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# QC performance specification – what do we need for accreditation?

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# Definitions

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**Quality Control (QC)** refers to procedures for monitoring the work processes, detecting problems, and making corrections prior to delivery of products or services. Statistical process control, or statistical quality control, is the major procedure for monitoring the analytical performance of laboratory methods.

**Quality Assessment (QA)** refers to the broader monitoring of other dimensions or characteristics of quality. Characteristics such as turnaround time, patient preparation, specimen acquisition, etc., are monitored through QA activities. Proficiency testing (EQA) provides an external measure of analytical performance (also some pre and post analytical).

**Quality Improvement (QI)** is aimed at determining the causes or sources of problems identified by QC and QA. May require problem-solving tools (such as the flowchart, Pareto diagram, Ishikawa cause and effect diagram, force field analysis, etc)

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# ISO 15189:2012 - what does it say?

- **Design**– 5.6.2. The laboratory shall design quality control procedures that verify the attainment of the internal quality of results. Special attention should be given to elimination of mistakes in the pre and post examination processes.

- **Material**– 5.6.2.1 QC shall react to the exam system in a manner as close to patient samples as possible. QC should be periodically examined along with patient samples, with a frequency that is based on the stability of the procedure.
- Note: The lab should choose conc. of QC especially at or near clinical decision values that ensure the validity of decisions made.
- Note: Use of 3rd part QC should be considered, either instead of, or in addition to any QC material supplied by the reagent or instrument manufacturer.

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# ISO 15189:2012 - what does it say?

- QC Data – 5.6.2.2 The lab shall have a procedure to minimise the risk of significantly different or aberrant patient examination results being reported in the event of QC rule failure . This is poor wording as for a method that is excellent (6S) two results could be statistically different but not clinically significant and a method that is poor (2S), two results could be statistically insignificant but clinically significant.
- Note: When QC rules are violated, examination results should normally be rejected and relevant patient samples re-examined after the error condition has been corrected and within specification performance is verified. The lab should also evaluate the results from patient samples that were examined after the last successful QC event.
- QC data shall be reviewed at regular intervals to **detect trends** in exam performance that may indicate problems in the exam system. When such trends are noted preventive actions shall be taken and recorded.
- Note: Established statistical techniques such as Shewhart/ Levey-Jennings charts and process control rules should be used wherever possible to continuously monitor examination system performance.

# Internal quality control: best practice

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**ABSTRACT**
There is a wide variation in laboratory practice with regard to implementation and review of internal quality control (IQC). A poor approach can lead to a spectrum of scenarios from validation of incorrect patient results to over investigation of falsely rejected analytical runs. This article will provide a practical approach for the routine clinical biochemistry laboratory to introduce an efficient quality control system that will optimise error detection and reduce the rate of false rejection. Each stage of the IQC system is considered, from selection of IQC material to selection of IQC rules, and finally the appropriate action to follow when a rejection signal has been obtained. The main objective of IQC is to ensure day-to-day consistency of an analytical process and thus help to determine whether patient results are reliable enough to be released. The required quality and assay performance varies between analytes as does the definition of a clinically significant error. Unfortunately many laboratories currently decide what is clinically significant at the troubleshooting stage. Assay-specific IQC systems will reduce the number of inappropriate sample-run rejections compared with the blanket use of one IQC rule. In practice, only three or four different IQC rules are required for the whole of the routine biochemistry repertoire as assays are assigned into groups based on performance. The tools to categorise performance and assign IQC rules based on that performance are presented. Although significant investment of time and education is required prior to implementation, laboratories have shown that such systems achieve considerable reductions in cost and labour.

samples. By definition, this is not completely true for random errors. However, the error detection rate of an IQC system can be maximised by using (i) appropriate IQC material analysed at (ii) appropriate intervals and interpreted using (iii) appropriate IQC ranges with (iv) appropriate IQC rules. Patient data algorithms (such as delta checks and absurd value recognition) should be used as adjuncts to IQC to aid detection of random error.

An audit of IQC practice conducted in 2006 showed a wide variation in the laboratory approach to implementation, review and troubleshooting of IQC across the UK.[4] This variation in practice needs to be addressed so that IQC procedures are compatible with the progression towards pathology harmonisation and the formation of laboratory networks. This article sets out practical guidelines to promote best practice and limit variation at all stages of IQC management.

## SELECTION OF IQC MATERIAL

The success of a quality control procedure depends on the selection of appropriate IQC material. First, in order to minimise matrix effects on the measurement of analytes, IQC material should mimic the composition of patient samples as closely as possible. In the UK, this is more frequently achieved for serum rather than non-serum analytes.[4] To optimise the detection of analytical errors, variation in the IQC material also needs to be minimised. Therefore, IQC materials with long-term stability

