ECAT:

Towards sustainable EQA

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ECAT Foundation
The Netherlands

The start of the ECAT Foundation

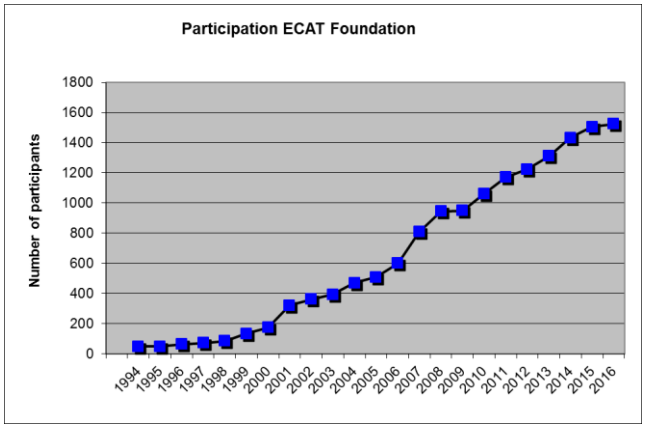
The ECAT Foundation started in 1994 as a small international EQA programme in thrombophilia testing.

One module: Thrombophilia parameters
- Antithrombin
- Protein C
- Protein S
- APC-Resistance

Participants: Approx. 60 from Western European countries

The development of the ECAT Foundation

Since 1994 the ECAT Foundation has been developed to one of the largest EQA organisations in specialised coagulation testing.



Participants: 60 → 1525

Modules: 1 → 30

Parameters: 4 → 46
(11) → (65)

No. of samples: 1 → 2
(for most parameters)

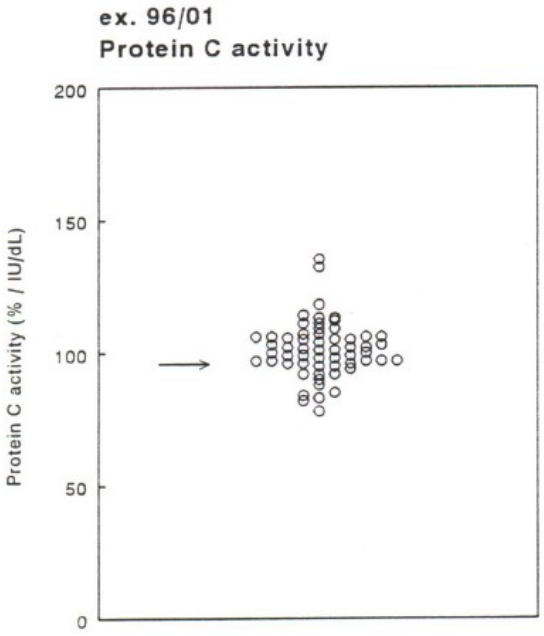
No. of vials per year

1994	2016
± 1.000	± 45.000

Report in 1996

Protein C activity assay (%, IU/dL)(Test plasma 96.02)

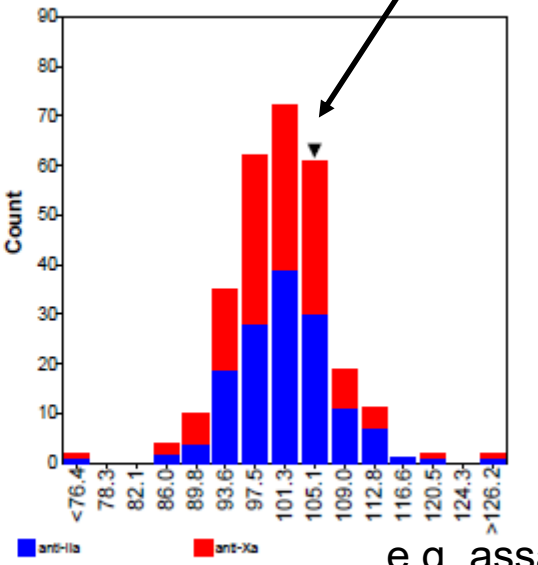
	Your result	Median	Range
Protein C activity	107	100.5 (n=58)	78-132
Protein C antigen		102.0 (n=10)	91.5-112



Report in 2016

	n	assigned value	CV (%)	range	your result	z-score
Total Group	281	101	5.9	35 - 130	104	0.51
Chromogenix, anti-IIa	144	101	6.1	36 - 130	104	0.43
Renam Reachrom ATIII	1	97				
Siemens Antitrhombin III	53	98	5.8	36 - 130		
Stago/Roche Stachrom/Antithrombin	89	103	5.4	88 - 119	104	0.14
Tcoag TriniCHROM Antitrhombin IIa	1	97				
Chromogenix, anti-Xa	137	101	5.7	35 - 130		
Chromogenix Coamatic Antithrombin	17	100	7.7	85 - 109		
Chromogenix Coamatic LR Antithrombin	1	95				
DG-Chromat ATIII	1	103				
Helena Chromz-AT	2	100		98 - 103		
Hyphen Biophen Antithrombin (anti-Xa)	2	102		99 - 105		
Hyphen Biophen AT (LRT)	5	98		87 - 107		
I.L. HemosIL Antithrombin	5	107		93 - 109		
I.L. HemosIL liquid Antithrombin	57	103	5.2	35 - 130		
Other	1	96				
Siemens Innovance AT	46	98	5.0	89 - 107		

