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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

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13th International Scientific Meeting

THE INTERNAL QUALITY CONTROL IN THE TRACEABILITY ERA

MILANO, ITALY
November 28th, 2019

# Redesigning analytical quality control to meet metrological criteria: A brief story of CIRME contribution

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Clin Chem Lab Med 2010;48(1):7–10 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.020

Editorial

# Application of traceability concepts to analytical quality control may reconcile total error with uncertainty of measurement

Mauro Panteghini


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Clin Chem Lab Med 2010;48(1):7–10 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.020

Editorial

# Application of traceability concepts to analytical quality control

Mauro Panteghini

***L'Origine du monde*** ("The Origin of the World") is a picture painted in oil on canvas by the French artist Gustave Courbet in 1866.

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**Profession (e.g. JCTLM, IFCC):** Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fit for purpose)

**Diagnostic manufacturers:** Implement suitable measuring systems (platform, reagents, calibrators, controls) fulfilling the above established goals

**End users (clinical laboratories):** Survey assay and laboratory performance through IQC and EQA redesigned to meet metrological criteria

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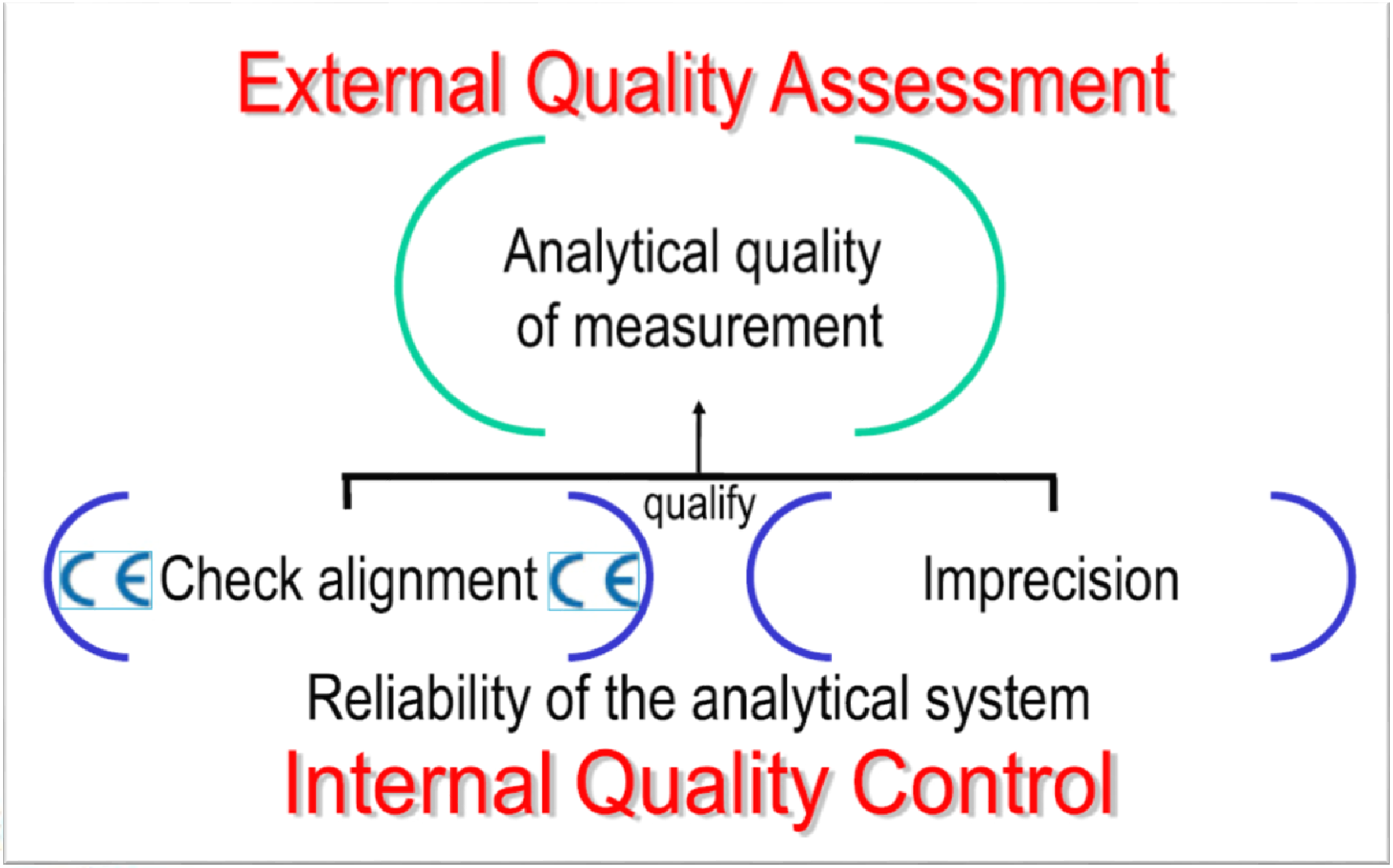
Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

