St Vincent's Hospital
A facility of St Vincents & Mater Health Sydney

SYDPATH
ST VINCENT'S PATHOLOGY

Common performance goals in EQA, is it possible?

Graham Jones
Department of Chemical Pathology
St Vincent's Hospital, Sydney
EQALM symposium - Bergen, 2015

Acknowledgements

EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

RCPAQAP
RCPA Quality Assurance Programs

ifcc
International Federation of Clinical Chemistry and Laboratory Medicine

JCTLM

aacb
testing for health

ASIA-PACIFIC FEDERATION FOR CLINICAL BIOCHEMISTRY AND LABORATORY MEDICINE

RCPA
The Royal College of Pathologists of Australasia

SYDPATH
ST VINCENT'S PATHOLOGY

ST VINCENT'S HOSPITAL
SYDNEY

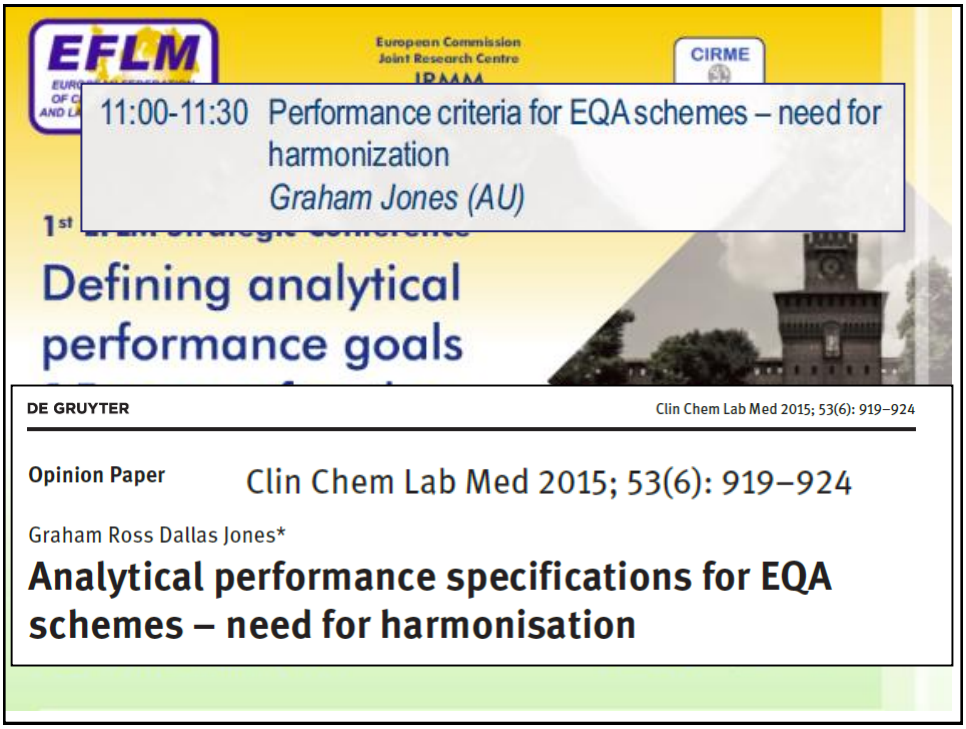
STRATEGIES TO SET GLOBAL QUALITY SPECIFICATIONS IN LABORATORY MEDICINE

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

International Union of Pure and Applied Chemistry

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Nobelforum,
Karolinska Institutet
Stockholm April 24-26, 1999



EFLM Task and Finish Group

- Chair: Graham Jones (AU)
- Stéphanie Albarède (FR)
- Gabriela Gutiérrez (SP)
- Mauro Panteghini (IT)
- Marc Thelen (NL)
- Anne Vegard Stavelin (NO)
- Annette Thomas (UK)
- Pat Twomey (UK)
- Emma Ventura (SP)

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Terminology

- Performance Goals *(title)*
- Quality Specifications *(Stockholm)*
- Analytical Performance Goals *(Milan)*

- Quality standards
- Allowable Limits of Performance
- Quality Goals
- etc ….

- **“Analytical Performance Specifications (PS)”**
  - Sandberg S et al. Clin Chem Lab Med 2015;53:833–5

Applying Performance Specifications

Can be applied to:

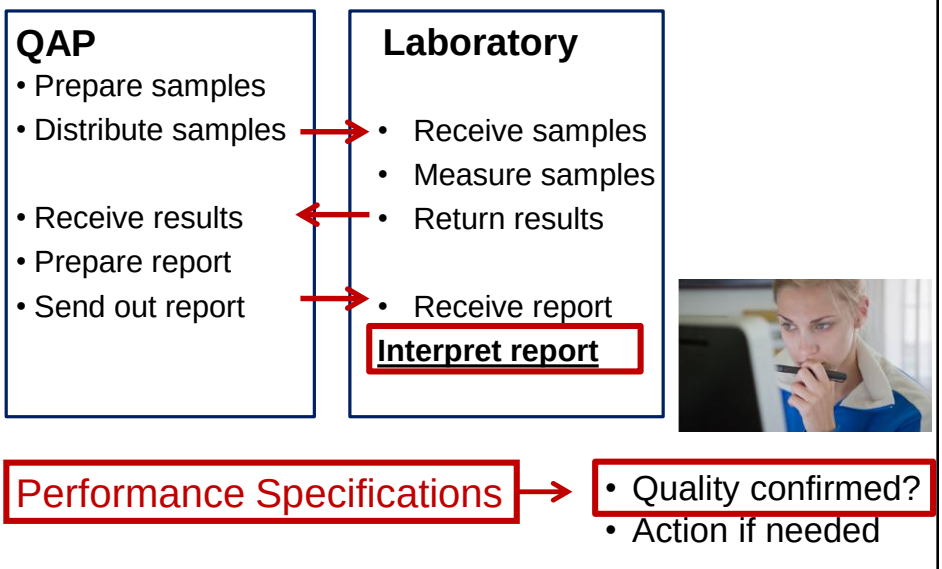
- Assay/method selection
- Assay/method validation/verification
- QC planning/review
- Measurement Uncertainty estimation/interpretation
- EQA

What affects assay performance?

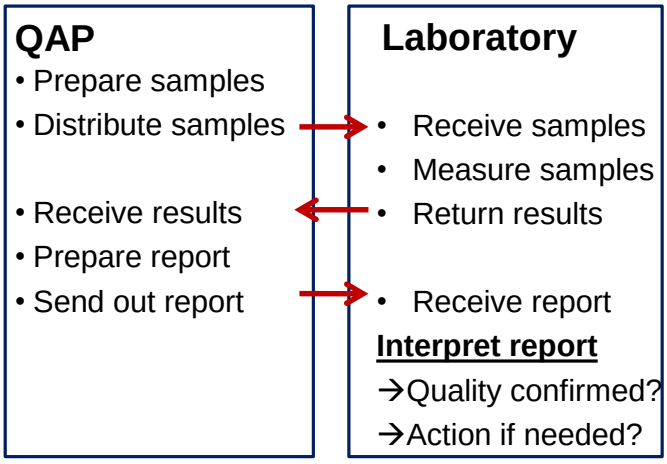
- Instrument manufacturing
- Instrument maintenance
- Reagent / calibrator manufacturing / delivery
- Reagent / calibrator handling
- Water / temperature / electricity
- QC planning / response
- Troubleshooting

- **EQA measures them all!**
  (an excellent place to apply performance specifications)

Quality Assurance Process



Quality Assurance Process



M'facturers, Metrologists etc: Analytical problems

Pathology Community: Can we share reference intervals, decision points, monitor a patient across labs

EQA Reports (RCPAQAP terminology)

"Interim" Report

- After each set of measurements
- Small number of samples (1,2,5)
- May include previous data
- Usually analysed as **single results**

End-of-Cycle / Summary Report

- summary of a period
- Larger number of samples
- Statistical analysis (bias, precision) based on **multiple results**

Interpreting **Single** Results

- A **single result** includes effects of both bias and imprecision
- Bias and imprecision effects cannot be separated
- Quality standards assess **"total error"**
- Applies to multiple samples, if they are analysed separately
- Most Interim Reports / some summary reports

Interpreting **Multiple** Results

- From **multiple results: bias** and **imprecision** can be separately identified
- Based in summary statistics
- More results → better information
- Only applies to multiple samples
- Most Summary Reports / some interim reports

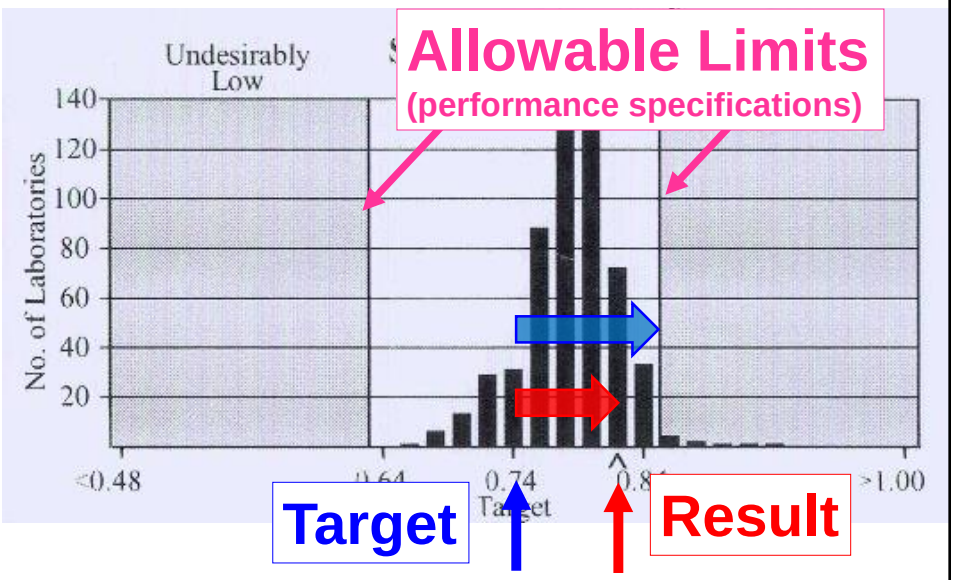
Interpreting **Single** Results

- My focus today is on Quality Standards for interpreting **Single** results
- **Bias** and **imprecision** assessment are vital, but take time to gather quality data
- Bias and imprecision also need Performance Specifications