Position participant



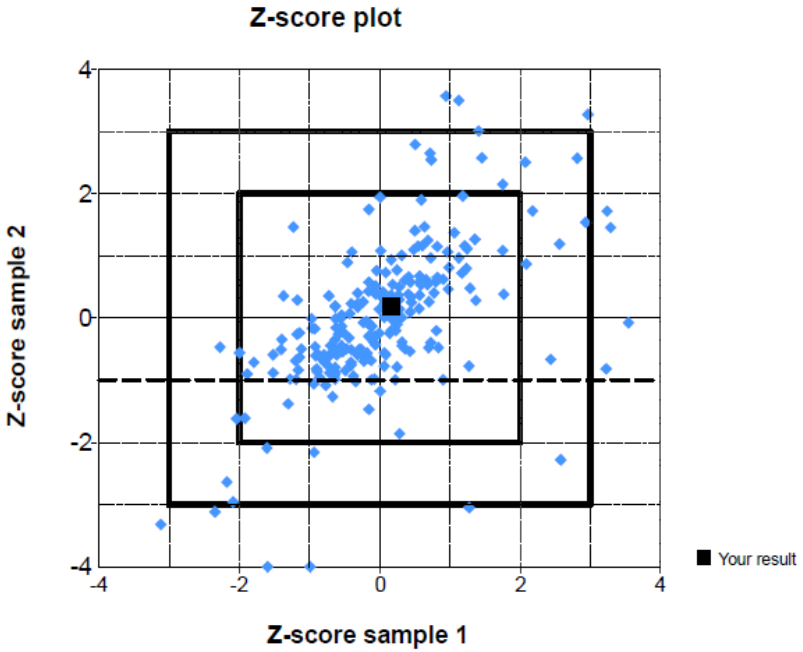
e.g. assay types

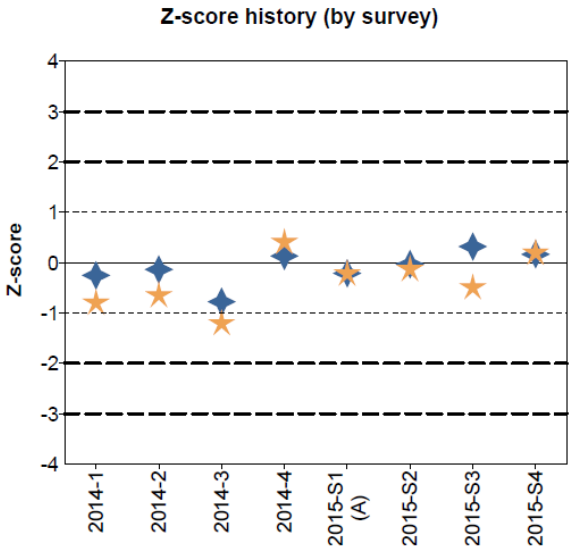
Total distribution

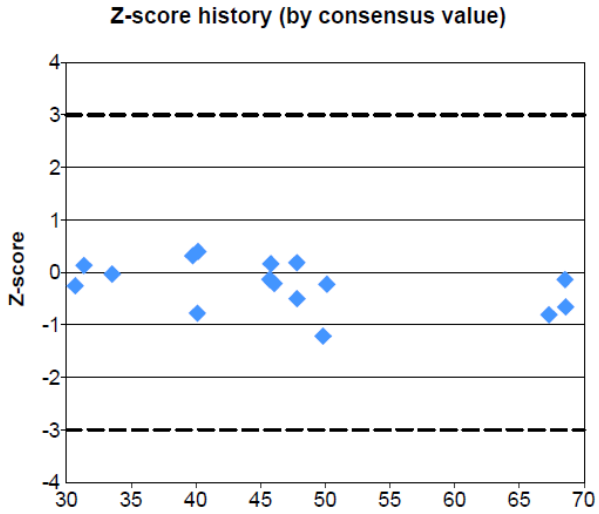
Z-score plots

Z-score = (lab – cons)/s

A numerical indicator representing the position of the individual lab result with respect to the consensus value – measure for accuracy







Is the current EQA concept fit-for-purpose and future proof?

ISO 15189:2012

5.6 Ensuring quality of examination results

5.6.3 Interlaboratory comparisons

5.6.

The laboratory shall participate in an EQA programme appropriate to the examination and interpretations of examination results.

NOTE The laboratory should participate in interlaboratory comparison programmes that substantially fulfil the relevant requirements of ISO/IEC 17043.

The laboratory shall establish a documented procedure for interlaboratory comparison participation that

The EQA programme should provide clinically relevant challenges that mimic patient samples and have the effect of checking the entire examination process.

Table 3. Evaluation capabilities of PT/EQA related to scheme design.

	Sample characteristics			Accuracy			Reproducibility	
				Individual laboratory				
					Relative to participant results			
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group	Individual laboratory intralab CV	Measurement procedure interlab CV
1	Yes	Yes	Yes	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X
3	Yes	No	Yes		X	X	X	X
4	Yes	No	No		X	X		X
5	No	No	Yes			X	X	X
6	No	No	No			X		X

procedure.

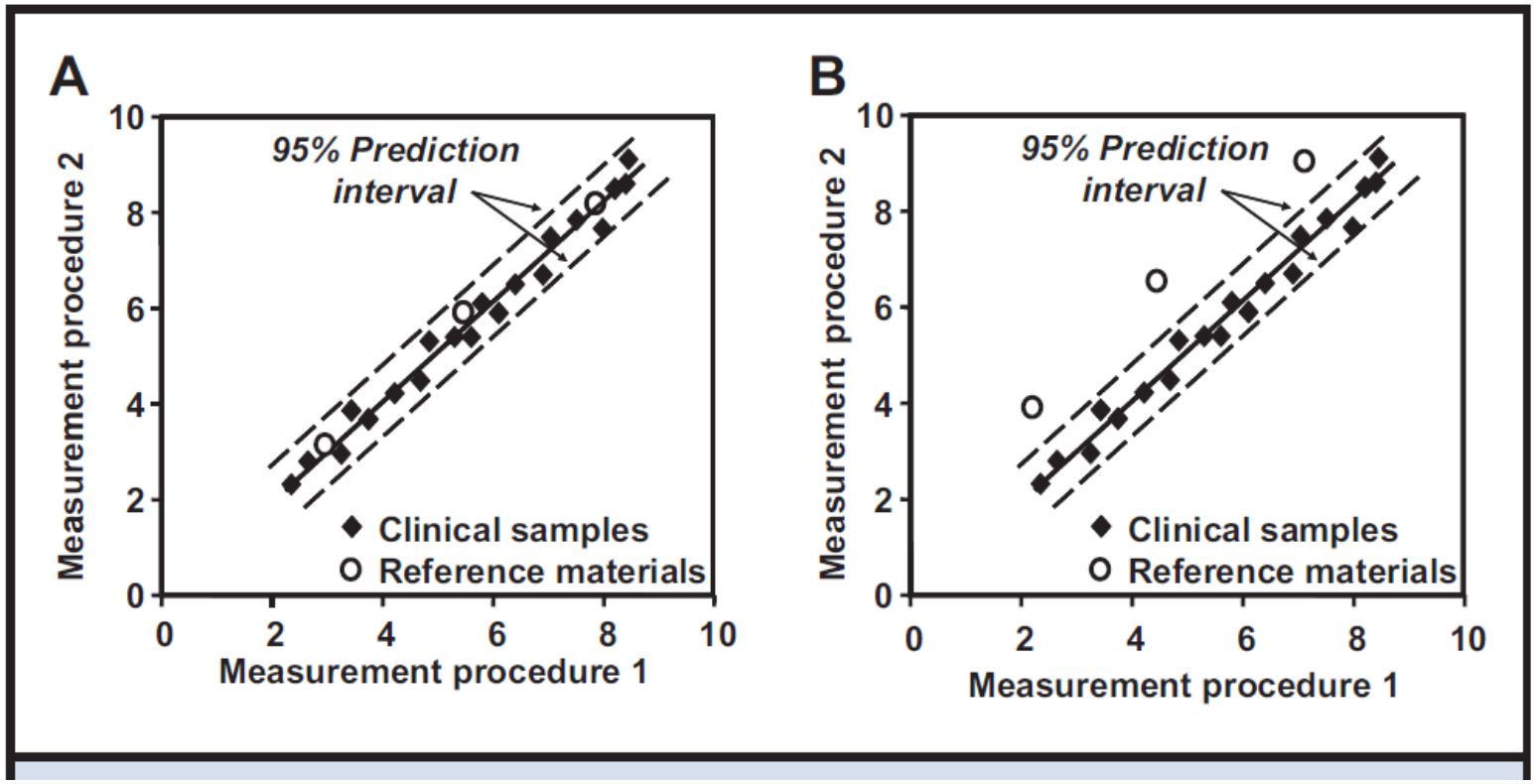
W.G. Miller *et al. Clin Chem (2012) 57: 1670 - 1680*