# Analytical Quality Control in the Traceability Era

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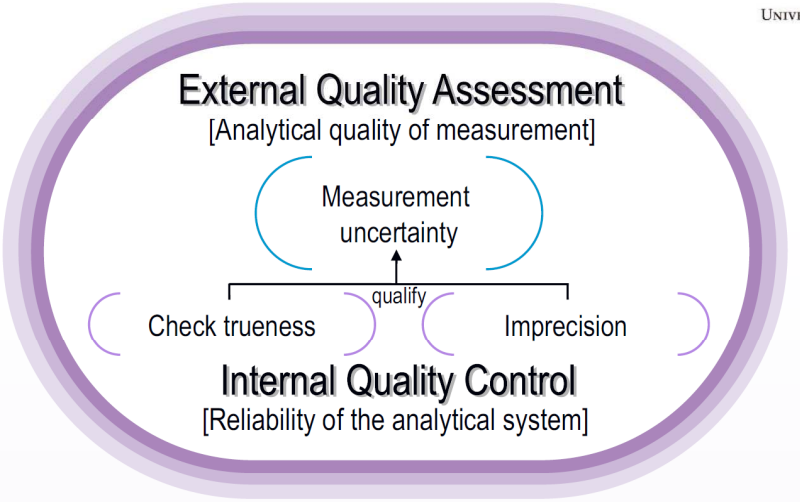


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**Centro Interdipartimentale per la Riferibilità Metrologica in Medicina di Laboratorio (CIRME)**

under the auspices of

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

JCTLM The Joint Committee for Traceability in Laboratory Medicine

4th International Scientific Meeting

# RETHINKING QUALITY CONTROL IN THE TRACEABILITY ERA

**MILANO**

***NOVEMBER 30th, 2010***

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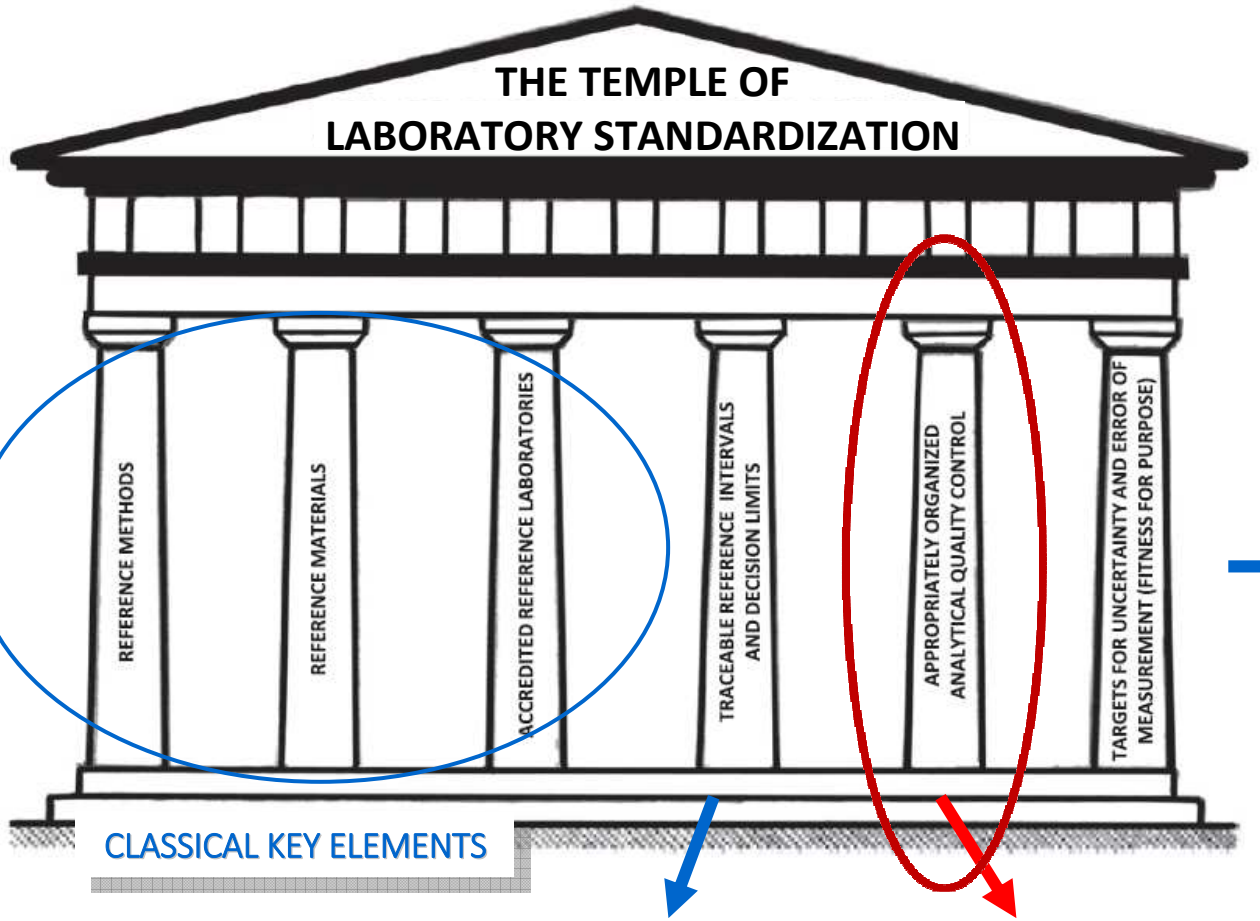
The implementation of standardization in clinical practice needs first the availability of the 3 main pillars:

- Reference measurement procedures
- Reference materials
- Accredited reference laboratories

Then, it needs to define a 4th pillar:

- Traceable reference intervals/decision limits

And, an appropriately organized analytical (internal and external) quality control should become the 5th pillar.




*6th pillar*
TARGETS FOR UNCERTAINTY AND MEASUREMENT ERROR THAT FIT FOR PURPOSE

*4th pillar*
TRACEABLE REFERENCE INTERVALS AND DECISION LIMITS

*5th pillar*
ANALYTICAL (INTERNAL AND EXTERNAL) QUALITY CONTROL THAT MEETS METROLOGICAL CRITERIA

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Braga F & Panteghini M, Clin Chim Acta 2014;432:55

# Roles and responsibilities of clinical laboratories



- Verification of availability and quality of INFORMATION about IVD metrological traceability and uncertainty

- DAILY SURVEILLANCE of IVD system traceability

- Estimation of the MEASUREMENT UNCERTAINTY due to the random effects and calculation of uncertainty of laboratory measurements ($u_{cal} + u_{random}$)

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# Sources of variability of a measured quantity value (that contribute to measurement uncertainty)

- Repeatability of the analytical system
- Calibration
  - Value assigned to the calibrator (and its uncertainty)
  - Frequency of calibration
  - How calibration is performed
- Reagent stability on board
- Lot to lot variability
- Frequency of maintenance
- Operators
- Environmental conditions

Random errors

Systematic errors

Both random and systematic errors

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# Can the IQC provide enough information on all these sources of variability?
# Is the information reliable?

This may require that the Internal Quality Control (IQC) used to monitor the analytical performance of the methods should be reorganised into two independent components; the former to check the trueness of CE-marked systems (as described above) and the latter (using a different control material) to evaluate system imprecision (Figure 1).


Panteghini M, Clin Chem Lab Med 2010;48:7

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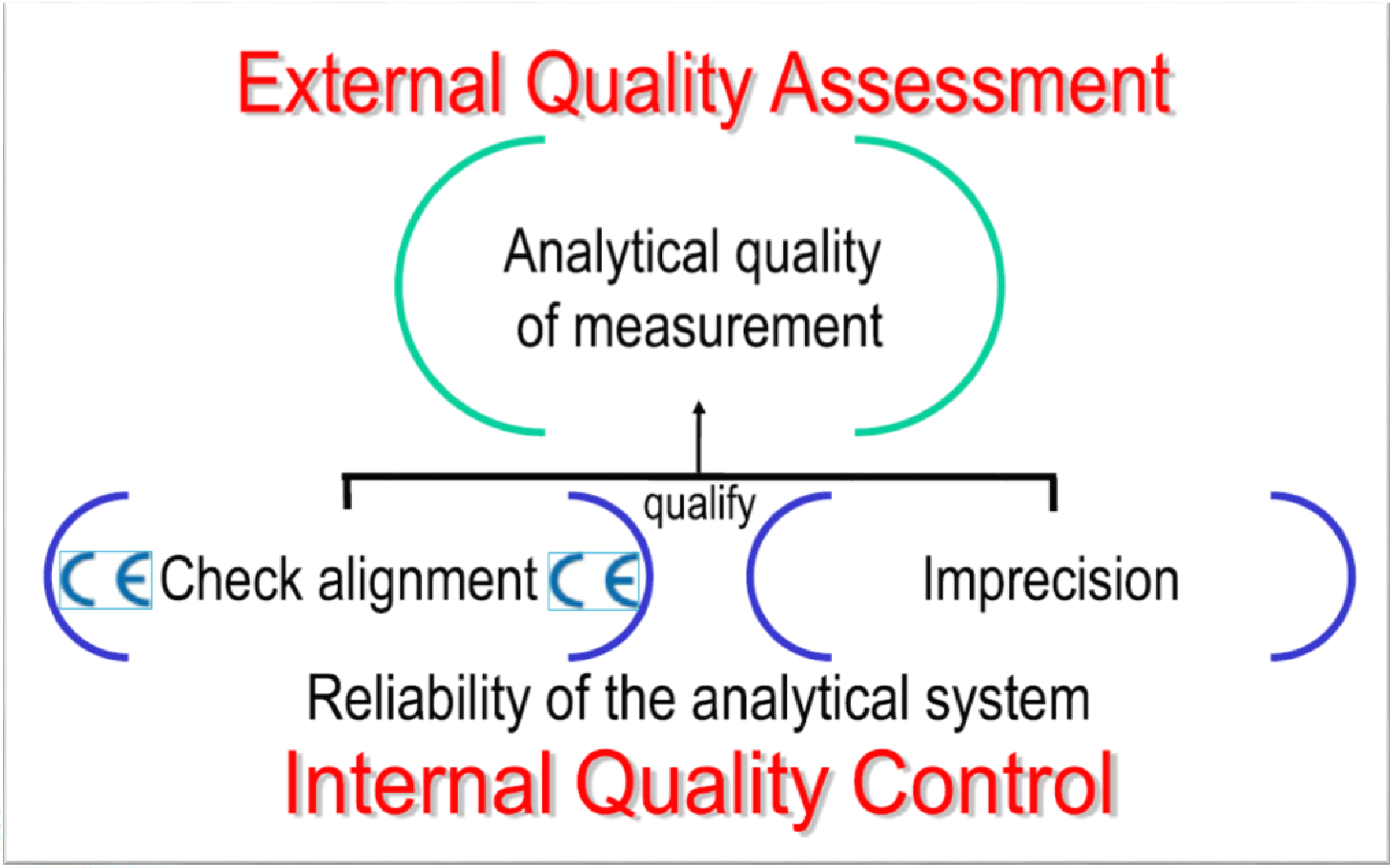
# Analytical Quality Control in the Traceability Era

