13th International Scientific Meeting

THE INTERNAL QUALITY CONTROL IN THE TRACEABILITY ERA

MILANO, ITALY
November 28th, 2019

IQC: is it possible to obtain all the needed informatio using only one type of material?

Ferruccio Ceriotti

Clinical Laboratory, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

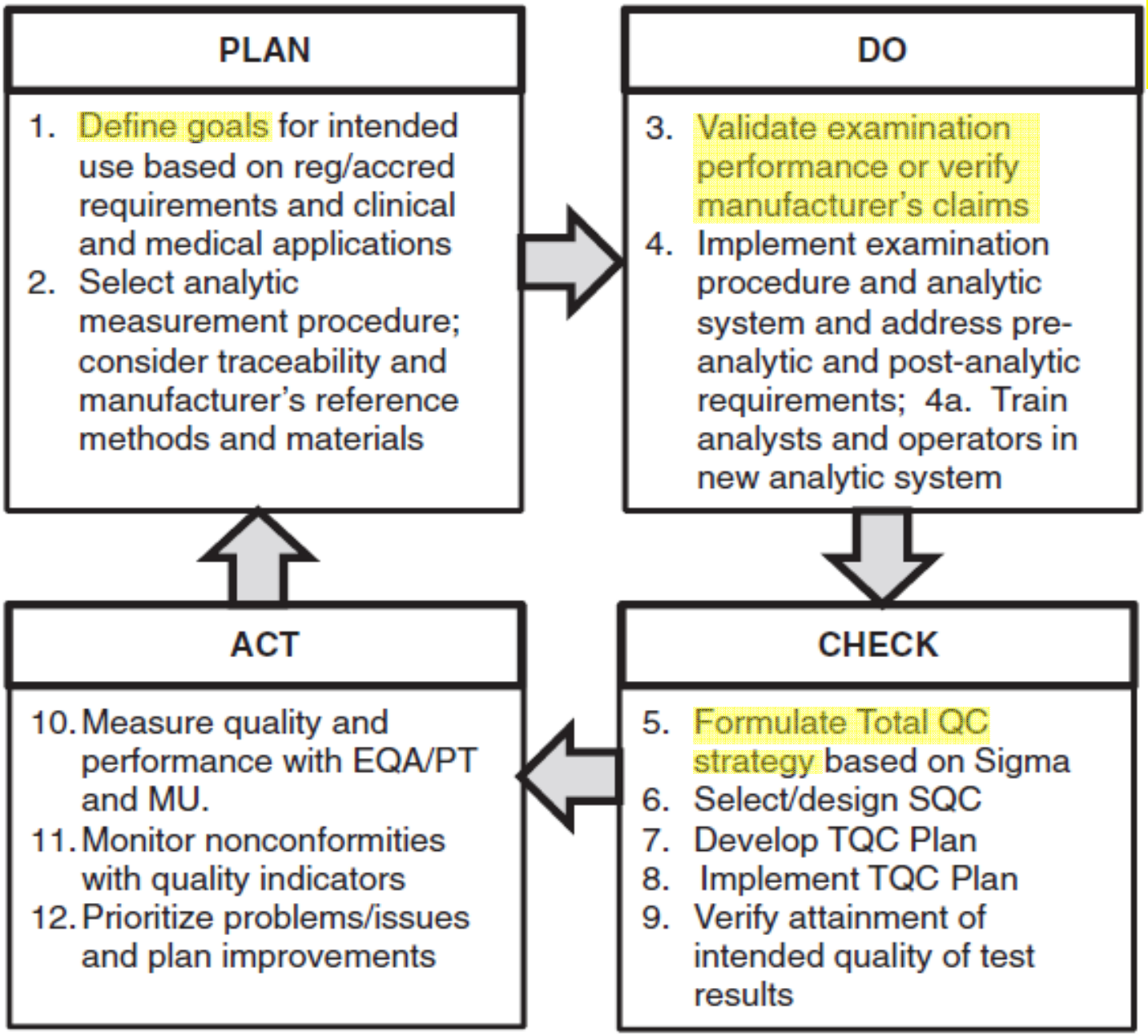
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Sistema Socio Sanitario Regione Lombardia

Planning of Internal Quality Control (IQC)

1. Define the requested quality level $\Rightarrow$ analytical performance specifications (APS)
2. Assess the typical performances of the analytical method
   - Precision
   - Trueness
3. Identify the strategies: organization and rules
4. Implement the appropriate IQC.