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# Design of IQC

Define the quality required of the assay

Determine the quality the assay can provide

Identify candidate IQC strategy

Select appropriate QC rules

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# Specification Hierarchy


**Analytical performance specification based on clinical outcomes**

- What we need but data not readily available

**Analytical performance specification based on biological variation**

- Data available but not always achievable

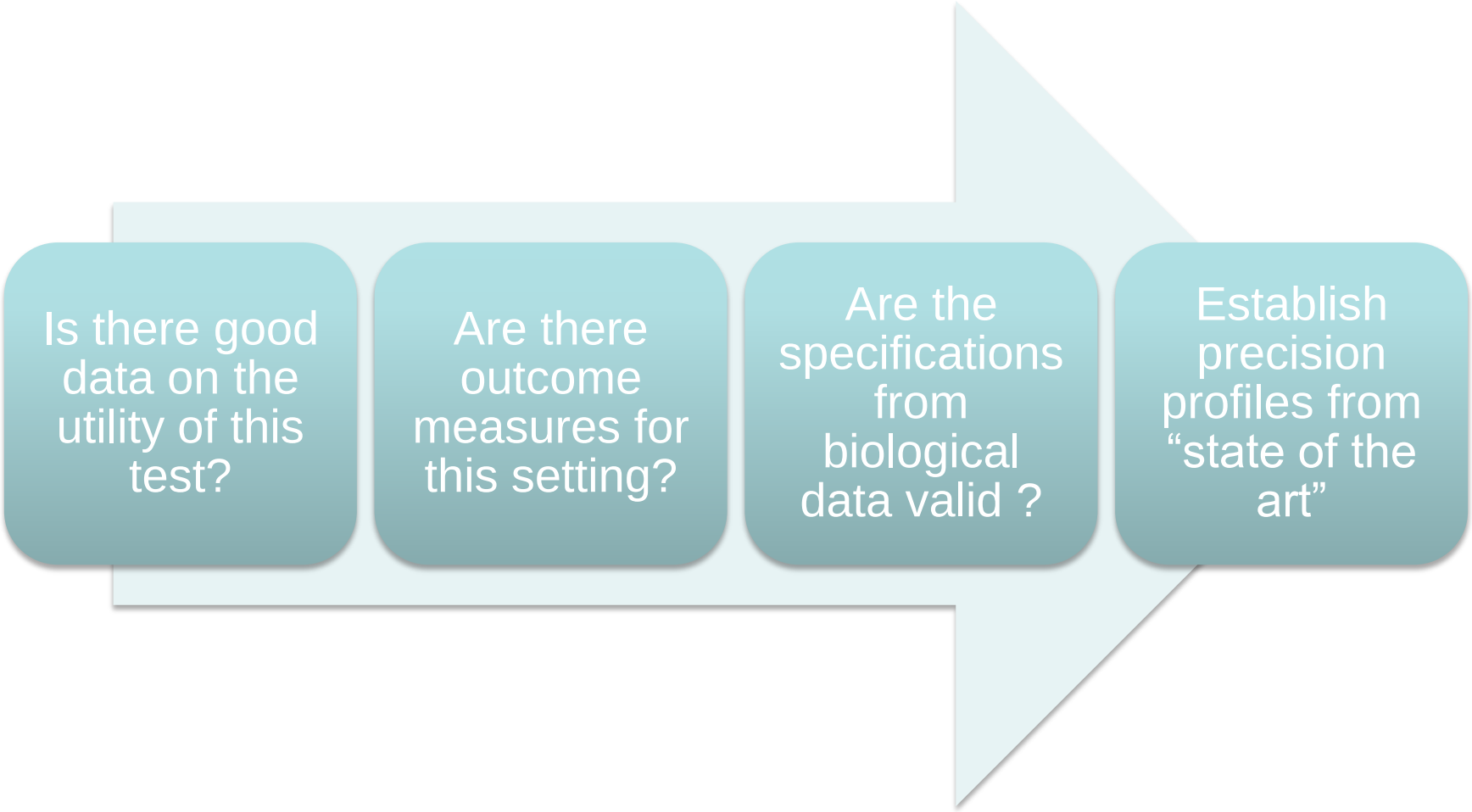
**"State of the art" - Interlaboratory variation**

- What we can achieve but may not be "fit for purpose"

Data from outcome studies

Improvements in methods / technology

# How to choose analytical specification



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# Biological Data

| Test | I (%) | B (%) | TE (%) (0.05) | TE (%) (0.01) |
|---|---|---|---|---|
| **Glucose** | 2.2 | 1.9 | 5.5 | 7.0 |
| **Cholesterol** | 2.7 | 4.1 | 8.6 | 10.4 |
| **Sodium** | 0.4 | 0.3 | 1.0 | 1.2 |
| **HbA1c** | 1.7 | 1.5 | 4.3 | 5.5 |

**Desirable performance specification can be calculated from:**

**$I < 0.5CV_w$**

**$B < 0.25 (CV_w^2 + CV_b^2)^{½}$**

**$TE_a = 1.65\ I + B\ (a<0.05)$**

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## QUALITY REQUIREMENTS

### Biological Variation Database references

**Dr. Carmen Ricos and colleagues update this database on within-subject and between-subject biologic variation. From this data, they also calculate desirable specifications for imprecision, inaccuracy, and total allowable error. We are honored to be able to host this database. This article lists the references that were used to develop the specifications. Updated for 2012.**

### Desirable Specifications for Total Error, Imprecision, and Bias, derived from Intra- and Inter-Individual Biologic Variation

This most recent and extensive listing of biologic goals has been provided by Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress." Scand J Clin Lab Invest 1999;59:491-500. *Updated analytes for 2001, 2004, 2006, 2008, 2010, 2012 included.*

DE GRUYTER

Opinion Paper

Anna Carobene*

# Reliability of biological variation data available in an online database: need for improvement

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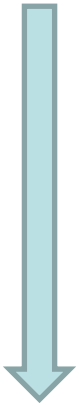
# Performance specification of Test related to disease process

- Specification should be designed to provide performance assessment that best meets the needs of the service.
- What laboratory service is being provided?
  - Diagnosis
  - Prognosis
  - Monitoring
  - Screening



Performance specification may be different for the same analyte used in different settings