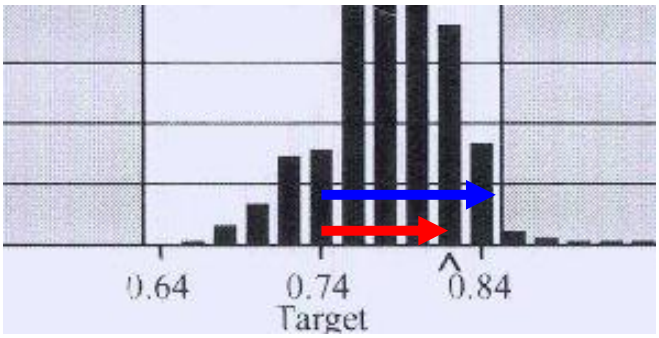
Single Results – the information

- **Result** from laboratory
- **Target** from EQA program
- **Distance** from Target
- Assess Acceptability (**Performance Specification**)
  - Qualitative
  - Quantitative

Single Result Report (RCPAQAP)



Interpret Report



- "All aspects of pathology are determined by comparison" *(Per Hyltoft Petersen, Sydney, 2005)*
- In this setting: Compare with a Quality Standard

Targets

- These indicate the “correct” result
- Two main types
  - Overall analyte target
    - Reference Method / Material
    - Median
    - Assumes commutability of material in methods
  - Laboratory-specific target
    - Based on method / instrument / reagents etc

Distance from Targets

- Distance: Lab result value - target value

Assessment of Distance from Targets

- Compare distance with **Performance Specification**
- Which performance specification?

Eur J Clin Chem Clin Biochem 1996; 34:159–165

External Quality Assessment: Currently Used Criteria for Evaluating Performance in European Countries, and Criteria for Future Harmonization

Carmen Ricós[1], *Henk Baadenhuijsen*[2], *Jean-Claude Libeer*[3], *Per Hyltoft Petersen*[4], *Dietmar Stöckl*[5], *Linda Thienpont*[6] and *Callum G. Fraser*[7]

Tab. 3 Currently used European EQA limits (given in % deviation from the target)

	Cholesterol	P_i	Lithium	Lactate dehydrogenase	Urate	Alkaline phosphatase
Denmark	8.1	12.0	–	12.0	13.0	10.0
Netherlands	8.1	–	5.0	3.0	10.0	8.0
Belgium	8.4	14.0	10.0	15.0	15.0	10.0
Germany[a]	18.0	15.0	12.0	21.0	18.0	21.0
Finland	5.0	5.0	0	10.0	5.0	10.0
Switzerland	3.0	10.0	0	15.0	10.0	15.0
Croatia	10.0	10.0	0	20.0	10.0	20.0
Lithuania	7.0	5.0	–	7.0	7.0	7.0
United Kingdom	7.6	7.8	11.0	13.0	7.7	15.0
Spain	9.8	12.0	22.0	17.0	15.0	22.0
Italy	5.5	9.5	–	10.0	8.0	18.0
France	16.5	–	10.0	20.0	16.0	20.0
Portugal	5.0	8.0	–	16.0	9.0	29.0

1996

RCPAQAP(%)	5.0	10.0	8.0	15.0	7.8	15.0
CLIA (%)	10.0		20.0	20.0	17.0	30.0
Range (%):	**3-18**	**5-14**	**5-22**	**3-21**	**5-18**	**7-30**