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Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

# Two IQC components

- Two independent components: one devoted mainly to checking the alignment of the measuring system and verification of the consistency of declared traceability during routine operations performed in accordance with the manufacturer's instructions (IQC component I) and the other structured particularly for estimating the measurement uncertainty due to random effects (IQC component II).


Panteghini M, Clin Chem Lab Med 2010;48:7

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# IQC component I or how to check the alignment of measuring systems Sara Pasqualetti

- Aim: testing system alignment according to manufacturer's specifications
- Materials: control materials supplied by the system's manufacturer with system specific assigned values and acceptability range
- Use: acceptance/rejection of analytical runs
- Rules: results within a stated acceptability range.

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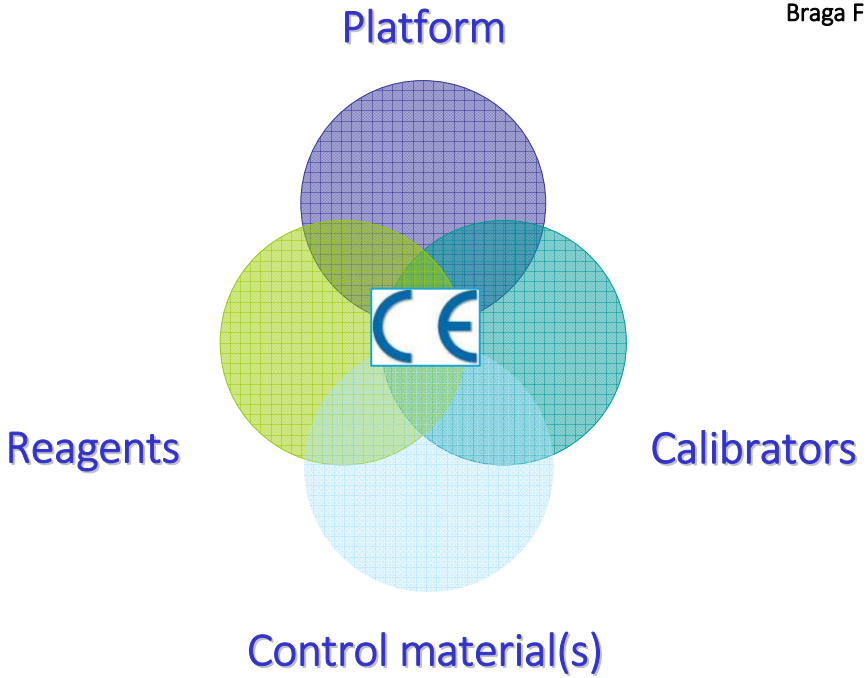
# Monitoring the reliability of the measuring system through Internal Quality Control: Component I. Check alignment ("system traceability")

Braga F et al. J Med Biochem 2015;34:282
Braga F et al. Clin Chem Lab Med 2015;53:905




Clinical laboratories must verify the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions, by checking that values of control materials provided by the manufacturer as component of the measuring system show no clinically significant changes in the assumed traceable results.