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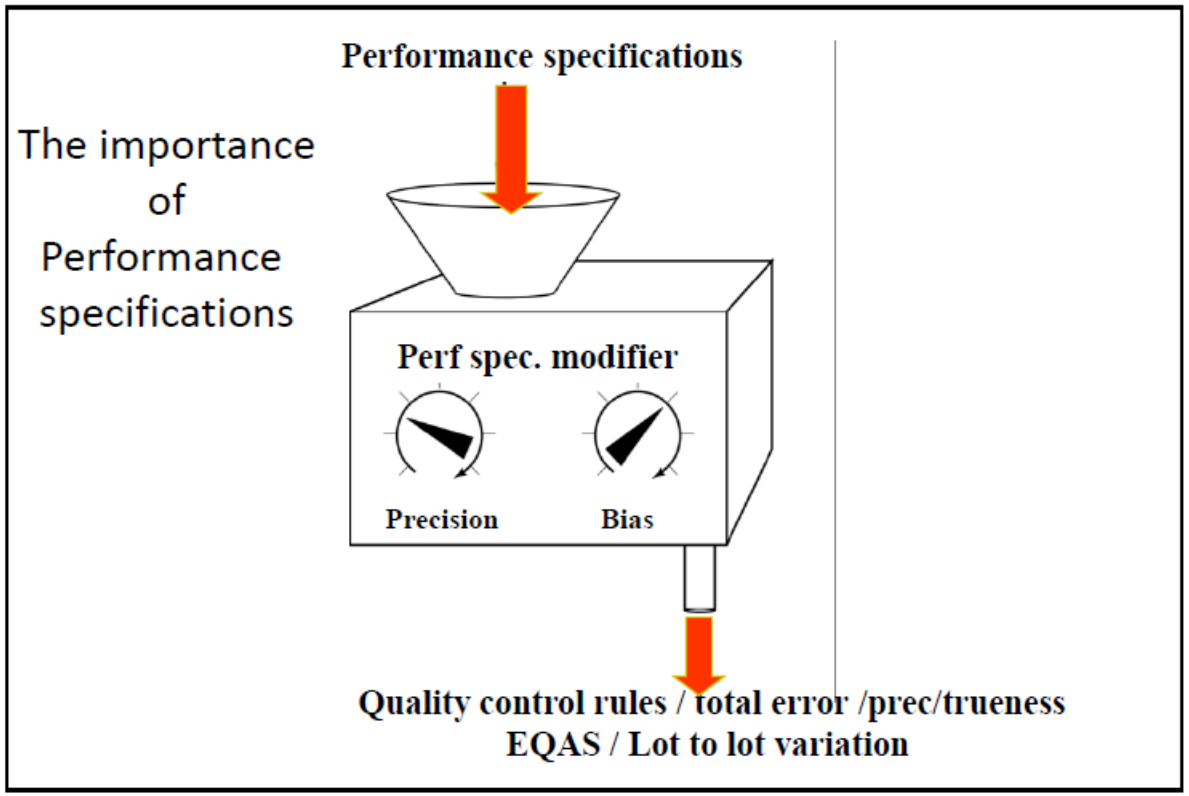
# Cholesterol performance specification

- Laboratory diagnosis
- Chronic disease management
- Population “health checks”

Total Error ± 8%

16%

# Importance of Performance Specifications



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# Design of IQC

Define the quality required of the assay

**Determine the quality the assay can provide**

Identify candidate IQC strategy

Select appropriate QC rules

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# Design of IQC

**Define the quality required of the assay**

- This is usually the total allowable error $TE_a$ or ATE
- **$TE_a$** determined from Milan Models 1 -3.

**Determine the quality the assay can provide**

- **Total Analytical Error** (TAE) can be estimated from replication and comparison of methods.
- **Precision**, in the form of a **CV,** can be estimated from replication.
- **Bias** can be estimated from EQA or comparison of methods.

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# EP21-Ed2


**EP21-Ed2 | *Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures, 2nd Edition***

This guideline provides manufacturers and end users with an understanding of concepts related to total analytical error (TAE) for quantitative measurement procedures. An experimental protocol and data analysis method are provided to estimate TAE based upon a comparison of methods experiment with patient specimens, and to assess it relative to a pre-established goal for clinical acceptability.

**Chairholder:** J. Rex Astles, PhD, FACB, DABCC
**Organization:** Centers for Disease Control and Prevention
**Date of Publication:** July 12, 2016
**ISBN Number:** 1-56238-940-8
**Edition:** Second Edition
**Pages:** 68

TAE is defined as the percentage (usually 95%) of the analytical error for a measurement procedure.

<u>Example Protocol</u>

125 patient samples assayed singly on candidate method and compared with comparative method assayed in in duplicate over 10 days (10-15 samples per day). Undertake non parametric analysis of the differences between the methods calculating the 2.5$^{th}$ centile (low Limit) and 97.5$^{th}$ centile (High limit). Compare with the ATE.

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# Sigma Metrics

Simple measure of the quality of the assay can be obtained using Six sigma approach.

Sigma metric = (TEa – bias (observed)/CV (observed)

- Can identify assays that require improvement
- Can be used to determine optimal QC rules
- Can provide guidance on the frequency of IQC

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# How to Calculate Sigma

Calculate the **Sigma metric** for the testing process, as follows:

**Sigma metric = ($TE_a$ – Bias)/CV**

e.g., for testing process assume $TE_a$ = 10.0%

Effect of bias

- if CV = 2.0% and Bias = 0.0%, then Sigma = 5.0 [10.0-0)/2]
- if CV = 2.0% and Bias = 1.0%, then Sigma = 4.5 [(10.0-1)/2]
- if CV = 2.0% and Bias = 2.0%, then Sigma = 4.0 [10.0-2)/2]
  if CV = 2.0% and Bias = 3.0%, then Sigma = 3.5 [10.0-3)/2]

Effect of Imprecision

- if CV = 1.0% and Bias = 2.0%, then Sigma = 8.0 [10.0-2)/1]
  if CV = 1.5% and Bias = 2.0%, then Sigma = 5.3 [10.0-2)/1.5]
  If CV = 3.0% and Bias = 2.0%, then Sigma = 2.7 [10.0-2)/3]

Use the calculated Sigma metric to determine the appropriate QC, with the aid of available QC planning tools.

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# Calculating Sigma

| Analyte | Lab CV% | TEa % | Bias % | Sigma = (TE-Bias)/CV |
|---|---|---|---|---|
| Na | 0.72 | 2.25 | -0.73 | 2.11 |
| K | 0.67 | 3.7 | -0.26 | 5.11 |
| Cl | 0.97 | 3.4 | 2.43 | 1.01 |
| Bicarb | 3.27 | 10.2 | 14.18 | -1.22 |
| Urea | 2.33 | 10 | 4.71 | 2.27 |
| Creatinine | 1.21 | 8.42 | -13.29 | -4.02 |
| Glucose | 0.82 | 8 | -1.57 | 7.85 |
| Calcium | 1.63 | 4.88 | -3.61 | 0.78 |
| Albumin | 1.08 | 8 | -4.43 | 3.30 |
| Mg | 1.85 | 10 | 1.20 | 4.76 |
| Urate | 0.97 | 12 | -1.97 | 10.31 |
| CK | 1.18 | 15.4 | -16.06 | -0.56 |
| Chol | 2.47 | 8.5 | -1.77 | 2.72 |
| Trig | 1.54 | 27.8 | 11.28 | 10.70 |
| HDL | 1.26 | 16 | -9.45 | 5.22 |

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# Design of IQC

Define the quality required of the assay

Determine the quality the assay can provide

**Identify candidate IQC strategy**

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# Identify candidate IQC strategies

- the control materials used,
- the number of control samples analyzed,
- the location of these control samples in an analytical run,
- the **quality control rules**

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# The control material

**Selection of material**

- Is it commutable? – pooled patient samples is best
- Is it stable ? – commercial QC with long shelf life preferably from 3rd party.