DATA INNOVATIONS
Simple Ideas, Better Solutions

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Sort	Analyte	Fluid	Method	Limit	Source
ALB	Albumin			+/- 10%	1 CLIA, 2 WLSH, 3 NYS, 6 AAB
ALB	Albumin		AU640	10%	4 CAP
ALB	Albumin	S-		3.9%	5 BV
ALB	Albumin			2.0 g/L, 10%	7 RCPA
ALB	Albumin			10%	8 CFX
ALKP	Alkaline phosphatase			+/- 30%	1 CLIA, 2 WLSH, 3 NYS, 6 AAB
ALKP	Alkaline phosphatase	S-		11.7%	5 BV
ALT	Alanine aminotransferase (ALT, SGPT)			+/- 20%	1 CLIA, 2 WLSH, 3 NYS, 6 AAB
AMY	Amylase			+/- 30%	1 CLIA, 2 WLSH, 3 NYS, 6 AAB
AMY	Amylase		AU640	30%	4 CAP
AMY	Amylase			15 U/L, 15%	7 RCPA
AMY	Amylase			20%	8 CFX
AST	Aspartate aminotransferase (AST, SGOT)			+/- 20%	1 CLIA, 2 WLSH, 3 NYS, 6 AAB
BILI	Bilirubin, total			+/- 0.4 mg/dL or +/- 20% (greater)	1 CLIA, 2 WLSH, 3 NYS, 6 AAB
CA	Calcium, total			+/- 1.0 mg/dL	1 CLIA
CHOL	Cholesterol, total			+/- 10%	1 CLIA, 2 WLSH, 3 NYS, 6 AAB
CHOL-H	Cholesterol, high dens.			+/- 30%	1 CLIA, 2 WLSH, 3 NYS,

www.rhodes.com

http://www.dgrhoads.com/db2004/ae2004.php?B1=Chemistry+A-C&find=&start=1&NOLINKS=

http://www.datainnovations.com/products/ep-evaluator/allowable-total-error-table

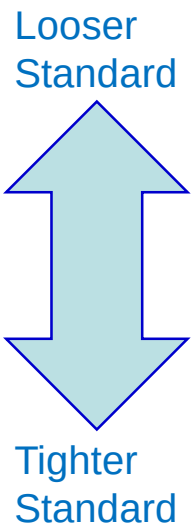
Common EQA performance goals?

- Why are the limits so different?
- Because they mean different things in different programs!

EQA Quality Standards

What type of standard?

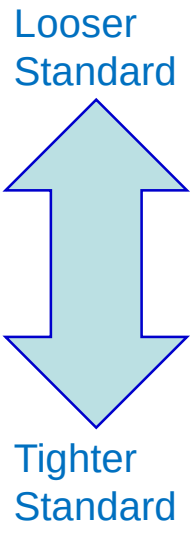
- **Minimum standard**
  - All should pass (except bad labs)
- **Expected standard**
  - Most should pass
  - Aim to improve those which don't
- **Aspirational standard**
  - Some will not pass
  - May need better methods



EQA Quality Standards

Response to failures?

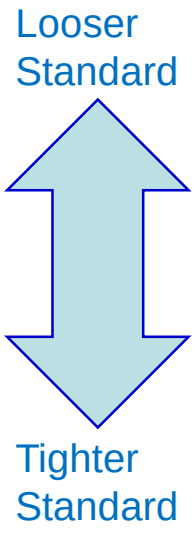
- **Affects registration**
  - USA (CLIA), Germany (RiliBAK)
- **Requires mandatory investigation**
  - Canada?
- **Should be followed up – effort depends on severity**
  - Australia (NATA RCPA)
- **Some failures are expected**



Accuracy Quality Standards

What does it mean to meet the standard?

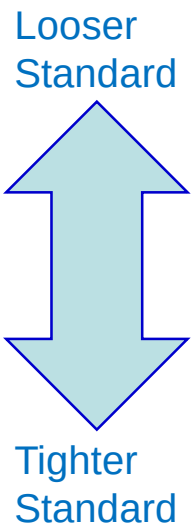
- There may still be benefits from assay improvement
- Most assays are satisfactory
- No further effort is needed on this analyte



Accuracy Quality Standards

What is the clinical effect of (not) meeting the standard?

- Assays may need different reference intervals
- The same lab should be used for monitoring a patient
- Assays can share the same reference interval / decision points
- Patients can be monitored across different labs



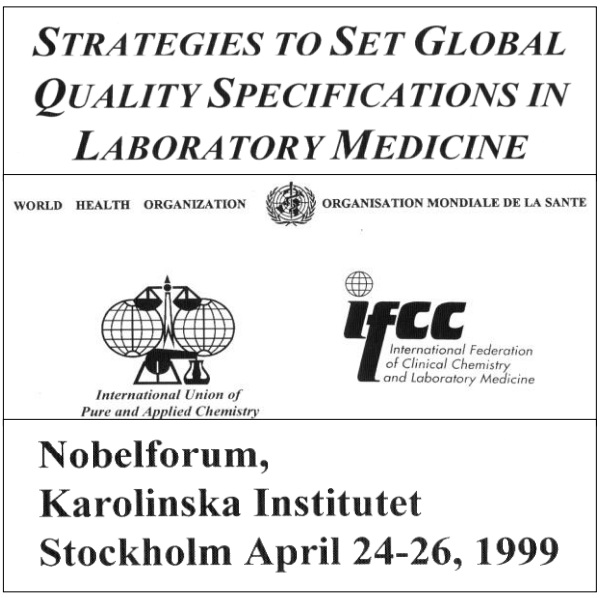
Summary - 1

EQA providers should state the following for their customer:

- High-level rationale for setting performance specifications
- Expected response to failures
- Clinical meaning of meeting / not meeting quality standards

What Limits?

