CV_w\)
• Allowable bias \(B = 0.25 \sqrt{(CV_w^2 + CV_b^2)}\)
• Medically significant difference
  \[\Delta_{med} = 2.77 \times \sqrt{(CV_a^2 + CV_w^2)} + \Delta_{SE}\]
  \[\Delta_{med} = 3.1 CV_w\] if \(\Delta_{SE} = 0\)
  \[\Delta_{SE} < 0.33 CV_w\] if \(CV_a = 0\)
Did we find the Grail?

- Post marketing surveillance is possible

- Does the traceability system guarantee patient security?
Post marketing surveillance is started but the Grail is not yet found

• Commutable plasma instead of serum?
• Reference method targets
• Variance criteria based on allowable bias and medically significant difference?