**Procedure for running IQC**

- Is it treated as patient sample ? i.e. pre-treatment or dilution
- What is the frequency?

**Concentration and number of levels**

- Does it cover the analytical/ pathological range?
- Do you cover the critical “cut points”? E.g. Tnt @ 11ug/L

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# Basic Principles

**Assigning the target**

- Determine the expected distribution of control values.
- "In house" – replicate analysis when the method is well controlled i.e. 20 data points over 20 separate events.
- Should be reviewed over longer period.

**Assigning the limits**

- "In house" - from replicate study as above
- calculate limits.

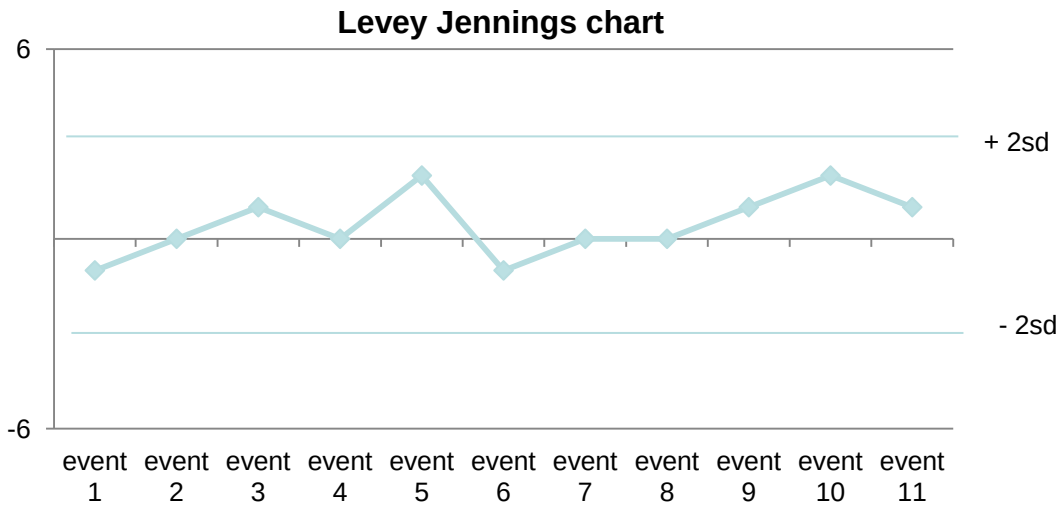
**Plotting the data**

- plot control values versus time on chart (Levey-Jennings)
  - 95% within 2SD
  - 99.7% within 3SD

**Identifying outliers**

- Identify unexpected values - use rules

# Levey-Jennings




| | Result | Diff |
|---|---|---|
| event 1 | 5 | -1 |
| event 2 | 6 | 0 |
| event 3 | 7 | 1 |
| event 4 | 6 | 0 |
| event 5 | 8 | 2 |
| event 6 | 5 | -1 |
| event 7 | 6 | 0 |
| event 8 | 6 | 0 |
| event 9 | 7 | 1 |
| event 10 | 8 | 2 |
| event 11 | 7 | 1 |

Mean = 6

SD = 1.5

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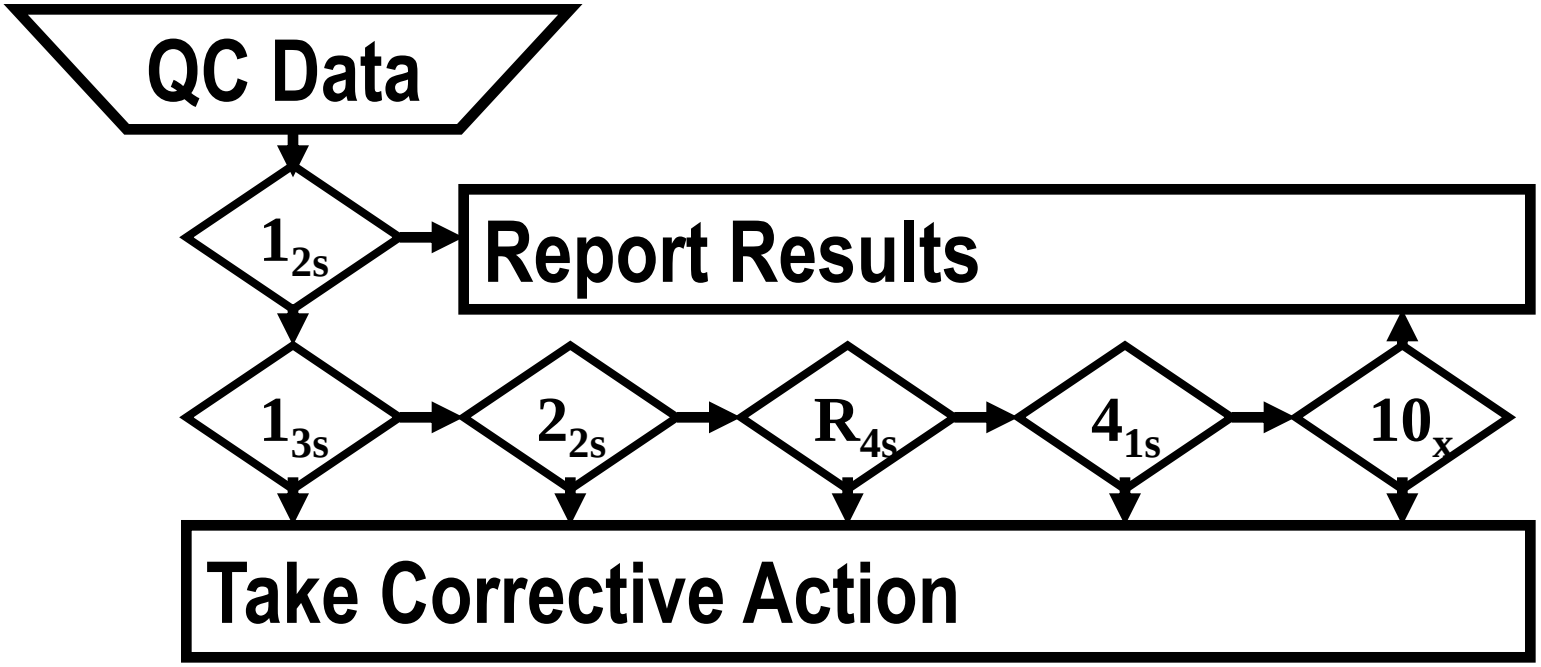
# “Westgard rules”