- How do we set the limits?

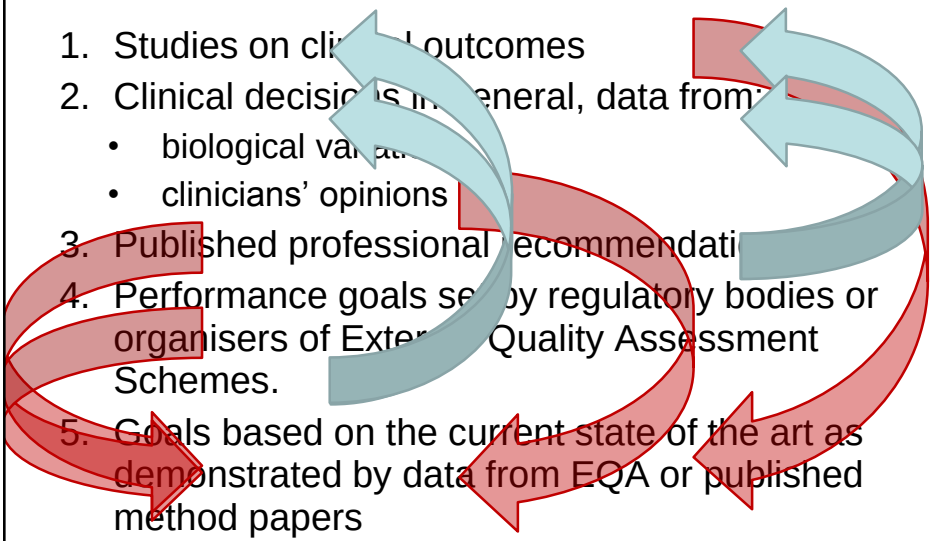


An internationally agreed hierarchy of preferred methods for establishing performance goals

Stockholm Hierarchy

1. Studies on clinical outcomes
2. Clinical decisions in general, data from:
   - biological variation
   - clinicians' opinions
3. Published professional recommendations
4. Performance goals set by regulatory bodies or organisers of External Quality Assessment Schemes.
5. Goals based on the current state of the art as demonstrated by data from EQA or published method papers

Stockholm Hierarchy



1. Studies on cli l outcomes
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5. Goals based on the current state of the art as demonstrated by data from EQA or published method papers

Stockholm Revision – Milan 2014

- *Model 1 - Based on the effect of analytical performance on clinical outcomes*

  Stockholm Level 1
- *Model 2 - Based on components of biological variation of the measurand*

  Stockholm Level 2
- *Model 3 - Based on state of the art*

  Stockholm Level 5
- *Model 4 – None of the above*

Stockholm Revision – Milan 2014

- *Model 1 - Based on the effect of analytical performance on clinical outcomes*
- *Model 2 - Based on components of biological variation of the measurand*
- *Model 3 - Based on state of the art*

Selected based on:
- Available data
- Quality of evidence
- Fit with analyte

Stockholm Revision – Milan 2014

- *Model 1 - Based on the effect of analytical*

Applying "Milan" more rational than "Stockholm"

- *Model 2 - Based on components of biological variation of the measurand*

- *Model 3 - Based on state of the art*

Selected based on:
- Available data
- Quality of evidence
- Fit with analyte

Multiple Standards

Multiple levels of same type of standard:

- Eg: Analytical performance meets:
  - Optimal
  - Desirable
  - Minimal levels

Different types of standards

- Eg: Statistical and clinically based standards on same report
  - Same result(s) may meet one and fail another (eg SKML The Netherlands)

Applying the Stockholm/Milan Criteria

Done by ***People*** in ***Organisations***

- Using background principles
- Using information
- Common Information (eg Ricos Database)
- Specific information (local EQA data)

Pofessional Variation

EQA Quality Standards

- EVEN given the same data, laboratory scientists WILL interpret it differently.
- Add in variability of data reviewed
- Variation in intervals:
  - Always seen
  - AN EXPECTED OUTCOME!

EQA Quality Standards

Centre Suisse de Contrôle de Qualité
Schweizerisches Zentrum für Qualitätskontrolle
Centro Svizzero di Controllo della Qualità
Quality Control Centre Switzerland

With thanks to Xavier Albe and CSCQ

How is poor performance defined among EQA organisations?