The principles for “perfect” EQA

- Commutable samples
- Value assignment with RMP or CRM
- Replicate samples in surveys

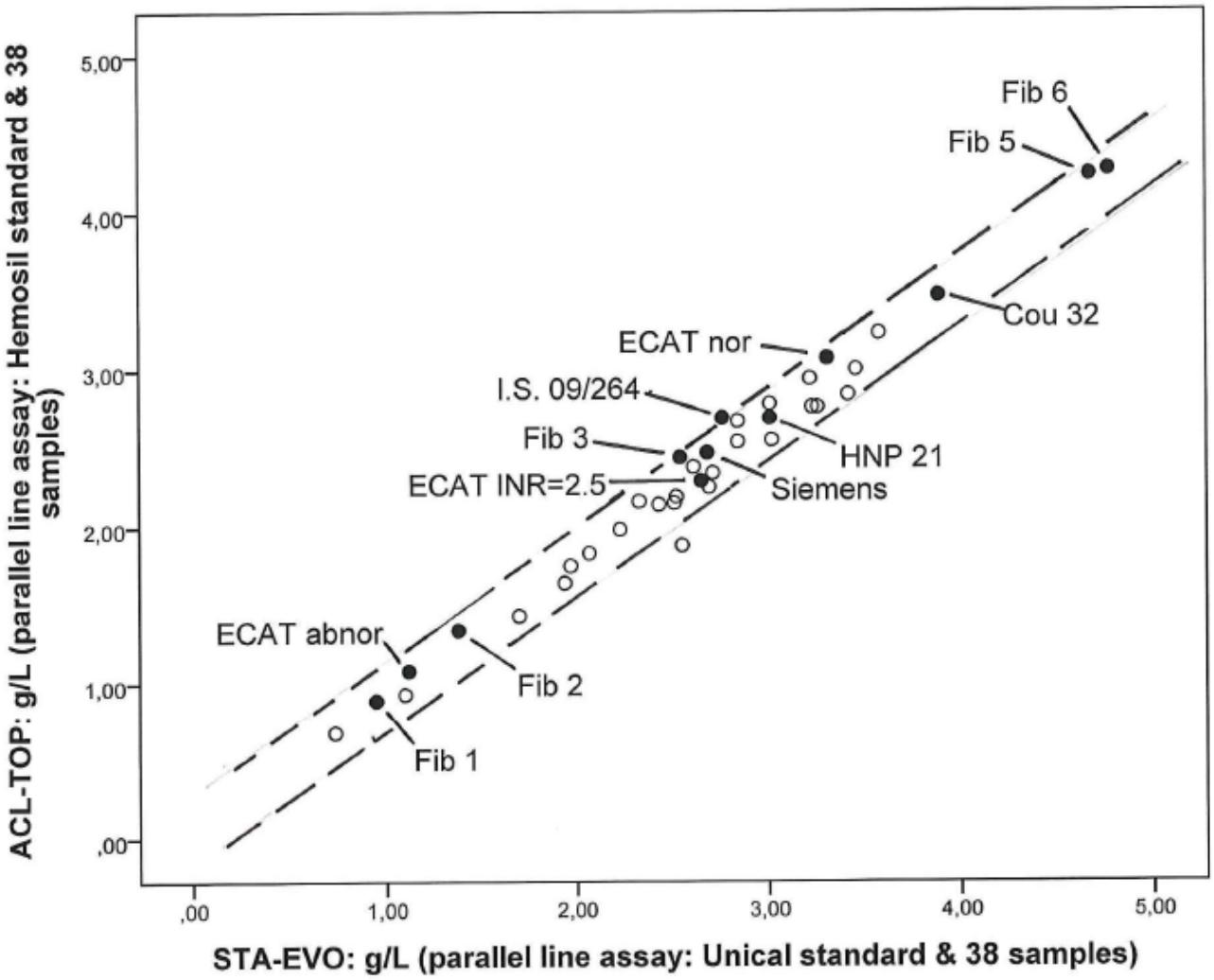
Commutable samples

Commutable EQA samples behave like real patient samples in the different methods used in the clinical laboratory.



W.G. Miller *et al. Clin Chem (2012) 57: 1670 - 1680*

Fibrinogen


ACL-TOP: g/L (parallel line assay: Hemosil standard & 38 samples)
5,00
4,00
3,00
2,00
1,00
,00
,00
1,00
2,00
3,00
4,00
5,00
STA-EVO: g/L (parallel line assay: Unical standard & 38 samples)
Fib 6
Fib 5
Cou 32
ECAT nor
I.S. 09/264
Fib 3
HNP 21
ECAT INR=2.5
Siemens
ECAT abnor
Fib 2
Fib 1