# IQC component II or how to estimate the random source of measurement uncertainty - Elena Aloisio

- Aim: checking system variability (lot-to-lot variations, analytical drifts, etc.)
- Materials: third-party control materials, commutable, concentrations at clinical decision limits
- Use: provide data for measurement uncertainty calculation
- Rules: fulfil allowable performance specifications

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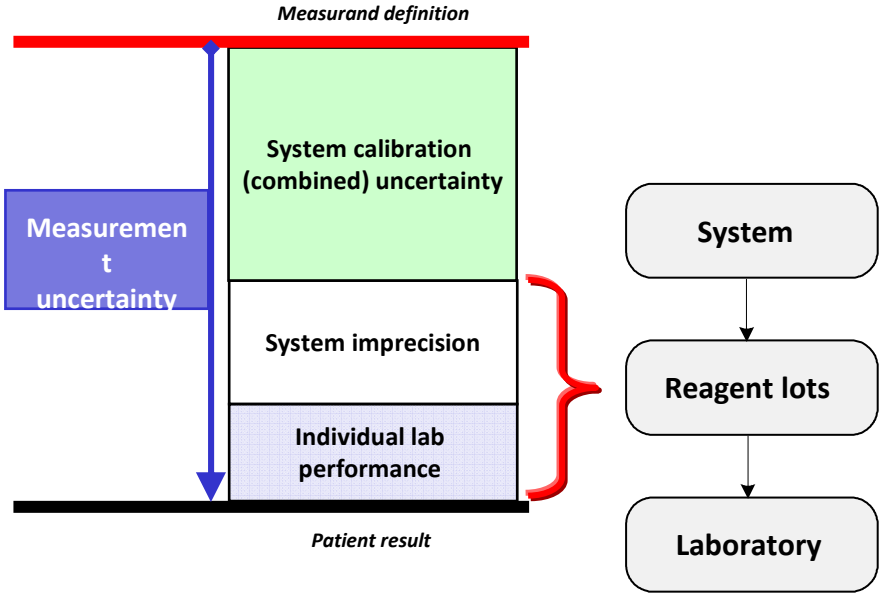
# Monitoring the reliability of the measuring system through Internal Quality Control: Component II. Estimating the measurement uncertainty due to random effects ("imprecision")

Braga F et al. J Med Biochem 2015;34:282
Braga F et al. Clin Chem Lab Med 2015;53:905




Main characteristics for a control material to be used in the IQC component II program in order to derive the uncertainty of the measuring system due to the random effects

| Requirement | Comment |
|---|---|
| Material from a third-party independent source should be used | Material must be different from the system control material used for checking alignment (IQC component I) |
| Material should closely resemble authentic patient samples (fulfil commutability) (e.g., fresh-frozen pool) | Commercial non-commutable controls may provide a different impression of imprecision performance |
| Material concentration levels should be appropriate for the clinical application of the analyte measurement | When clinical decision cut-points are employed for a given analyte, materials around these concentrations should preferentially be selected |