Xavier Albe
Quality Control Centre Switzerland

Centre Suisse de Contrôle de Qualité
Schweizerisches Zentrum für Qualitätskontrolle
Centro Svizzero di Controllo della Qualità
Quality Control Centre Switzerland

Participants to the survey

ÖQUASTA, Austria	Hospital Clinic . University of Barcelona, Spain
Institute of Public Health, Belgium	SEQC, Spain
SEKK, Czech Republic	Sociedad Española de Hematología y Hemoterapia, Spain
DEKS, Denmark	CSCQ, Switzerland
Labquality, Finland	Academic Medical Center, The Netherlands
Reference Institute for Bioanalytics, Germany	ECAT Foundation, The Netherlands
Instande e.V., Germany	Erasmus Univ. Medical Center, The Netherlands
CMCEQAS, India	Maastricht Universitu Medical Center,The Netherlands
IEQAS, Ireland	Radboud University Hospital Nijmegen, The Netherlands
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Noklus, Norway	Randox, UK
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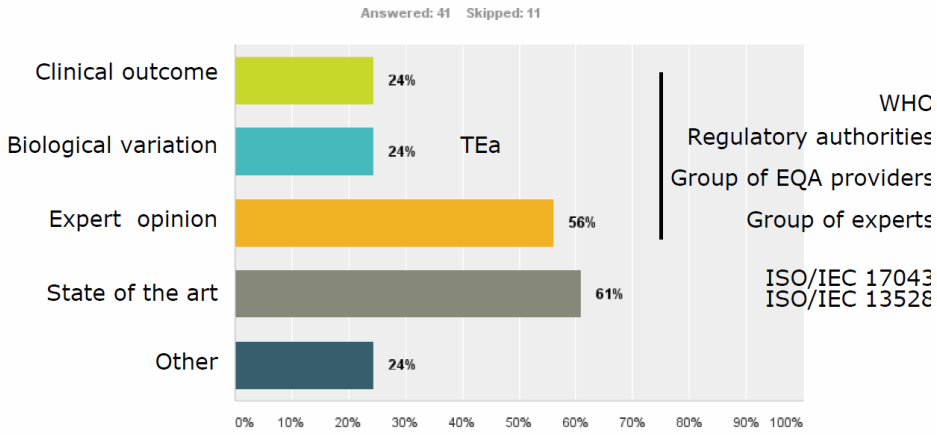
RoEQALM, ROMANIA	UK NEQAS for Immunology, Immunochemistry & Allergy, UK
National Centre for External Quality Assessment in Laboratory Medicine, Russia	UK NEQAS for Microbiology, UK
University Medical Centre Ljubljana, Slovenia	

N=29

sorted by country

Centre Suisse de Contrôle de Qualité
Schweizerisches Zentrum für Qualitätskontrolle
Centro Svizzero di Controllo della Qualità
Quality Control Centre Switzerland

2. On what basis is poor performance evaluated?



An old saying:

- "If you have seen one implementation of the Stockholm Hierarchy…

  … you have have seen one implementation of the Stockholm Hierarchy"

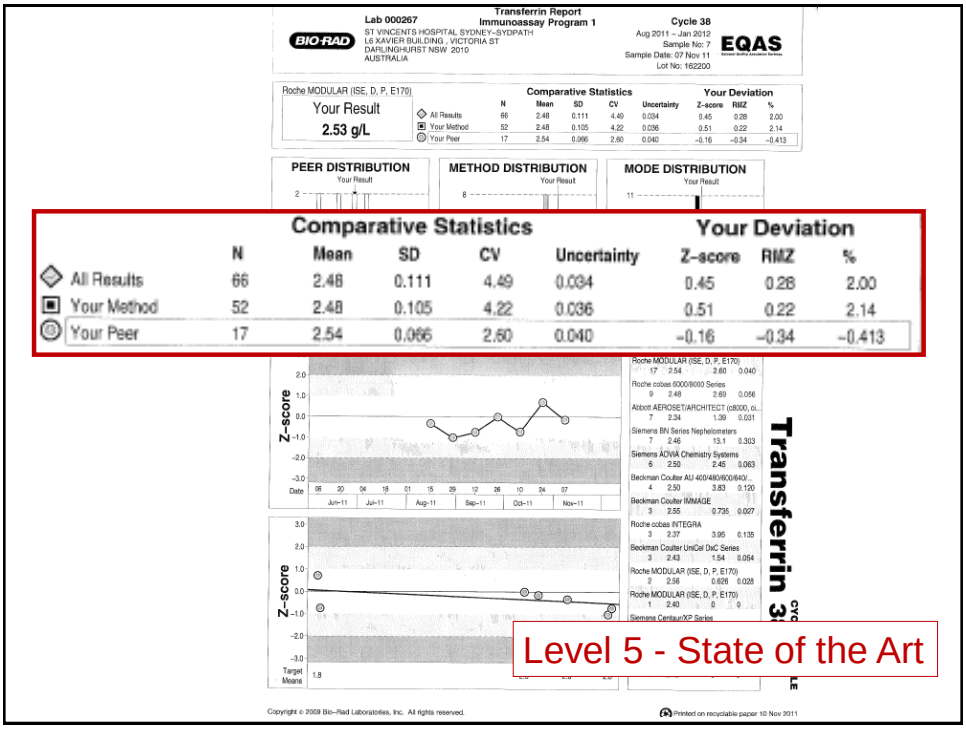
Applying the Criteria…

Level S5 / M3 – State of the Art

Statistical analysis (State of the art)