James O Westgard Internal quality control: planning and implementation strategies *Ann Clin Biochem* 2003; 40: 593–611

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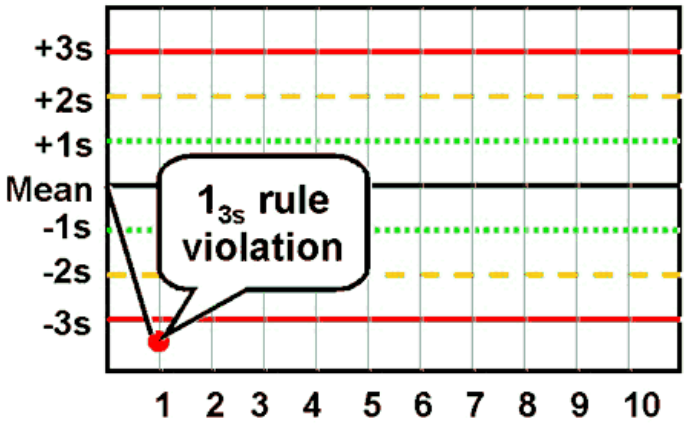
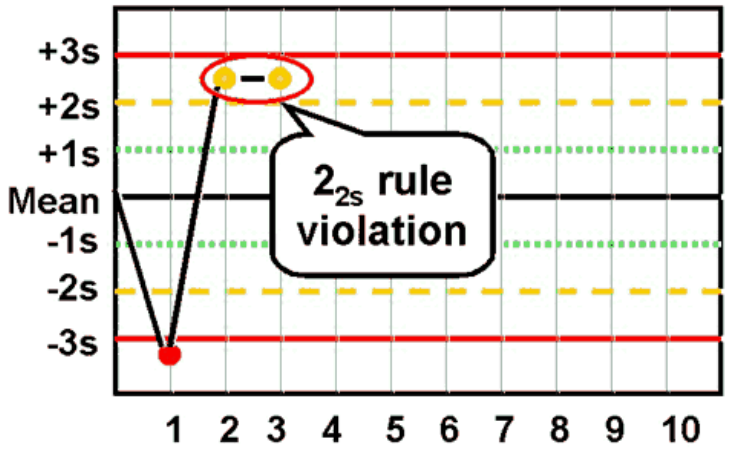
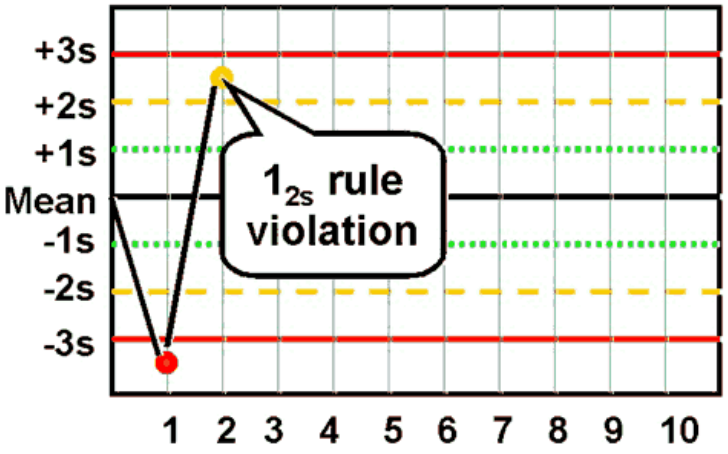
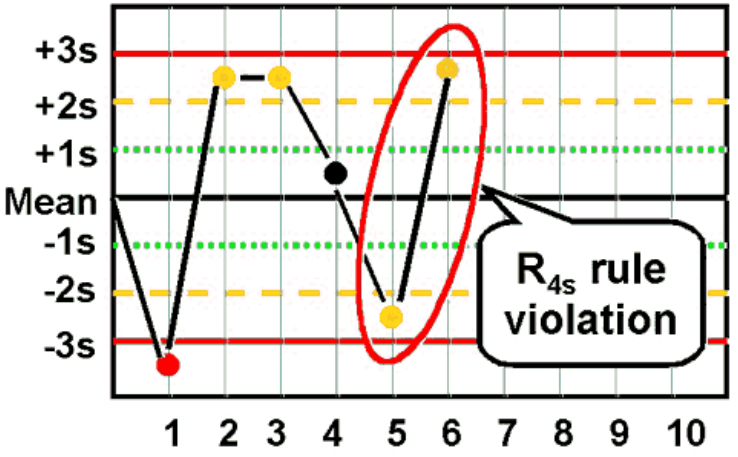
# Control rules




**Generally used for 2 or 4 controls per run.**

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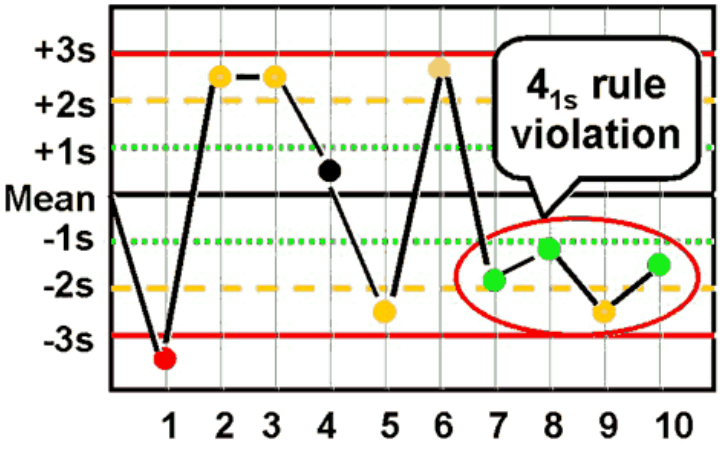