Implementing a Six Sigma quality system



Westgard JO, Westgard S
Clin Biochem 2016;53:35-

Implementing a Six Sigma quality system

"Method validation and acceptable method performance are prerequisite to the design and implementation of SQC procedures. ***If performance is NOT acceptable under stable operating conditions, no amount of QC can change or improve that performance****. QC can only monitor performance, and when properly designed, alert analysts to the presence of additional errors that occur because of unstable performance."*

Westgard JO, Westgard S. Ann Clin Biochem 2016;53:35-50

IQC

- **Main aim**: to provide alarms when the analytical system is deviating from the typical performances thus increasing the risk of providing erroneous results to the patients.
- Other aims: to provide elements to calculate measurement uncertainty, to identify trends and to monitor long-term stability

Types of control materials

1. Manufacturer related materials (with system assigned target values)
2. Third party materials (with or without system assigned target values)
3. In house prepared pools

- When speaking about an IQC program based on a single type of material, types 2 and 3 are considered, type 1 is typically part of a 2 components IQC program

Typical performances

- Two components:
  - **Imprecision** = Stability of the analytical system
  - **Trueness** = bias from the reference = if the analytical system is traceable to the reference = ability to obtain the performances defined by the manufacturer for the analytical system

How to control both?

- **Imprecision**: short term easy; intermediate: the control material has to react to changes in reagent lots or environmental conditions in a way similar to the real patient samples
- **Trueness**: we need an alternative reference
  - Experiments performed for method verification at the implementation of the method
    - Setting of the traceability references
  - Participation in an interlaboratory program to compare with peers
    - Daily checking of the bias from the group

Initial set up

- Possible approaches
  - Direct comparison with a reference method on patients' samples
  - Commutable reference materials with reference method assigned values
  - **Control materials provided by the manufacturer with values assigned for the specific analytical system**

CLSI EP15-A3:2014 User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition

- **Chapter 3 Estimation of Bias by Testing Materials With Known Concentrations**
- 5 x 5 precision experiment
- Calculation of the bias from the Target Value
  - Calculation of the “verification interval” depending on the imprecision of the method and the uncertainty of the TV
  - If the grand mean obtained with the precision experiment is within the verification interval the method can be considered insignificantly biased

