The Association for Clinical Biochemistry & Laboratory Medicine

Better Science, Better Testing, Better Care

IQC monitoring in laboratory networks

Background and instructions for use

Modern Laboratories continue to produce large quantities of internal quality control data (IQC) despite the trend to reduce the numbers of IQC measurements made per analyte on measuring systems that are perceived to be more stable than previous generations of instruments. Laboratories are familiar with the statistical calculations and graphical presentations used to evaluate analytical performance. The evaluation is fairly simple if single measuring systems are considered but becomes complicated when several instruments are run in parallel and incoming samples may be randomly distributed to several instruments or when several laboratories collaborate and samples may be sent to any of the collaborating laboratories. As a result, the combined uncertainty of measurements made across several instruments is bound to be greater than that of measurements made on a single, dedicated instrument. Consequently, if there were a choice of mode of operation, optimal analytical performance is more likely to be obtained if samples from each individual patient were always allocated to the same analyzer. Because this is impractical, the quality system must take into account the complexity of sample distribution and analysis.

The present program offers a tool to assess the performance of one to twelve collaborating instruments. Although it can be used as stand-alone it is designed to be part of a package which facilitates the import of data from the instruments' data manager or any other data storage system that can produce an export file containing IQC results from multiple instruments. The full package is capable of producing summary reports over time.

Comparisons, by definition, require input of data from at least two groups but the performance of a single unit will be critical and central. Regulations and convention require that at least two concentrations of control material is simultaneously monitored. The input data and calculations are therefore presented in two identical sections.

Overview

All cells that are open for input are blue and cells in which results are presented are red.

The program accommodates monitoring of twelve measuring systems and up to 500 measurements of two samples i.e. in total 12,000 observations.

It should be noted that the Excel function "Cut and Paste" usually interferes with all depending formulas and calculations. "Cut and Paste" must therefore not be used. Functions "Copy" and "Delete" do not have that effect and are recommended.

The program has been developed in Excel 2010 and tested for compliance with older versions, including Excel 2003.

Precision sheet

Data input

The name of the component should be entered in cell C36 and O36. It is recommended that the name is limited to 20 characters. The results of measurements can be entered, modified or deleted at any time. The package will populate the sheet correctly and update relevant information. Missing data will not be considered. All calculations are carried out in real time.

	Instrument	FER : RANDOXIA2 - 1288EC									Non-signficant difference between instruments		FER : RANDOXIA3 - 1289EC									Non-signficant difference between instruments	
									Instrument															
	Instrument	Centaur 1	Centaur2	Homer										Centaur 1	Centaur 2	Homer								
Replicates	1	87.66	101.79	91.51										302.37	339.66	293.99								
	2	93.53	94.29	89.45										312.11	290.12	300.22								
	3	96.00	87.34	95.87										312.94	310.50	301.12								
	4	91.85	89.07	88.09										303.57	289.88	294.34								
	5	87.71	86.35	90.59										302.27	278.87	303.88								
	6	78.51	88.26	85.49										280.42	272.13	289.48								
	7	88.84	94.06	89.03										306.83	302.83	303.41								
	8	89.81	93.83	89.81										309.54	293.23	320.45								
	9	80.22	90.71	90.07										288.28	297.01	287.20								
	10	91.84	87.22	86.13										286.17	271.02	285.02								

Figure 1. Data input fields. The name of the reference material (row 36) must be entered before any calculations will be carried out. The reference material with the lower concentration is represented in the left part and the names of the measuring systems entered will be copied to the part for the high concentration material.

The maximum (red) and minimum (green) results are identified in each column and the actual values can be found in rows 539-540. Clearly there can be more than one maximum or minimum result in each column. Rules for detecting outliers are not included in the spreadsheet.

An applicable ID, e.g. code, lab, trust, period, or operator should be entered in row 36 as a prerequisite for the program to perform calculations. The row 38 is meant for defining the instrument or measuring system. The information entered in the first 12 cells of row 38 is copied to the second 12, representing the second concentration. Unless a character is entered above a column with data, it will not be included in the calculations.
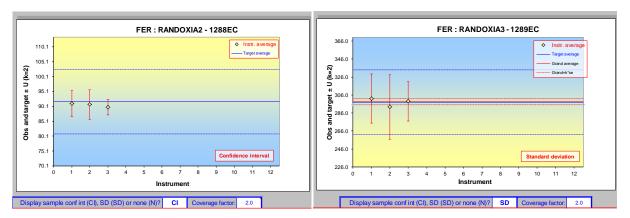

Figure 2. Average and distribution of observations of the two reference materials. Each measuring system is represented on the X-Axis. Target values and allowable variation or, optionally, the grand average and distribution of all observations are shown.