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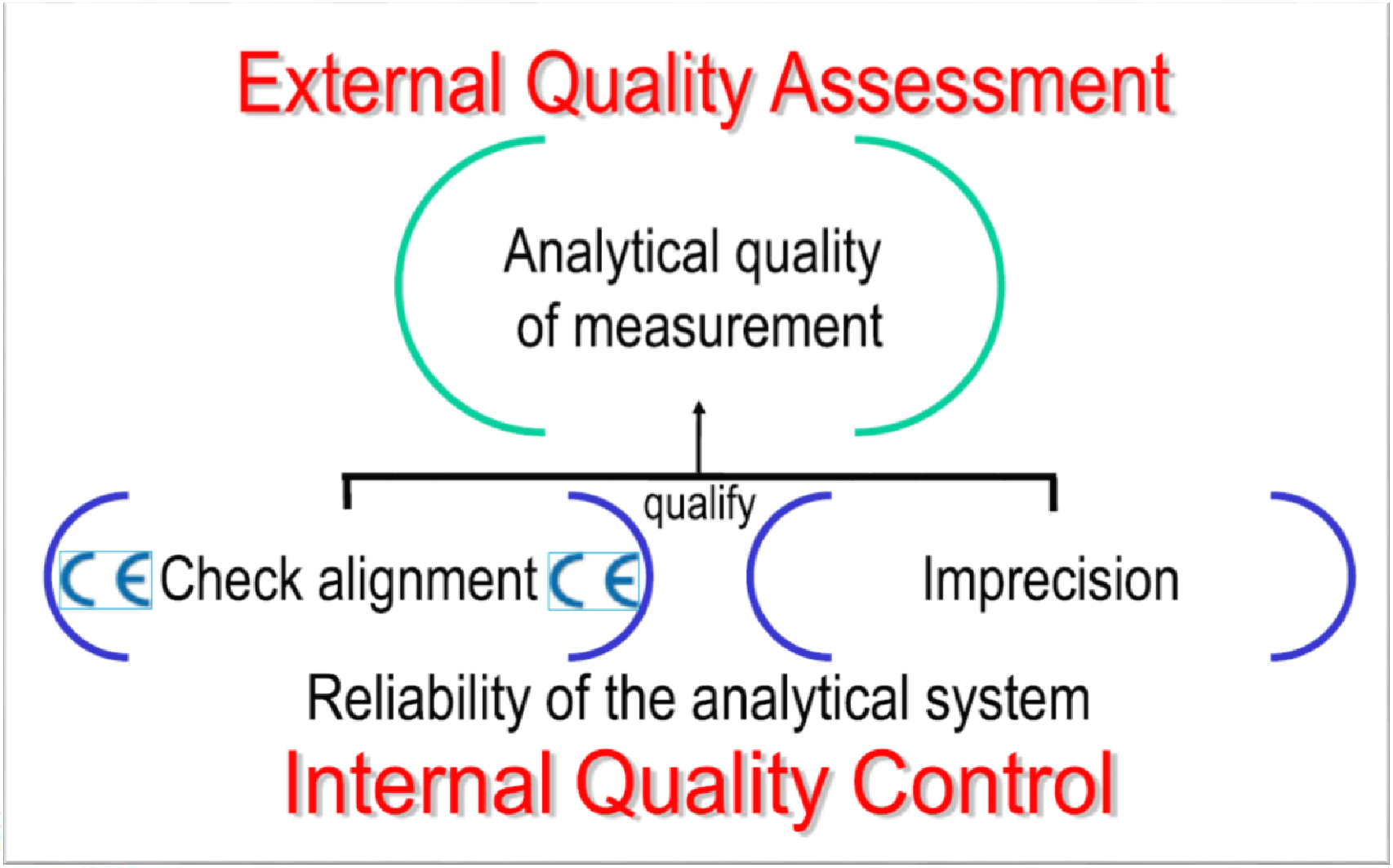
# Analytical Quality Control in the Traceability Era

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Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

# Requirements for the applicability of EQA results in the evaluation of the performance of participating laboratories in terms of traceability of their measurements

| Feature | Aim |
|---|---|
| EQA materials value-assigned with reference procedures | To check traceability of commercial system to reference measurement systems |
| Proved commutability of EQA materials | To allow transferability of participating laboratory performance to the measurement of clinical samples |
| Definition and use of allowable performance specifications | To verify the suitability of laboratory measurements in clinical setting |

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Panteghini M. Clin Chem Lab Med 2010;48:7
Infusino I et al. Clin Chem Lab Med 2010;48:301
Braga F, Panteghini M. Clin Chem Lab Med 2013;51:1719
Braga F, Panteghini M. Clin Chim Acta 2014;432:55
Infusino I et al. Clin Chem Lab Med 2017;55:334
Braga F et al. Clin Biochem 2018;57:23

**Table 1:** Unique benefits of External Quality Assessment Schemes meeting metrological criteria.

| |
|---|
| – Giving objective information about quality of individual laboratory performance |
| – Creating evidence about intrinsic standardisation status/ equivalence of the examined assays |
| – Serving as management tool for the clinical laboratory and IVD manufacturers, forcing them to investigate and eventually fix the identified problem |
| – Helping those manufacturers that produce superior products and systems to demonstrate the superiority of those products |
| – Identifying analytes that need improved harmonisation and stimulating and sustaining standardisation initiatives that are needed to support clinical practice guidelines |
| – Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality |

# Conventional External Quality Assessment

- Non-commutable samples
- Consensus ('peer') group assessment
- Performance specifications not clinically oriented


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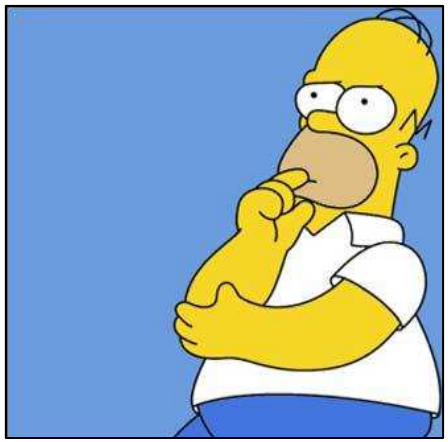
**Box 1 Factors influencing choice of External Quality Assessment (EQA) Scheme**