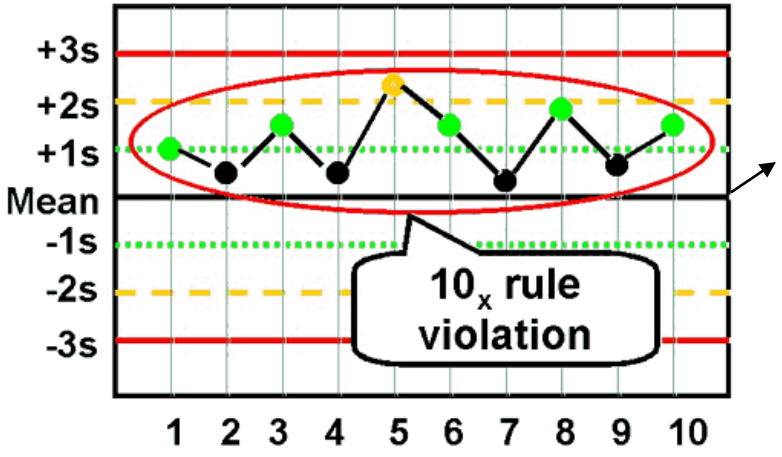


Also use 8 or 12

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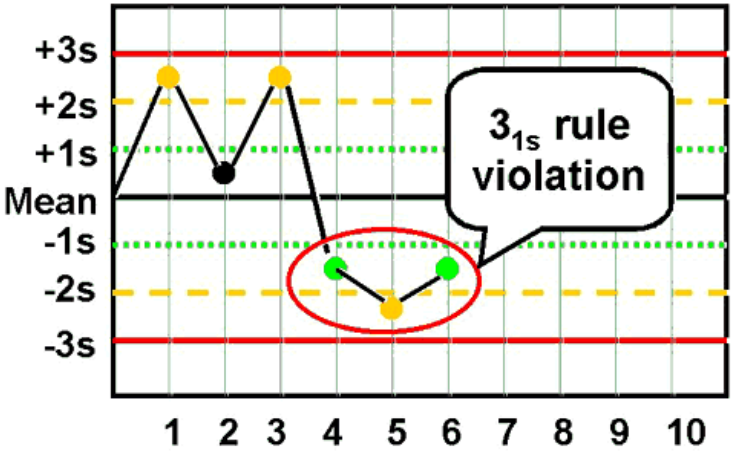


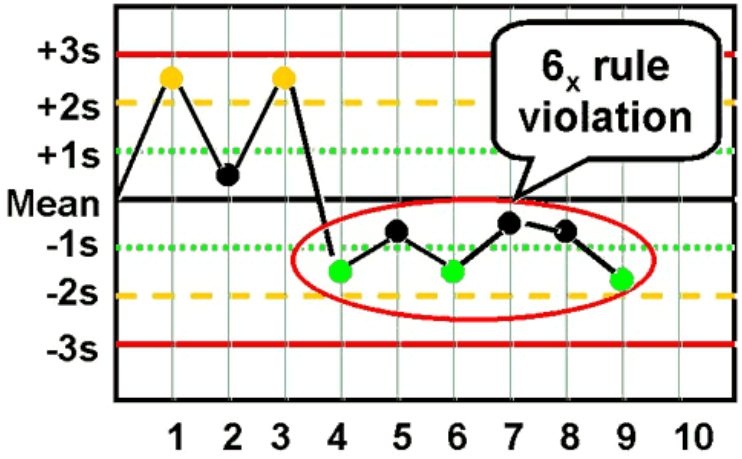


For 3 controls

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# Design of IQC

Define the quality required of the assay

Determine the quality the assay can provide

Identify candidate IQC strategy

**Select appropriate QC rules**

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# QC Tools to determine appropriate QC rules

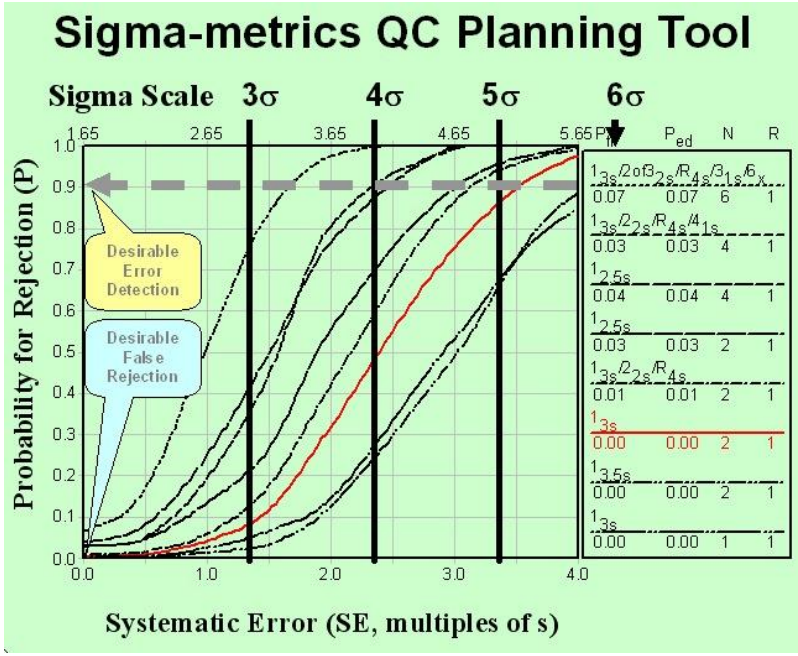
The tools include **power function graphs** , **critical-error graphs** , **QC Selection Grids**, charts of operating specifications (**OPSpecs chart**), and the **QC Validator** and **EZ Rules 3** computer programs .