Commutable samples

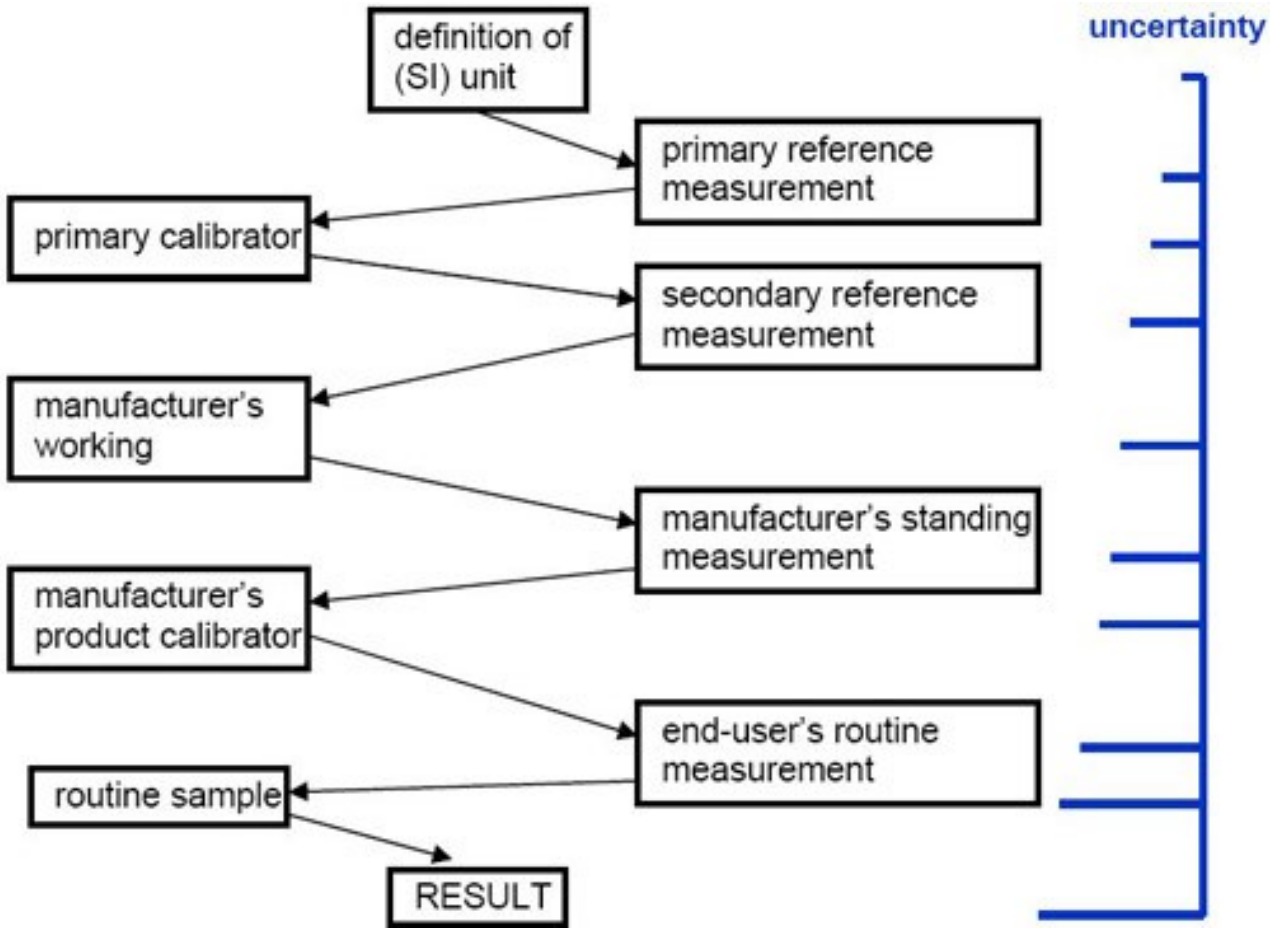
In principle commutability should be established for each parameter and for each type of EQA samples used in the surveys.

Currently ECAT has started a project to investigate the commutability for Antithrombin.

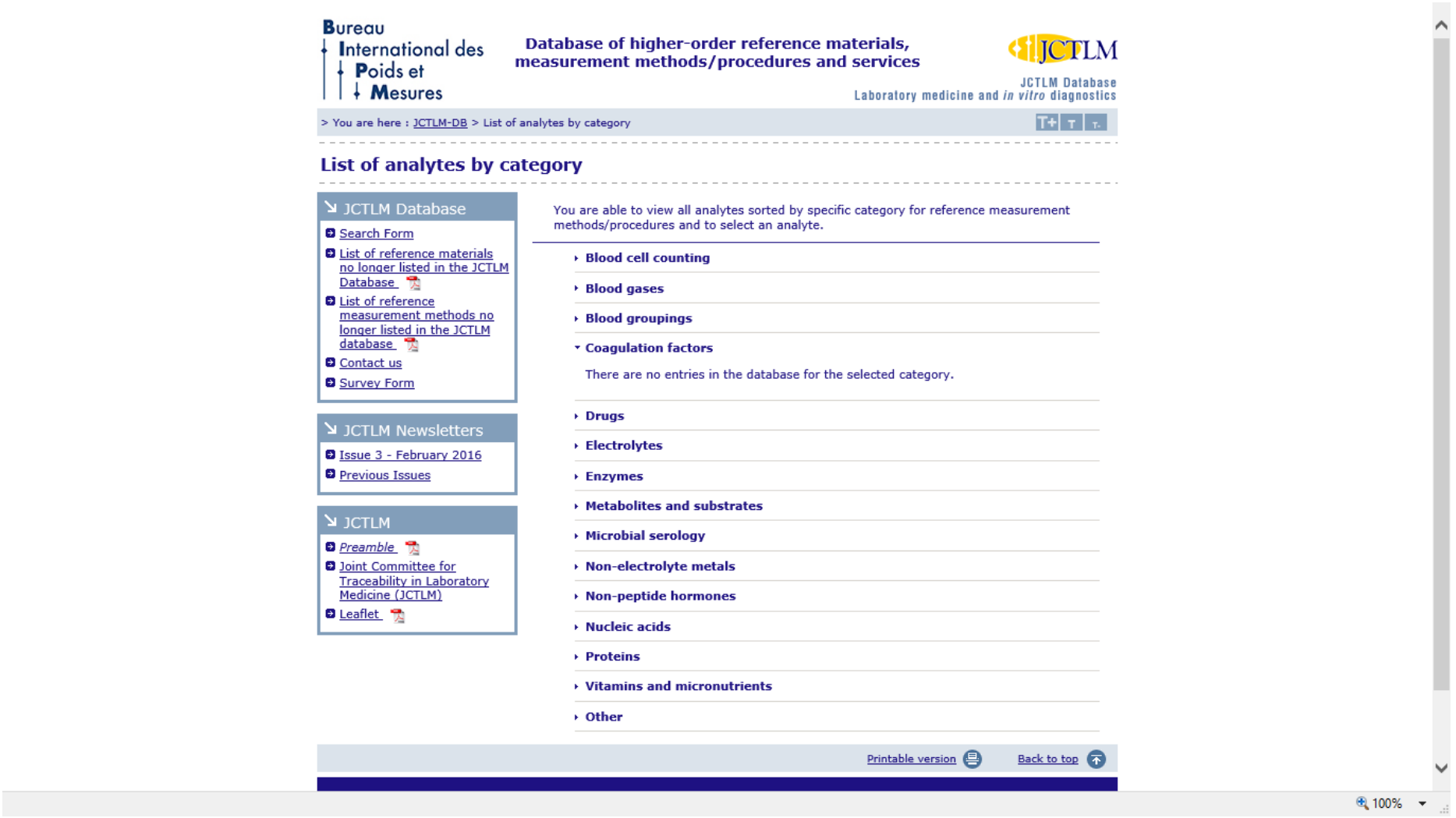
► The current samples in use in the EQA programme

► Future: commutable samples with known values: trueness verifiers

Value assignment with RMP or CRM



Value assignment with RMP or CRM



Value assignment with RMP or CRM

Results of the search for higher-order reference materials

JCTLM Database

- Search Form
- List of reference materials no longer listed in the JCTLM Database
- List of reference measurement methods no longer listed in the JCTLM database
- Contact us
- Survey Form

JCTLM Newsletters

- Issue 3 - February 2016

Your search criteria: Higher-order reference materials; Analyte: thromboplastin; Analyte category: Coagulation factors; Matrix category: -

Results of the search

Your search criteria produced 1 summary result.
Select one or several higher-order reference material summary descriptions amongst the following list and click on 'View' to access more information.