- Accreditation status of provider. Preference should be given to schemes accredited to ISO 17043 or equivalent (eg, those still Clinical Pathology Accreditation (CPA) accredited within the UK). If a non-accredited provider is chosen, the reason(s) should be clearly documented. Under International Laboratory Accreditation Cooperation (ILAC),[11] accreditation bodies should support the use of appropriate proficiency testing programmes which meet the essential requirements of ISO/IEC 17043, where applicable.
- Appropriateness of distribution frequency. Distributions should be at a frequency sufficient to identify performance issues in a timely manner. For core tests, this probably equates to at least monthly distributions.
- Range and number of EQA samples. Samples within the distribution cycle should cover an appropriate range of values for each analyte to verify performance across clinically relevant concentrations. Each cycle should supply sufficient samples to provide evidence of reproducibility; 3–4 samples in each distribution would probably fulfil this requirement. Samples should be 'blinded' to participants in relation to expected results.
- Scheme management and development. The scheme should be designed and overseen by appropriately competent professionals (clinical, technical and statistical). The scheme should also have an independent medical and scientific committee.[12]
- Poor performance issues. Mechanisms should be in place for reporting of poor performance to the appropriate regulatory/oversight body.
- Variety of sample provided. 'Challenging' samples should be included in selected distributions.
- Education. Educational input should be provided.
- Manufacturers. Participation of the EQA provider in postmarketing vigilance of in vitro diagnostics.[12]
- Materials. EQA providers should demonstrate use of commutable materials.[13]



*James D et al., J Clin Pathol 2014;67:651*

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Clinical Biochemistry 57 (2018) 23–28

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

# The role of external quality assessment in the verification of in vitro medical diagnostics in the traceability era

Federica Braga*, Sara Pasqualetti, Mauro Panteghini

*Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy*

What appears clear from the published experiences is that sometimes we probably have an optimistic perception of analytical quality in clinical laboratories, due to the conventional EQA approaches for evaluating their performances.

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## 1st EFLM Strategic Conference

# Defining analytical performance goals 15 years after the Stockholm Conference

### 8th CIRME International Scientific Meeting

Milan (IT)
24-25 November 2014

with the auspices of IFCC International Federation of Clinical Chemistry and Laboratory Medicine

# The Essential Question…


"What degree of quality is needed and what measurement error can be tolerated without jeopardizing patient safety."

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Defining performance specifications for IQC – Federica Braga




Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

# Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

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

a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcomes;

b. Done by indirect outcome studies – investigating the impact of analytical performance of the test on clinical classifications or decisions and thereby on the probability of patient outcomes, e.g., by simulation or decision analysis.

*Model 2: Based on components of biological variation of the measurand.*

*Model 3: Based on state of the art of the measurement (i.e., the highest level of analytical performance technically achievable).*

# The importance of grading different quality levels for APS

To move, in case, from desirable to minimum quality goals and, in the meantime, ask reference providers/IVD manufacturers to work for improving the quality of assay performance

DE GRUYTER DOI 10.1515/cclm-2012-0840 — Clin Chem Lab Med 2013; 51(8): 1579–1584

Opinion Paper

Nuthar Jassam*, John Yundt-Pacheco, Rob Jansen, Annette Thomas and Julian H. Barth

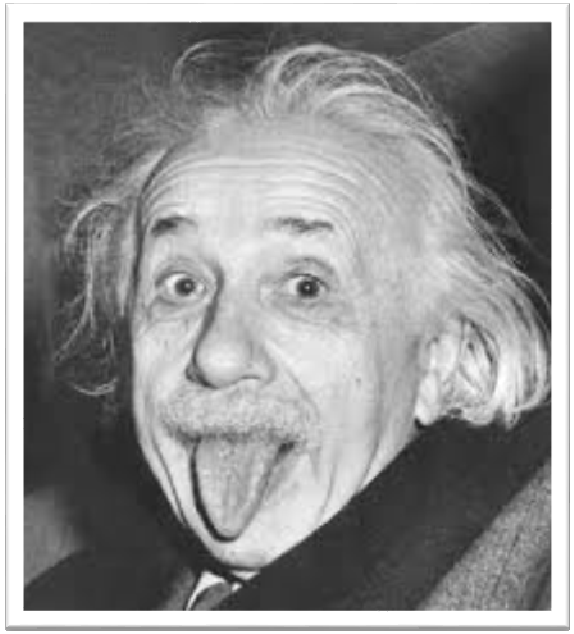
# Can current analytical quality performance of UK clinical laboratories support evidence-based guidelines for diabetes and ischaemic heart disease? – A pilot study and a proposal

Evidence from our data shows that analytical quality remains a major issue, and data from IQC do not consistently demonstrate that the results from clinical laboratories meet evidence-based quality specifications. There are two possible reasons for the lack of agreement between the *proposed* limits and the *routinely achieved* analytical variation by laboratories. First, currently used technology is inherently insufficiently robust to allow the achievement of a narrow analytical variation regardless of the effort to control the analytical process (i.e., creatinine Jaffe method). Second, there is sub-optimal control over the IQC process and a lack of defined limits.