– Simplest is to use:

**Westgard Sigma Rules™**

# Power function graphs

- $P_{fr}$ probability of false rejection should be close to zero (max 5%, 1% desirable)
- $P_{ed}$ probability for error detection should be close to 1.00 (desirable 0.90 – 90% chance of detecting a critical systematic shift.)
- Determine critical systematic shift,
- Calculate Sigma metric



# Power function graphs

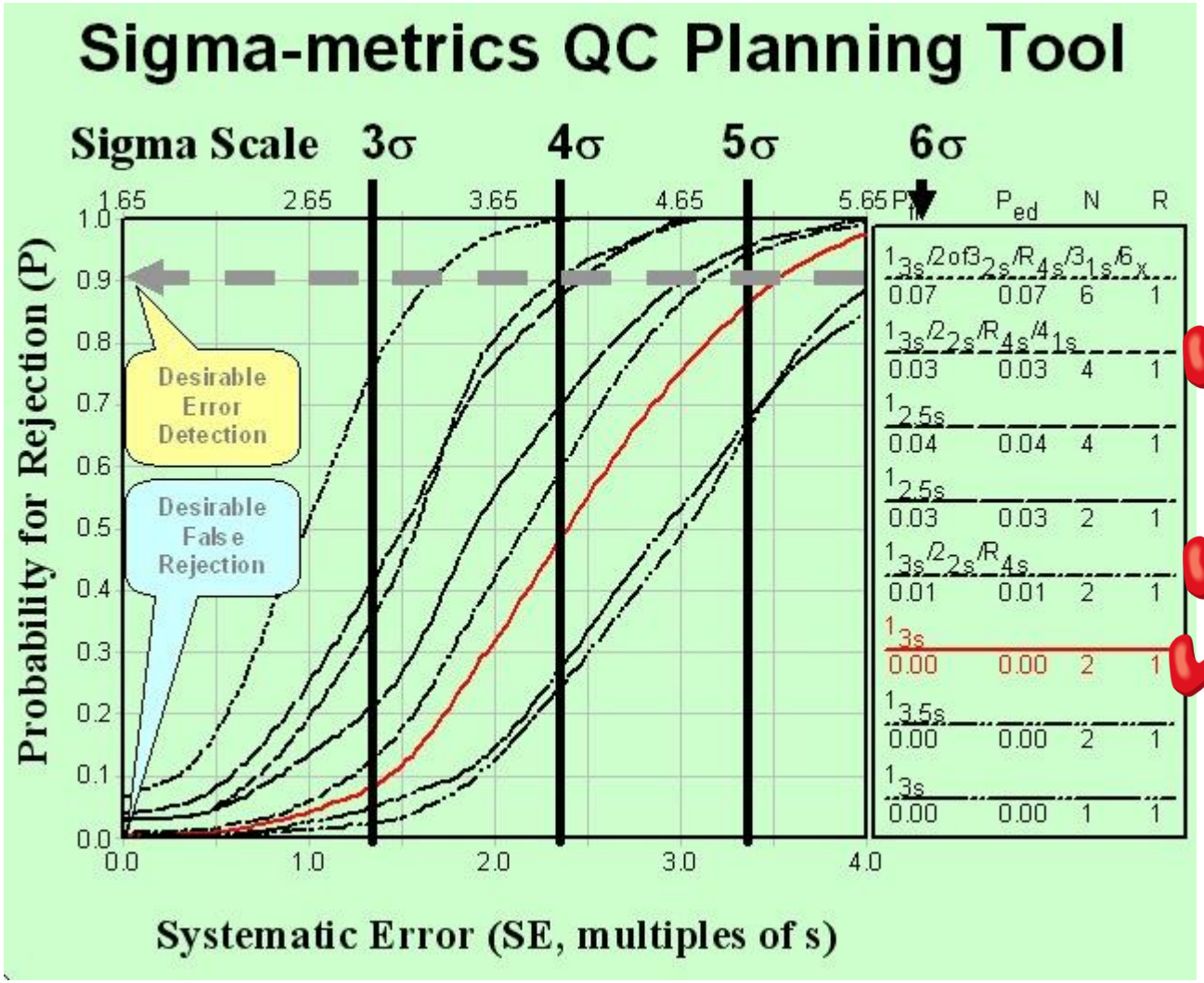
Rule complexity

Multi rule

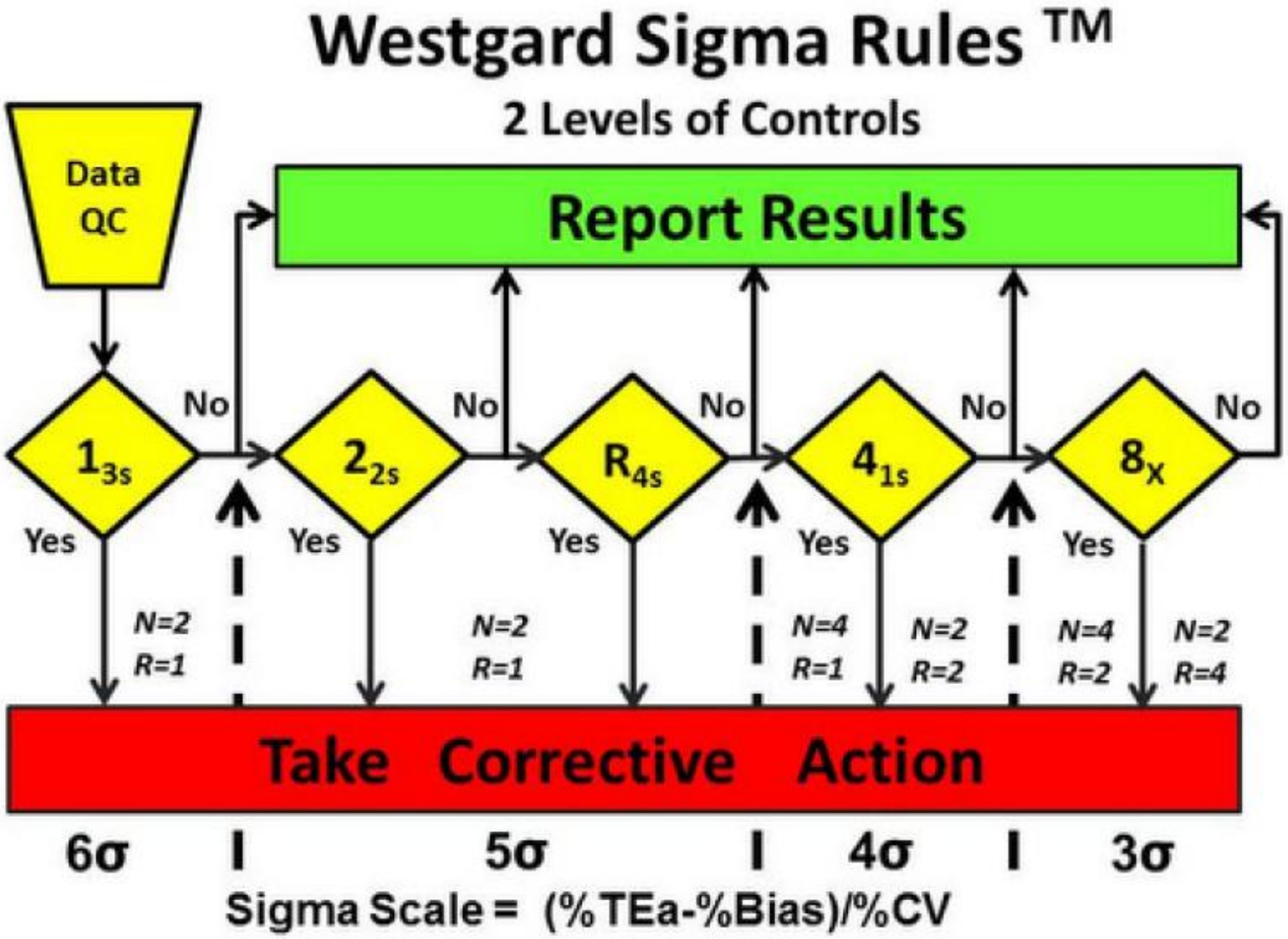
4σ a multirule with n=4

5σ $1_{3s}/2_{2s}/R_{4s}$ with n=2

6σ $1_{3s}$ rule with n=2




1 3s 1 control




The dashed vertical lines that come up from the Sigma Scale show which rules should be applied based on the sigma quality determined in your laboratory. For example:
6-sigma quality requires only a single control rule, $1_{3s}$, with 2 control measurements in each run one on each level of control). The notation N=2 R=1 indicates that 2 control measurements are needed in a single run.

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# Selecting the Rule

| Analyte | Lab CV% | TEa % | Bias % | Sigma = (TE-Bias)/CV | Rule | Frequency |
|---|---|---|---|---|---|---|
| Na | 0.72 | 2.25 | -0.73 | 2.11 | Max Multirules | 3 levels 3 x daily |
| K | 0.67 | 3.7 | -0.26 | 5.11 | $1_{3s}/R_{4s}/2_{2s}$ | 2 levels 1 x daily |
| Cl | 0.97 | 3.4 | 2.43 | 1.01 | Max Multirules | 3 levels 3 x daily |
| Bicarb | 3.27 | 10.2 | 14.18 | -1.22 | Max Multirules | 3 levels 3 x daily |
| Urea | 2.33 | 10 | 4.71 | 2.27 | Max Multirules | 3 levels 3 x daily |
| Creatinine | 1.21 | 8.42 | -13.29 | -4.02 | Max Multirules | 3 levels 3 x daily |
| Glucose | 0.82 | 8 | -1.57 | 7.85 | $1_{3s}$ | 1 level 1 x daily |
| Calcium | 1.63 | 4.88 | -3.61 | 0.78 | Max Multirules | 3 levels 3 x daily |
| Albumin | 1.08 | 8 | -4.43 | 3.30 | $1_{3s}/2_{2s}/R_{4s}/4_{1s}/8x$ | 3 levels 2 x daily |