Select all items from the list

Sort by : (•) Analyte ( ) Matrix/Material ( ) Organization

Select	Analyte	Analyte category	Matrix/Material	Organization
☐	thromboplastin	coagulation factors	rabbit brain isolate	IRMM

Value assignment with RMP or CRM

Is standardisation in coagulation feasible? C. Kluft

- Development of RMP and CRM is a time-consuming process
- At the moment just one measurand under investigation
- It will take many years before for all clinical relevant measurands RMP's and CRM's are developed.

Value assignment based on participants results

As precisely as possible approximation of the “true" value based on the results of participants using appropriate statistics. This means that there should be a negligible effect of any existing outliers.

► **Robust statistics (Algorithm A)**

	n	assigned value	CV (%)	range	your result	z-score
Total Group	314	95	5.7	50 - 115	93	-0.33

Z-score = (lab – cons)/s

Measure for the accuracy (bias)

NIBSC/WHO standards

Currently the highest order CRM in Haemostasis

Value assigment by consensus studies

Description
Protein C Plasma, Human(2nd International Standard) WHO International Standard
Protein S, Plasma, Human(2nd International Standard) WHO International Standard
Blood Coagulation Factor XI Plasma, Human(1st International Standard) WHO International Standard
Antithrombin, Plasma (3rd International Standard) WHO International Standard
C1 Inhibitor (Plasma)(1st International Standard) WHO International Standard
Blood coagulation Factors II, VII, IX, X Plasma (4th International Standard 2010) WHO International Standard

Antithrombin (U/dL)

	No.	Mean ± SD
Total	314	95 ± 5
Anti-IIa	154	94 ± 5
Anti-Xa	160	95 ± 5
Siemens Antithrombin III	51	92 ± 5
Stago Stachrom ATIII	101	96 ± 5
IL HemsoIL liquid AT	79	96 ± 5
Siemens Innovance AT	58	93 ± 4

Factor VIII:C (U/dL)

	No.	Mean ± SD
One-stage clotting assay	219	101 ± 11
IL HemosIL SynthasIL	61	93 ± 7
Siemens Actin FS	29	106 ± 12
Siemens Pathromtin SL	24	100 ± 5
Stago Cephalin/Kaolin/CK Prest	32	105 ± 8
Stago PTT / STA APTT	26	109 ± 11

Evaluation of accuracy

	Sample characteristics			Accuracy		
				Individual laboratory		
					Relative to participant results	
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group
1	Yes	Yes	Yes	X	X	X
2	Yes	Yes	No	X	X	X
3	Yes	No	Yes		X	X
4	Yes	No	No		X	X
5	No	No	Yes			X
6	No	No	No			X

Replicate samples in surveys

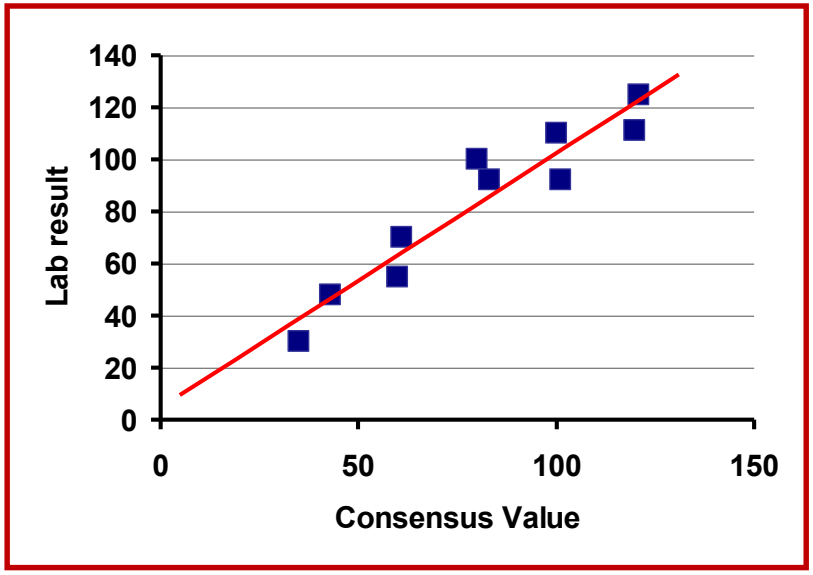
Replicate samples used in the same survey cylce.

W.G. Miller *et al. Clin Chem (2012) 57: 1670 - 1680*

- Individual laboratory intra-lab CV

				Evaluation capability				
				Accuracy				
				Individual laboratory				
	Sample characteristics				Relative to participant results		Reproducibility	
Category	Commutable	Value assigned with RMP[a] or CRM	Replicate samples in survey	Absolute vs RMP or CRM	Overall	Peer group	Individual laboratory intralab CV	Measurement procedure interlab CV
1	Yes	Yes	Yes	X	X	X	X	X
2	Yes	Yes	No	X	X	X		X
3	Yes	No	Yes		X	X	X	X
4	Yes	No	No		X	X		X
5	No	No	Yes			X	X	X
6	No	No	No			X		X

LONG-TERM EVALUATION MODEL



IMPRECISION

$$LCV_a = \frac{(s_{y|x}/b)}{\bar{X}} \bullet 100\%$$

BIAS

$$B = \frac{\sqrt{\frac{n-1}{n} \bullet (b-1)^2 \bullet s_x^2 + (\bar{Y} - \bar{X})^2}}{\bar{X}} \bullet 100\%$$

X = consensus value ; $\bar{X}$ = mean value for X.