- Commonly Used
- Compare results against other submitted results
- Target: Usually middle of group
- Limits: typically +/- 2 or 3 SD
- Severity assessment: z-score (or similar)
- ISO 13528

Level 5 - State of the Art



Level 5 - State of the Art

Statistical Analysis

- Compares lab with other similar labs
- Alerts to possible analytical / work practice problem.
- (clinical meaning uncertain)

Level 5 - State of the Art

Statistical Issues - Standardisation

- Selection of target
- Outlier exclusion
- Limit at 2SD, 3SD or other
- Small method groups
- Identification of method groups
- Use with other limits

Level 5 - State of the Art

Higher Level Quality Standards (1&2)

(in practice: Biological Variation)

Options (levels 1 & 2)

- Choose one level for all analytes
- Select best option for each analyte

One Level for all analytes

For **all** analytes select the same criterion:

Example: CVi and CVg at desirable level

(TE = 0.250 (Cvi^2 + CVg^2)^{½} + 2.33 x ½ Cvi)

Benefits:

Same criteria for all analytes – simpler to apply

Highlights poor (and good) methods

Costs:

Some analytes always flagged (eg sodium)

Quite good assays not pushed for improvement

Analyte-Specific Levels

For **every** analyte select a separate criteria:

- Based on CVi ***or*** CVi + CVg
- Optimal ***or*** Desirable ***or*** minimal

(use State-of-the-Art to decide)

Benefits:

Analyte-specific ***achievable*** targets

Choice of principle illustrates quality

Costs:

Variable meaning in meeting targets

Complexity of setting and interpreting

Revision of ALP - RCPAQAP

- Use highest suitable level on the hierarchy
  (in practice – biological variation)
- Do not set unachievable goals
  (state of the art)
- Aim to improve laboratory performance
  (not a minimal standard)
- Not a regulatory standard

RCPAQAP
RCPA Quality Assurance Programs

Commentary

‘Allowable Limits of Performance’ for External Quality Assurance Programs – an Approach to Application of the Stockholm Criteria by the RCPA Quality Assurance Programs

***Graham RD Jones,[1,2] Kenneth Sikaris,[3,4] Janice Gill[5]**
[1] SydPath, StVincent’s Hospital, Darlinghurst, NSW, 2010, [2]University of NSW, Randwick, NSW, [3]Melbourne Pathology, Melbourne, Vic. [4]Melbourne University, Melbourne, Vic.[5] RCPA Quality Assurance Programs Pty Ltd, Adelaide, SA, Australia.
*For correspondence: Dr Graham Jones, gjones@stvincents.com.au

Clinical Biochemist Reviews 2012;33:133-9

RCPAQAP
RCPA Quality Assurance Programs

RCPA ALP

We are producing:

- An agreed definition
- An agreed set of criteria
- An agreed process
- Testing of proposed changes

To produce defensible, robust quality standards

RCPAQAP
RCPA Quality Assurance Programs

Revision of ALP

ALP are **applied** to Total Error

Used in interim reports

Single results include bias and imprecision

Will use categories of CV:

1,2,3,4,5,6,8,10,12,15,20,25,30%

Round to nearest category

Change between absolute and percentage based on precision profile

RCPAQAP
RCPA Quality Assurance Programs

Process

- Aim to use tightest limits possible
- Within limitations of State of the art (can be achieved by ~80% of labs)
- Analyte-specific criteria

Ranking of criteria:

- Based on within-subject biological variation
  - Optimal, Desirable, Minimal **(monitoring)**
- Based on within and between subject BV
  - Optimal, Desirable, Minimal **(diagnosis)**

The Equations

	Monitoring (ALP = 2 x CV_a)	Diagnosis (ALP = TE)
Optimal	$CV_a = ¼\ CV_i$	$TE = 0.125\ (CV_i^2 + CV_g^2)^{½} + 2.33 \times ¼\ CV_i$
Desirable	$CV_a = ½\ CV_i$	$TE = 0.250\ (CV_i^2 + CV_g^2)^{½} + 2.33 \times ½\ CV_i$
Minimal	$CV_a = ¾\ CV_i$	$TE = 0.375\ (CV_i^2 + CV_g^2)^{½} + 2.33 \times ¾\ CV_i$

RCPAQAP
RCPA Quality Assurance Programs

ALP (www.rcpaqap.com.au)