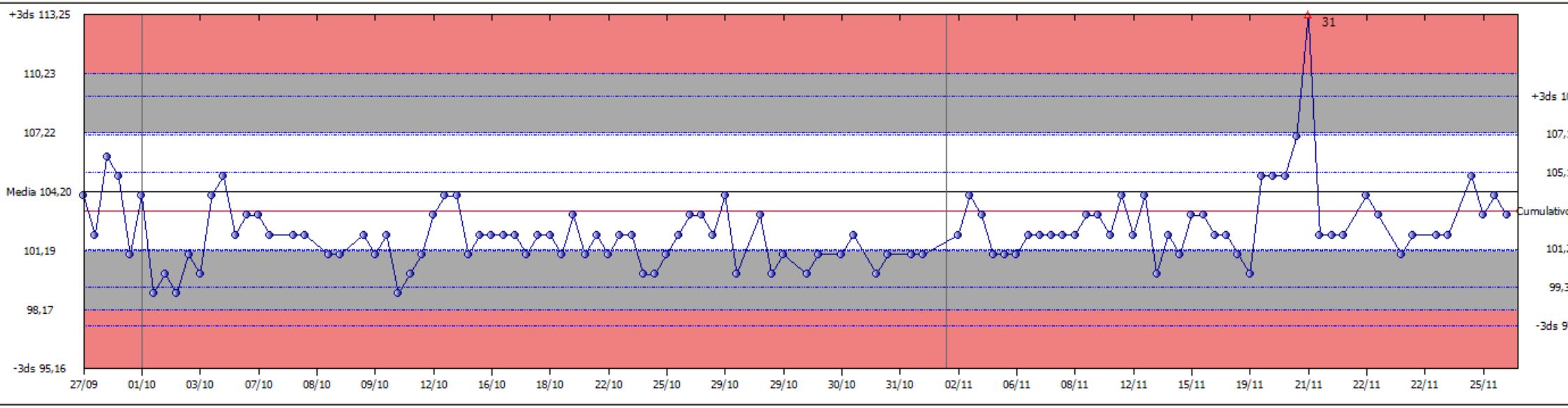
Note

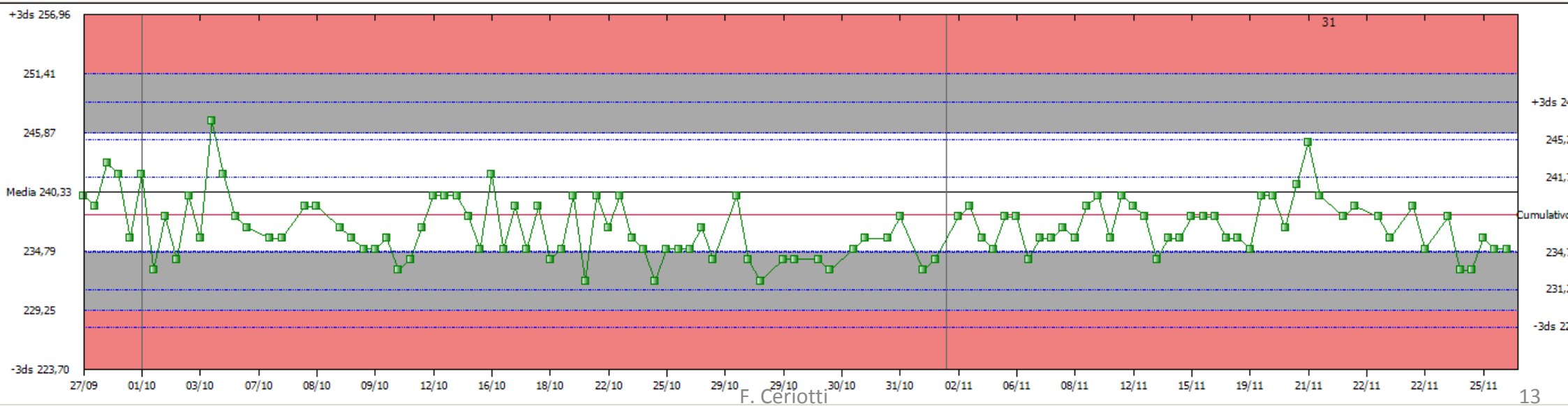
- When working with a commercial QC material supplied with a TV for which the standard error cannot be estimated, set seRM = 0. In effect, this scenario defaults to assuming that the material's concentration is known without any uncertainty. Accordingly, the verification interval will be narrower, and the probability of the user's average result falling outside that interval will be higher than if the TV's uncertainty were known.

Implementation of an Interlaboratory IQC

- Select the correct peer group
- Define the QC rules to apply (based on Sigma metric)
- Define the type of QC charts to be used
- If you want a daily check of the trueness you can have QC charts that identify the performances of the peer group

te di Levey-Jennings Periodo: 27/09/2019 - 26/11/2019
oratorio: 156085, **Cobas 1a NEW**
to: 31880, Unassayed Chemistry, 31/05/2020
esterolo, Totale, Colesterolo ossidasi, esterasi, perossidasi, mg/dL
dia cum/DS/CV: [1] 103,22/1,95/1,89, [2] 238,22/3,51/1,47
ortato in grafico rispetto a: Gruppo di consenso, Omogeneo, Cumulativo, Media/DS/CV: [1] 104,20/3,02/2,89, [2] 240,33/5,54/2,31
Test: calibrate