s_x = standard error of X

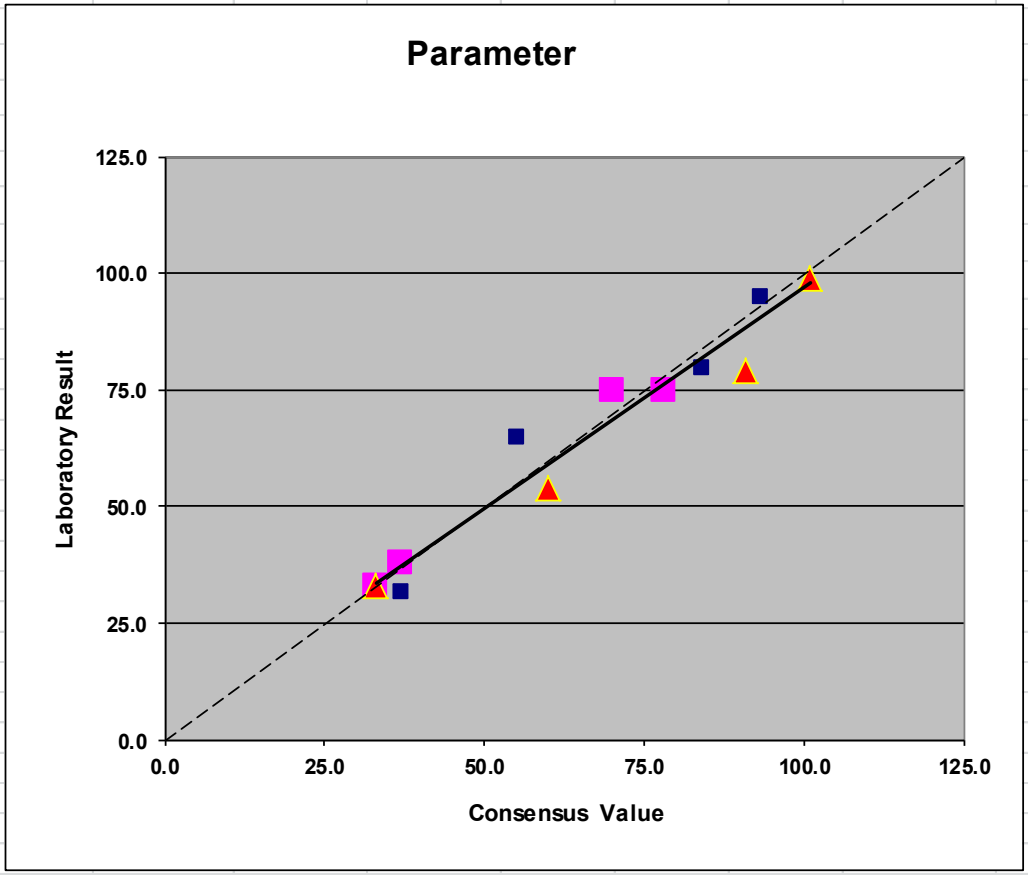
Y = laboratory value ; $\bar{Y}$ = mean value for Y.

b = slope

$s_{y|x}$ = variability of the regression line, which is calculated based on the least-square method.