GENERAL SERUM CHEMISTRY / CONDENSED SERUM CHEMISTRY Reviewed January 2012		Basis	Level
Albumin	± 2.0 up to 33.0 g/L; 6% > 33.0 g/L	Total Error	Desirable
Alkaline Phosphatase	± 15 up to 125 U/L; 12% > 125 U/L	Total Error	Desirable
ALT	± 5 up to 40 U/L; 12% > 40 U/L	Imprecision	Optimal
Amylase	± 10 up to 100 U/L; 10% > 100 U/L	Imprecision	Desirable
AST	± 5 up to 40 U/L; 12% > 40 U/L	Imprecision	Desirable
Bicarbonate	± 2.0 up to 20.0 mmol/L; 10% > 20.0 mmol/L	Total Error	Minimal
Bilirubin-Total	± 3 up to 25 µmol/L; 12% > 25 µmol/L	Imprecision	Optimal
Bilirubin Conjugated	± 3 up to 15 µmol/L; 20% > 15 µmol/L	Imprecision	Optimal
Calcium	± 0.10 up to 2.50 mmol/L; 4% > 2.50 mmol/L	Imprecision	Minimal
Chloride	± 3 up to 100 mmol/L; 3% > 100 mmol/L	Total Error	minimal
Cholesterol	± 0.30 up to 5.00 mmol/L; 6% > 5.00 mmol/L	Imprecision	Desirable
Cholinesterase	± 500 up to 5000 U/L; 10% > 5000 U/L	Prof. Opinion	
Creatine Kinase	± 15 up to 125 U/L; 12% > 125 U/L	Imprecision	Optimal
CK-MB	± 3 up to 15 U/L or µg/L; 20% > 15 U/L or µg/L	Imprecision	Desirable
Cortisol	± 15 up to 100 nmol/L; 15% > 100 nmol/L	Prof. Opinion	
Creatinine	± 8.0 up to 100.0 µmol/L; 8% > 100.0 µmol/L	Imprecision	Minimal
Ferritin	± 4.0 up to 27 µg/L; 15% > 27 µg/L	Imprecision	Desirable
Fructosamine	± 15 up to 250 µmol/L; 6% > 250 µmol/L	Imprecision	Minimal
Glucose	± 0.4 up to 5.0 mmol/L; 8% > 5.0 mmol/L	Imprecision	Desirable
GGT	± 5 up to 40 U/L; 12% > 40 U/L	Imprecision	Desirable
hCG-quantitative	± 1.0 up to 10.0 IU/L; 10% > 10.0 IU/L	Prof. Opinion	

Meaning of ALP

NDENSED SERUM CHEMISTRY Reviewed January 2012	Basis	Level
± 2.0 up to 33.0 g/L; 6% > 33.0 g/L	Total Error	Desirable
± 15 up to 125 U/L; 12% > 125 U/L	Total Error	Desirable
± 5 up to 40 U/L; 12% > 40 U/L	Imprecision	Optimal
± 10 up to 100 U/L; 10% > 100 U/L	Imprecision	Desirable
± 5 up to 40 U/L; 12% > 40 U/L	Imprecision	Desirable
± 2.0 up to 20.0 mmol/L; 10% > 20.0 mmol/L	Total Error	Minimal
± 500 up to 5000 U/L; 10% > 5000 U/L	Prof. Opinion	

Basis

"Total Error" – Can share reference interval

"Imprecision" – Can Monitor patient across labs

Level

"Optimal" – no need to improve

"Desirable" – satisfactory

"Minimal" – just satisfactory

RCPAQAP
RCPA Quality Assurance Programs

Definition

- The Allowable Limit of Performance (ALP) is the analytical range around a central value
- It provides a simple tool to allow a rapid, standardised assessment of QAP results in both numerical and graphical report formats.
- A result outside the ALP should alert the laboratory that that their assay may produce results that are at risk of detrimentally affecting clinical decision making.

RCPAQAP
RCPA Quality Assurance Programs

Allowable Limits of Performance

(RCPAQAP) ALP are the "reference intervals" of QAP reports

RCPAQAP
RCPA Quality Assurance Programs

Application - Common Reference Intervals

SPECIAL REPORT:

Adult and paediatric common reference intervals in Australia and New Zealand for a first panel of chemistry analytes

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- AACB, RCPA

towards global harmonisation

able 1 Australasian Harmonised Reference Intervals for Adults (AHRIA) *

Analyte	Male	Female
Sodium	135 – 145 mmol/L	
Potassium **	3.5 – 5.2 mmol/L	
Chloride	95 – 110 mmol/L	
Bicarbonate	22 – 32 mmol/L	
Creatinine ***	60 – 110 µmol/L	45 – 90 µmol/L
Calcium	2.10 – 2.60 mmol/L	
Calcium (albumin adjusted)	2.10 – 2.60 mmol/L	
Phosphate ****	0.75 – 1.50 mmol/L	
Magnesium	0.70 – 1.10 mmol/L	
Lactate Dehydrogenase [L to P] (IFCC) *****	120 – 250 U/L	
Alkaline Phosphatase ******	30 – 110 U/L	
Total Protein	60 – 80 g/L	

Conclusions

- Harmonised EQA Quality Standards?
- No (or at least not yet)
- Will only happen with collaborative effort

Harmonised quality standards

All EQA programs should:

- State the nature of the standards
- State the expected response to standards
- State how they were determined
- State what the effect of compliance means

EQA programs may

- Provide more than one type of standard
- Provide more than one level of standard of the same type

Thank you

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