Graphs and descriptive statistics (rows 26 to 35)

The graphs show the average (arithmetical mean) of the reported data (yellow diamond) and (optionally) the standard deviation (Figure 1, left panel) or standard error of the mean (confidence interval) as an error bar and, optionally the grand average and its standard error (Figure 2, right panel).as horizontal red lines. If cells C22-C23 and Z22-Z23, for the two control materials, respectively, are left blank (default) the grand average and standard deviation will be calculated from all observations. Alternatively, any target values may be entered in these cells.

The coverage factor is set to 2 by default but can be changed. This setting will be used for all calculated quantities in the sheet except the interpretation (row 35) which are under the control of the coverage factor in cell N22 and Y22, respectively.

The *p*-values reported under the graphs are based on the difference between the calculated mean and the target value estimated by *t*-statistics.

		Display	Y		Acceptable within		SD	Calc SD	%CV	Coverage factor:		1.0	Display	Y		Acceptable within		SD	Calc SD	%CV	Coverage factor:		2.0	
Target:		grand average			instr. uncertainty:		6.00						grand average			instr. uncertainty:			41.83	14.00				
u(target):																								
Difference																								
Instrument p-value:																								
Instrument average:		91.06	90.73	89.78	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	302.04	292.76	299.12	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
Uncertainty (k=2)±:		10.529	9.001	6.341										27.301	35.860	21.882								
Number of obs:		23	13	24										22	13	24								
Rel uncertainty (k=2) %:		11.56%	9.92%	7.06%										9.04%	12.25%	7.32%								
Instrument median:		91.73	89.07	90.13										302.97	289.88	300.67								
Conf. Int. (95 %)±:		4.39	4.99	2.59										11.64	19.89	8.93								
97.5 percentile		98.64	98.70	94.80										323.00	327.65	319.12								
2.5 percentile		79.60	86.19	84.32										281.94	271.48	283.08								
Min Sign Diff (MD)		14.59	12.47	8.79										37.84	49.70	30.33								
Interpretation (lab)		Accept	Accept	Accept										Accept	Accept	Accept								

Figure 3. Descriptive statistics. These tables are continuously updated as results are entered. The data is used as a basis in all calculations. In the panel, the acceptance of the measuring system is evaluated in relation to the defined limits in row 23.

The scales of the axes of the graph are calculated automatically by default. However, this may not be an optimal choice and the operator is encouraged to modify the Y-axis using the regular EXCEL procedure.

The "minimal significant difference" is the minimal significant difference between two consecutive measurements, based on the continuously modified standard deviation (uncertainty) and a level of confidence of 95 %. Note that this does not take biological variation into account.

Analysis of variance components

The size of the selected dataset is shown at the top of the table. It is assumed that a minimum of 30 samples from each measuring system will be included in an evaluation but calculations will always be carried out regardless of the number of results in the data set. Note that the between instrument variation may be considerably underestimated if less than four instruments are included.

The within- between- and combined variations are calculated using "analysis of variance components" based on the principles of ANOVA, one-way analysis of variance.

This assumes that the materials used in the instruments/laboratories are the same during the study period. The within- (repeatability) and between series standard deviations and coefficients of variation are reported in a table to the right of the graphs (figure 4). The

operator can chose which results will be included in the ANOVA by selecting the proper series in the Levy-Jennings sheet, row 2.

Component:	FER : RANDOX IA2 1288 EC	FER : RANDOX IA3 1289 EC
Number of observations:	60	59
Grand average:	90.48	298.81
SEM:	0.56	1.83
Target nominal:		
SEM Target:		
BIAS:	#VALUE!	#VALUE!
u(bias):		
Within instr uncertainty:	4.361	13.7
Between instr uncertatinty:		2.9
Within network: u(comb):	4.36	14.0
Relative within instr uncert %:	4.8	4.6
Relative between instr uncertainty %:		1.0
Within network rel. uncertainty; u(comb) %:	4.8	4.69
Min sign diff across inst/lab (MD):	12.1	38.9
F:	0.53	1.88
p-value:	0.59	0.16
Fcrit:	3.16	3.16
Interpretation (statistical):	Non-sign	Non-sign
Acceptable network uncertainty		
Youden plot	State k:	1
Within network 'u':		
Calculated SD:	13.57	44.82
Relativ within network 'u' (%):	15.00	15.00
Interpretation (network):	Accept	Accept

Figure 4. Table of analysis of variance components and evaluation of the findings. The statistical evaluation is transferred to above the input columns. The network can also specify "clinically oriented acceptance limits. These are available to define parameters in the Youden plot

The between instrument/laboratory variation may be smaller than the within instrument/laboratory variation.