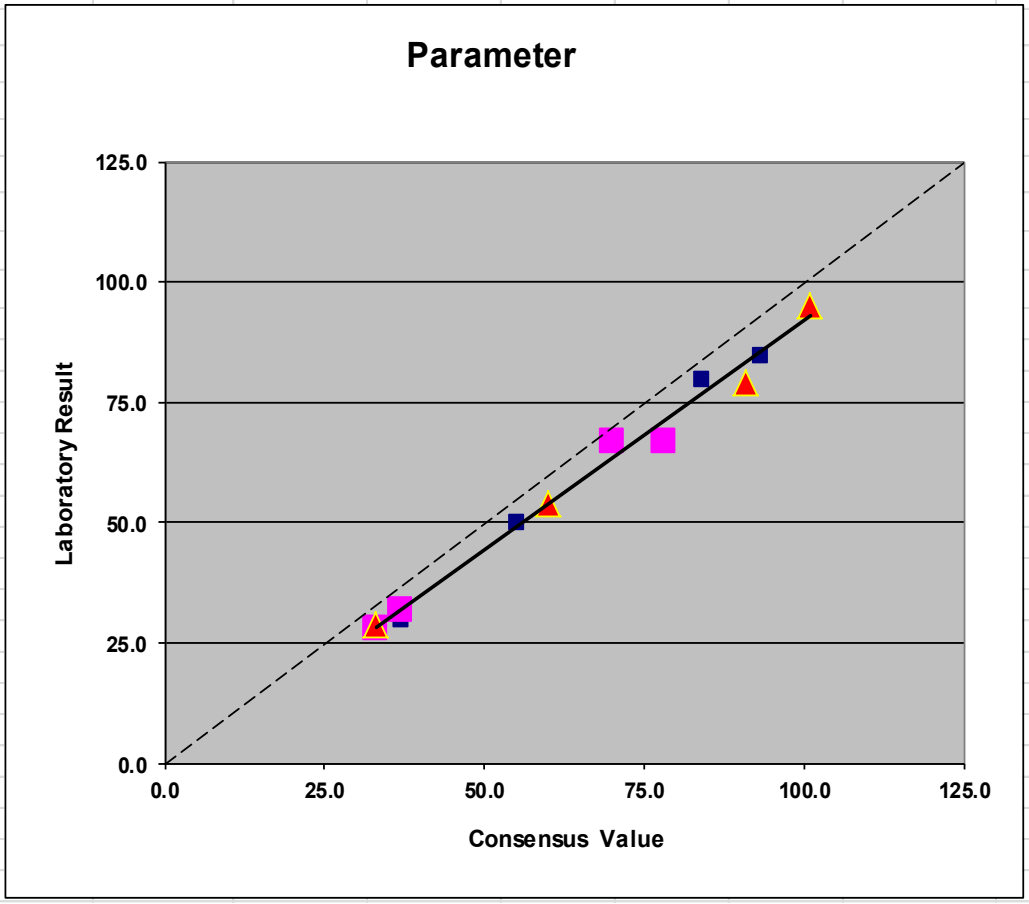
n = number of laboratory results

LONG-TERM EVALUATION MODEL



Long-term CVanalytical	9.4%
Bias	2.7%

LONG-TERM EVALUATION MODEL

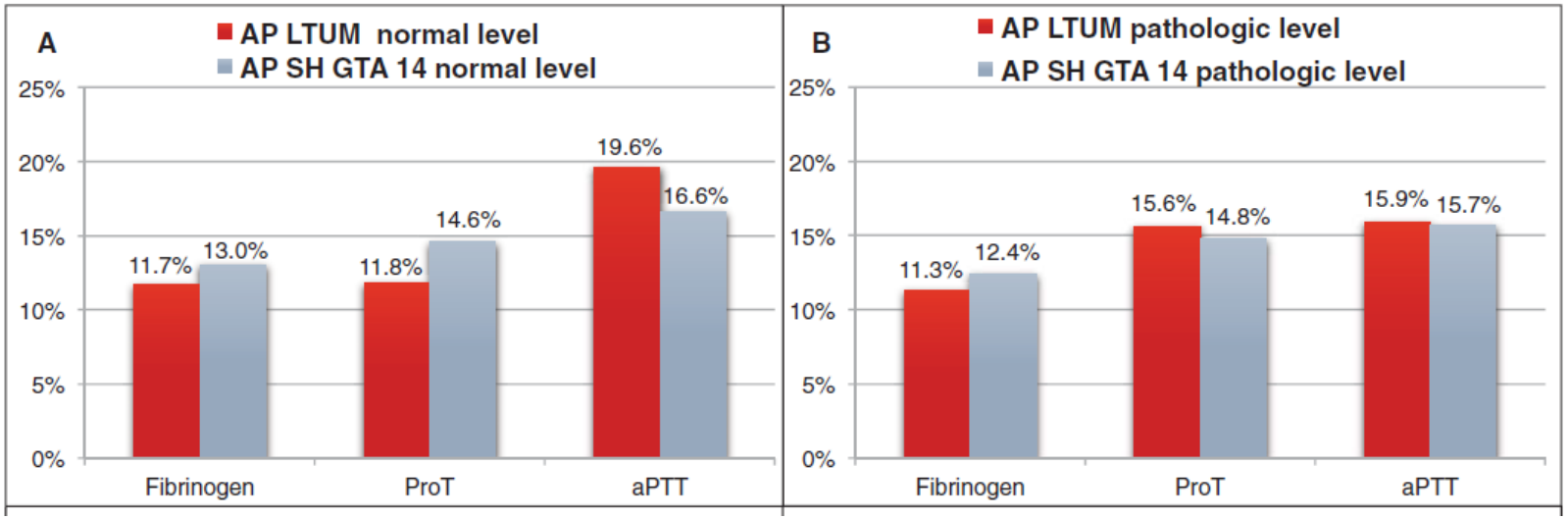


Long-term CVanalytical	4.3%
Bias	10.0%

Gladys Matar*, Bernard Poggi, Roland Meley, Chantal Bon, Laurence Chardon, Karim Chikh, Anne-Claude Renard, Catherine Sotta, Jean-Christophe Eynard, Regine Cartier and Richard Cohen

Uncertainty in measurement for 43 biochemistry, immunoassay, and hemostasis routine analytes evaluated by a method using only external quality assessment data

$$UM = 1.96 \times um = 1.96 \times \sqrt{LCV^2 + LTB^2}$$



Biological Variation of Hemostasis Variables in Thrombosis and Bleeding: Consequences for Performance Specifications

Moniek P.M. de Maat, Marianne van Schie, Cornelis Kluft, Frank W.G. Leebeek, Piet Meijer

Clinical Chemistry (2016) Online published September 2016

Variable	Diagnosis	Monitoring
PT	2.8	1.3
APTT	5.5	3.3
Fibrinogen	12.0	6.0
Antithrombin	5.2	2.2
Prot. C clot	14.0	4.5
Prot. C chrom	12.1	3.8
Prot. S act.	14.6	4.0
Prot. S total	11.1	3.7
Prot. S free	15.2	3.8
FVIII:C	17.4	7.9
FIX:C	11.8	4.6

LONG-TERM EVALUATION MODEL

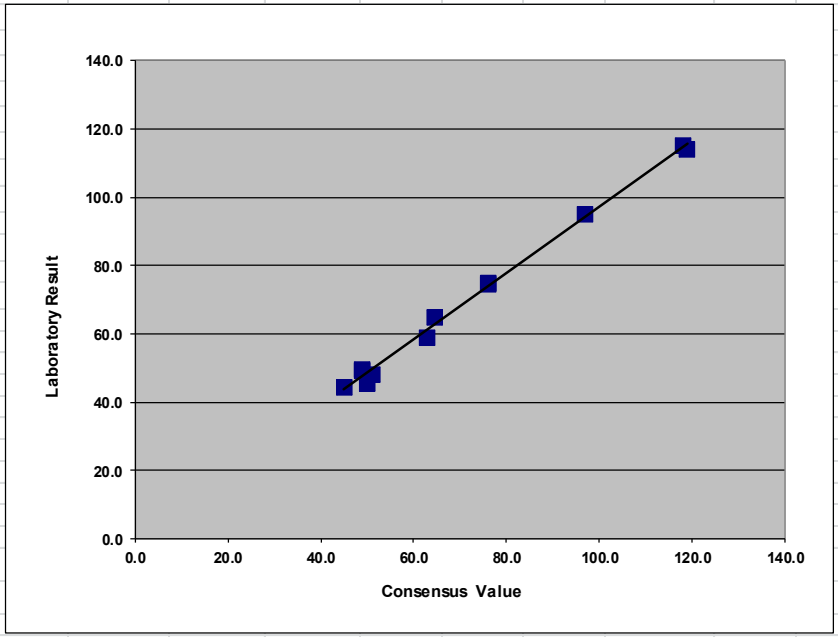
ANALYTE

Labcode:

Name	
Hospital	
Department	
City	
Country	

Survey	X (Cons. Value)	Y (Lab Result)
A1	64.5	65.0
A1	50.0	45.3
A2	118.0	115.3
A2	49.0	49.3
A3	76.0	74.8
A3	119.0	114.1
A4	49.0	49.6
A4	76.0	74.5
A5	97.0	94.9
A5	51.0	47.9
A6	45.0	44.2
A6	63.0	58.8

CVb within	5.0
CVb between	8.0



Long-term CVanalytical	2.7	%
Bias	3.0	%

Imprecision (Diagnostic)	5.5	√
Imprecision (Monitoring)	2.5	X
Bias	2.1	X

SIX SIGMA

Sigma = (TEa – Bias) / CV

$$TEa < 1{,}65 \times (0{,}5 \times CV_{ws}) + 0{,}25 \times (CV_{ws}^2 + CV_{BS}^2)^{1/2}$$

Example:

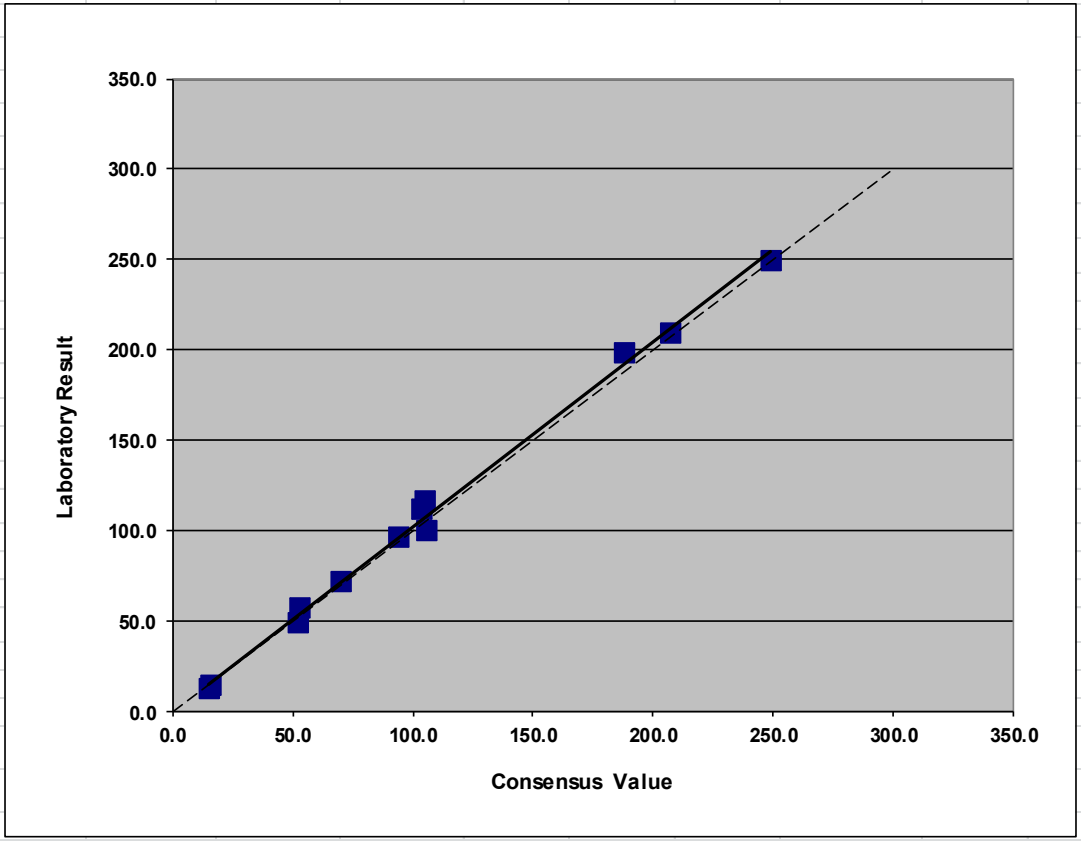
Factor VIII:C :