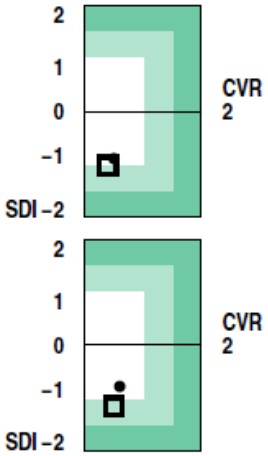




Total Cholesterol

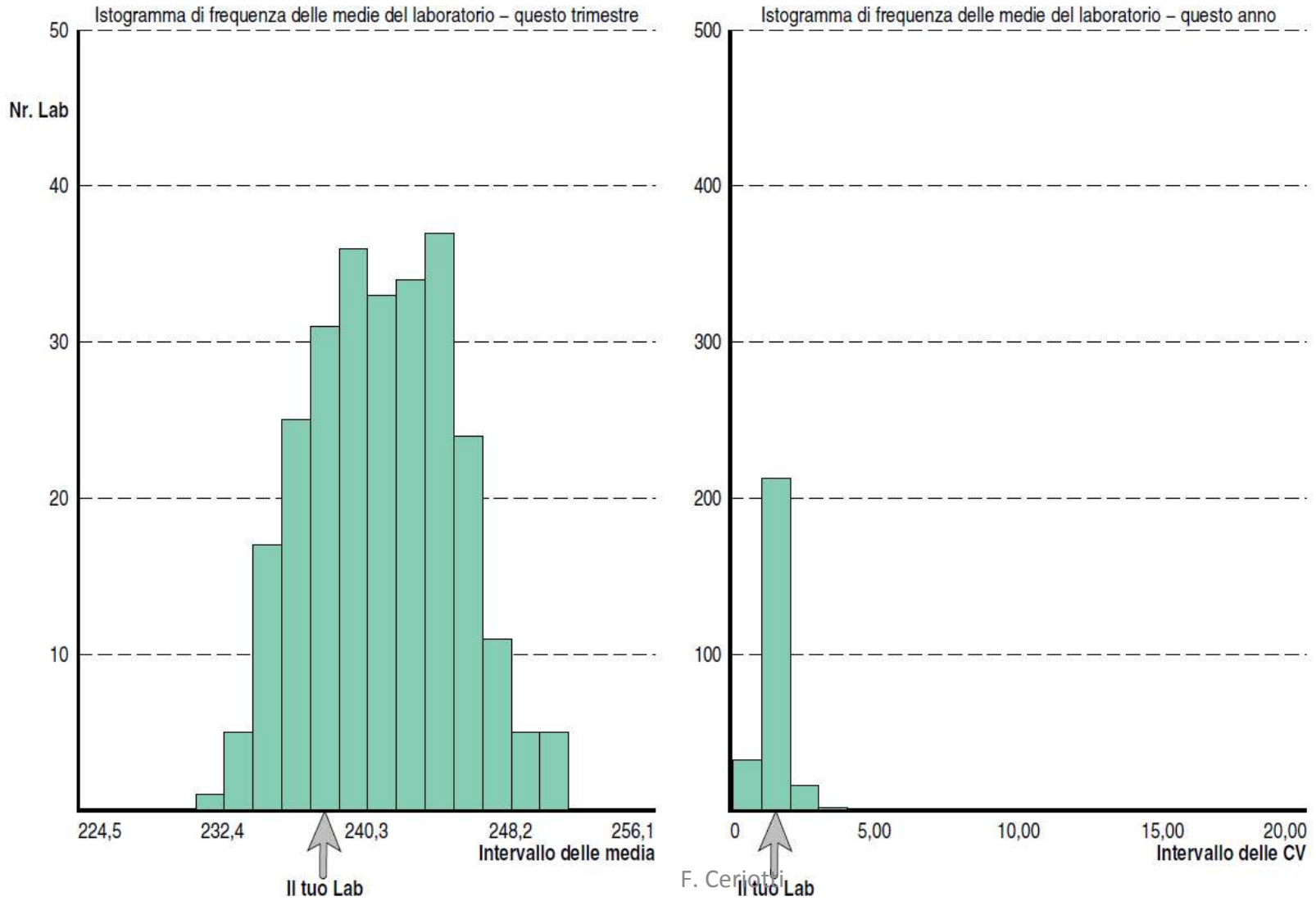
erolo, Totale **Colesterolo ossidasi, esterasi, perossidasi** mg/dL

	Livello	Mese	Cum
cobas 8000			
Omogeneo	1	0,5	0,7
CVR Metodo	1	0,4	0,6
Omogeneo	1	−0,89	−0,31
SDI Metodo	1	−1,02	−0,32
Omogeneo	2	0,6	0,7
CVR Metodo	2	0,5	0,6
Omogeneo	2	−0,78	−0,37
SDI Metodo	2	−1,15	−0,77



	Livello	Il tuo Lab Mese	Il tuo Lab Cum	Gruppo Omogeneo Mese	Gruppo Omogeneo Cum	Gruppo Metodo Mese	Gruppo Metodo Cum
				Roche cobas 6000/8000/c 311		Colesterolo ossidasi, estera perossidasi	
Media	1	101,6	103,3	104,0	104,2	104,8	104,4
DS	1	1,34	1,98	2,76	3,00	3,12	3,54
CV	1	1,3	1,9	2,7	2,9	3,0	3,4
Nr. Punti	1	60	569	12121	168K	33753	465K
Nr. Lab	1			243	343	771	1244
Media	2	236,6	238,3	240,6	240,3	243,9	243,4
DS	2	2,99	3,59	5,14	5,51	6,35	6,62
CV	2	1,3	1,5	2,1	2,3	2,6	2,7
Nr. Punti	2	60	566	12042	166K	33735	463K
Nr. Lab	2			242	340	770	1237