| Mg | 1.85 | 10 | 1.20 | 4.76 | $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ | 2 levels 2 x daily |
| Urate | 0.97 | 12 | -1.97 | 10.31 | $1_{3s}$ | 1 level 1 x daily |
| CK | 1.18 | 15.4 | -16.06 | -0.56 | Max Multirules | 3 levels 3 x daily |
| Chol | 2.47 | 8.5 | -1.77 | 2.72 | Max Multirules | 3 levels 3 x daily |
| Trig | 1.54 | 27.8 | 11.28 | 10.70 | $1_{3s}$ | 1 level 1 x daily |
| HDL | 1.26 | 16 | -9.45 | 5.22 | $1_{3s}/R_{4s}/2_{2s}$ | 2 levels 1 x daily |

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# Frequency of IQC

**Table 2** Summary of recommendations provided by the 2010 convocation of experts on laboratory quality for the use of six sigma to initiate internal quality control (IQC) design.[16]

| Sigma score | Performance | IQC design[16] |
|---|---|---|
| >6σ | Excellent | Once per day<br>One level per day (alternating levels)<br>$1_{3.5s}$ rule |
| 4σ–6σ | Suited to purpose | Once per day<br>Two levels per day<br>Single IQC rule |
| 3σ–4σ | Poor performers | Twice per day<br>Two levels of IQC per day<br>Multirule system |
| <3σ | Problematic | Three times a day<br>Three levels<br>Consider testing in duplicate<br>Maximum IQC rules |

Risk based approach.
Combining Sigma and risk i.e. No of samples processed, reagent stability, impact of incorrect result etc.

Clin.Chem Lab Med 2011; 49:793-802

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# Implementation strategies

- Don’t use 2sd control limits – $P_{fr}$ = 9% (n=2)
- Don’t use the same control rules for all tests
- Select IQC based on quality required for the test and the precision and accuracy of the method
- Minimize false rejections in order to maximise response to real problems
- Build in error detection necessary to detect medically important errors.
- Complement IQC with other QA and QI.