Mathematically this would require that the combined uncertainty only includes the within series variation. In such cases the between series variation is left blank.

Instrument :		
Average(row26):	91.06	302.04
Uncertainty (row 27):	10.53	27.30
Number of obs (row 28):	23	22
df:	27	
t-value:	67.83	
P-value (2-tail):	1.058E-31	
Crit t-value:	2.05	
Interpretation:	Sign diff	

Figure 5. To further identify differences between measuring systems calculation of Students's t-value is available. The three first rows of a suspect series of results is copied and pasted (as values) in the blue cells right of the analysis of variance components table.

The F-values displayed at the end of the table indicate if there is a significant difference between any of the participating measuring systems. The outcome is interpreted and reported in the table and in row 24 above the input area. The instrument or instruments which cause the alarm cannot be directly identified. However, visual inspection of the data and the graphs may alert the user to which instrument may be suspected. The operator may compare the averages of the IQC results from any 2 instruments using t-statistics. Calculation of t-statistics is available in cells AI15 to AJ18. (Figure 5).To perform a t-test copy

the average, uncertainty and the number of suspect observations and paste the **values** in cell AI15 and AJ15, respectively. **NB**. It is essential that the values, not the formulas, are pasted in the appropriate cells.

The "network" may define a clinically important uncertainty in cells AE27 and AF27 (if available in relative terms in AE29 and AF29). The outcome is evaluated in cells AE30 and AF 30. **NB**. The evaluation is not reported anywhere else.

Levy-Jennings plot

These are straight forward, continuous, graphs of all the observations. Since they may become rather complex there are options to simplify the graph. Thus, the observations that are wanted can be selected by changing the X-axis to include the numbers of interest. Further, certain measuring systems can be excluded by changing the options in the two rows above the graphs; the upper row represents the low concentration material.

The choice will have an impact on which measuring systems will be included in the calculations.

Calculated averages and/or set target values can optionally be included in the graphs. The set values are imported from the Precision sheet

Youden plot

A Youden plot is a graphical means to evaluate a combination of two measured control materials. The results are plotted pairwise in a graph which displays the median (average) of the low and high concentration results. This is known as the "Manhattan median (average)". A vertical and a horizontal line are drawn through the median (average). A rectangle (Manhattan rectangle) is defined by allowable variations in the quantities plotted along the X-axis and Y-axis. The coordinates of the rectangle are automatically set from the intra-laboratory claims defined in the "Precision" sheet but can optionally be defined in cells M9 to N11.
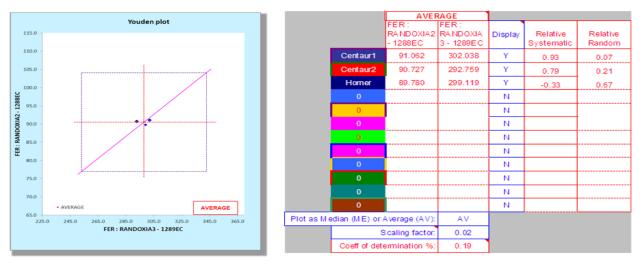

Figure 6. The Youden plot. The graph shows the distribution of the averages transferred from the descriptive statistics of the "Precision" sheet. There is an option to rather display the medians. The "Manhattan rectangle" can be defined either by default or in put in cells M9 to N11 in the present sheet. A relative distribution of the total deviation between systematic and random sources for each measuring system is shown. These numbers are expressed as Z-scores.

Results that are distant from the median along the diagonal indicate a systematic variation; those perpendicularly distant from the diagonal, a random variation.

The default of the display options (column N) is "N". It is important to make sure that if the input of results (columns L and M) is incomplete, then the display option must be "N".

The automatic scaling of EXCEL sometimes causes problems. Therefore the operator should manually optimize the scales and it is also possible to modify how far the vertical, horizontal and diagonal lines reach from the center.

If the scales and units are the same for both sets of results the random and systematic contributions of the deviation can be calculated. This is not possible with the two measured concentrations which by definition must be different but can be achieved if the average value of each measuring system is expressed in Z-values, i.e. the difference of the average from the "gross average" divided by the combined uncertainty. The relative distribution of the systematic and random variation is given for each measuring system in column O and P.