$CV_{WS} = 15.8\%$

$CV_{BS} = 25.2\%$

$Tea < 20.5\%$

SIX SIGMA

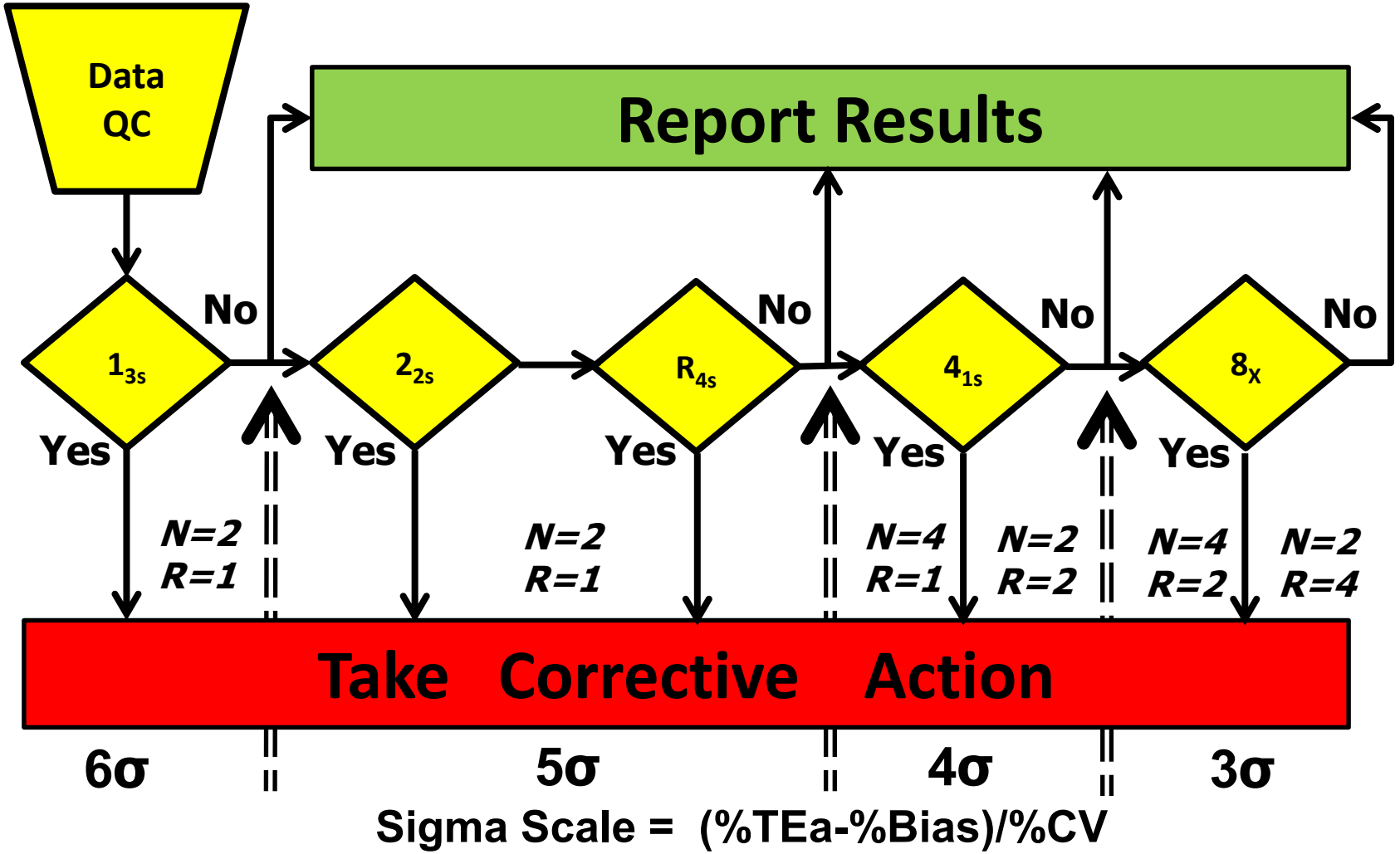


Long-term CVanalytical	5.0	%
Total Bias	2.6	%
Constant Bias	2.0	%
Proportional Bias	1.7	%

Imprecision (Diagnostic)	17.3	√
Imprecision (Monitoring)	7.9	√
Bias	6.4	√

SIGMA	3.6

Sigma value: 8.9
(Bias = 0 / CVa duplo values in BV study)



Source: Sten Westgard

Is the current EQA concept fit-for-purpose and future proof?

Although in haemostasis “perfect” (= traceable) EQA (with RMP and/or CRM) is not yet possible, further developments are possible:

- Inclusion of long-term evaluation in survey reports
- The introduction of the use of performance specifications
- The use of the parameters of the long-term evaluation for both measurement uncertainty and Sigma-value

► 2017: Further investigations will be done to see how and for which parameters these new features can be introduced.

Is this sustainable EQA?

With the features discussed the focuss is on analytical quality.
But that is just one part of the total testing process

> The EQA programme should provide clinically relevant challenges that mimic patient samples and have the effect of checking the entire examination process.
>
> ISO 15189

Sustainable EQA includes:

- Analytical state-of-the-art EQA
- Case studies
  - ► Combination of evaluation of analytical quality and interpretation of test results (post-analytical phase)
- Diagnostic EQA (combination of physician and laboratory)


Analytical EQA
EQA for pre- and post-analytical phase
Sustainable EQA
Case studies
Diagnostic EQA

THANK YOU FOR YOUR ATTENTION