Total Cholesterol - Level 2



Continuous monitoring of trueness

Participation in Interlaboratory IQC

- Some limitations:
  - Small number of participants in the peer group
  - Inaccurate method classification of some of the participants
  - Different lots of reagent in use at the same time
  - Different calibration approaches for the same method on the same analytical system

Estimation of measurement uncertainty from IQC results

- Using one type of control material you can apply 3 of the 4 possible approaches that I presented last year:
  1. IQC (imprecision) + the uncertainty of the value assigned to the calibrator
  2. IQC (imprecision) + bias from EQAS or interlaboratory IQC
  3. IQC (imprecision) + bias from the mean of the previous period

1. IQC + the uncertainty of the value assigned to the calibrator (COFRAC approach 4)

- *u(Rw)* = six months CV (single conc. level or as mean of two lev.)

- *u(bias)* = $u(\mathrm{cRef}) = \frac{U_{CAL}}{2}$ $\mathrm{u(cRef)\%} = \frac{\mathrm{u(cRef)}}{\mathrm{CAL}} \times 100$

$$\boldsymbol{U = 2\,x\,\sqrt{u(Rw)^2 + u(bias)^2}}$$

Note

- U_{CAL} not always easy to obtain;
- Calibrator concentration can be very different the one of the control;
- How to deal with multiple calibrators?

3. IQC + EQAS or interlaboratory IQC (COFRAC proposal 3) (Nordtest report)

- $u(Rw)$ = six months CV (single conc. level or as mean of two lev.)
- $u(cRef) = \frac{SD_{group}}{\sqrt{n(group)}}$ $\qquad bias = RMS_{bias} = \sqrt{\frac{\sum(bias_i)^2}{n}}$
- $u(bias) = \sqrt{(RMS_{bias})^2 + u(cRef)^2}$

$$\boldsymbol{U = 2\,x\,\sqrt{u(Rw)^2 + u(bias)^2}}$$

Note: the calculation of $u(cRef)$ is based on the most common situation in which the reference value derives from a consensus mean.

There is the risk of overestimating the bias component, in fact $u(Rw)$ already includes some bias effects, moreover $u(cRef)$ may be significant in case of small groups.

4. IQC + bias from the mean of the previous period [Brugnoni et al. Biochim Clin 2015;39:108-15]

- **The bias component of intermediate precision is minimized by calculating $u(Rw)$ as weighted mean of monthly CV**

$$u(Rw) = CV_{pooled} = \sqrt{\frac{(n_A - 1)\times CV_A^{\,2} + (n_B - 1)\times CV_B^{\,2} + .. + (n_i - 1)\times CV_i^{\,2}}{(n_A + n_B + .. + n_i) - n_{periods}}}$$

- $u(cRef) = \dfrac{CV_{pooled}}{\sqrt{mean\ num\ of\ monthly\ QC\ results}}$ $\qquad bias = RMS_{bias} = \sqrt{\dfrac{\sum(bias_i)^2}{n}}$

- $u(bias) = \sqrt{(RMS_{bias})^2 + u(cRef)^2}$

$$\boldsymbol{U = 2\,x\,\sqrt{u(Rw)^2 + u(bias)^2}}$$

Note: it implies that an unbiased initial situation

Pros and Cons of an IQC program based on a single type of material (third party material)

Pros

- Easier to perform (less training for the personnel, fewer vials to manage)
- Fewer number of QC analyses
- Able to detect possible bias introduced by new reagents' or calibrators' lots (it is independent from the manufacturer)
- Some IQC interlaboratory programs provide sophisticate IQC software

Cons

- Requires a very careful trueness evaluation at the method star up
- Only surrogate evaluation of trueness through the participation in Interlaboratory IQC (required)
- Commutability not always guaranteed
- Cost (?) (frequently system related controls are provided at no additional cost)

Conclusions

- It is possible to obtain all the needed information using a single type of material provided that:
  - At the implementation of the method a careful evaluation of its trueness has been performed
  - The participation in an Interlaboratory IQC with sufficiently large, well defined and controlled peer groups.

Thanks of your attention!