# Problems of the IQC process

- Need to balance the metrological complication and the practical simplicity needed for adoption by medical laboratories
- Need to establish a direct link between the performance characteristics of the method and the QC rules
- Improve control on the bias component
- Need to demonstrate that “fits for purpose”

Everything should be made as simple as possible, but not simpler…..



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# Traceability as Copernican Revolution in Analytical Quality Control


*Nicolaus Copernicus born in Torun, earth motor, sun and sky stator*

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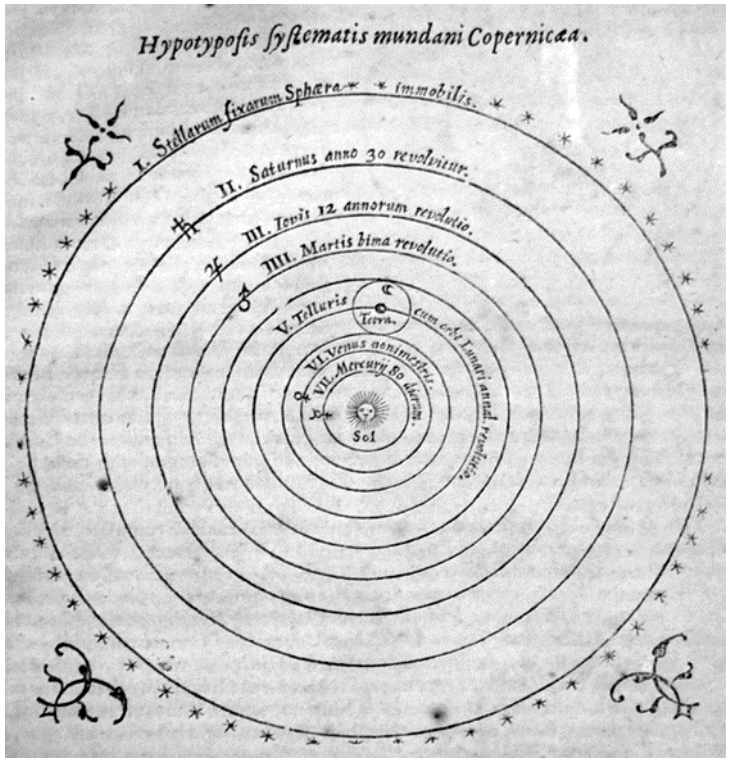
What COPERNICUS did was take the existing ‘a priori’ concept of the world and pose an alternative ‘a priori’ concept

The earth is flat and fixed in space


Equivalency-based grading

The earth is spherical and moves around the sun




Accuracy-based grading

CI What TRACEABILITY does is take the existing ‘a priori’ concept of the QC and pose an alternative ‘a priori’ concept

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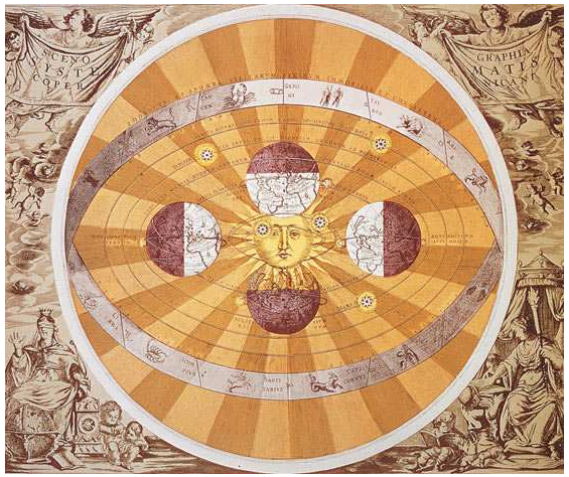

Do not forget that it was the acceptance of the Copernican revolution that distinguishes modern man from his medieval predecessors.

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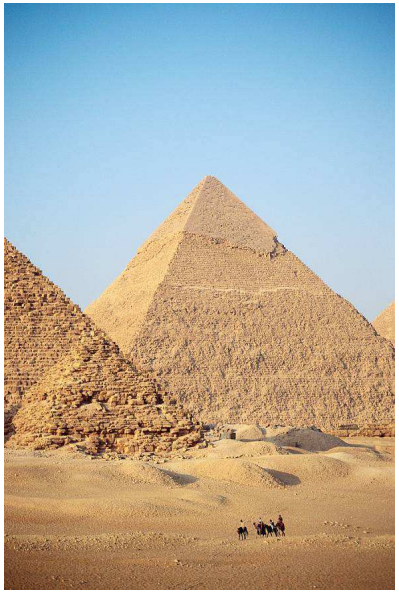
# Egyptian Cubit

- Used to build pyramids
- Missed calibration was punishable by death!



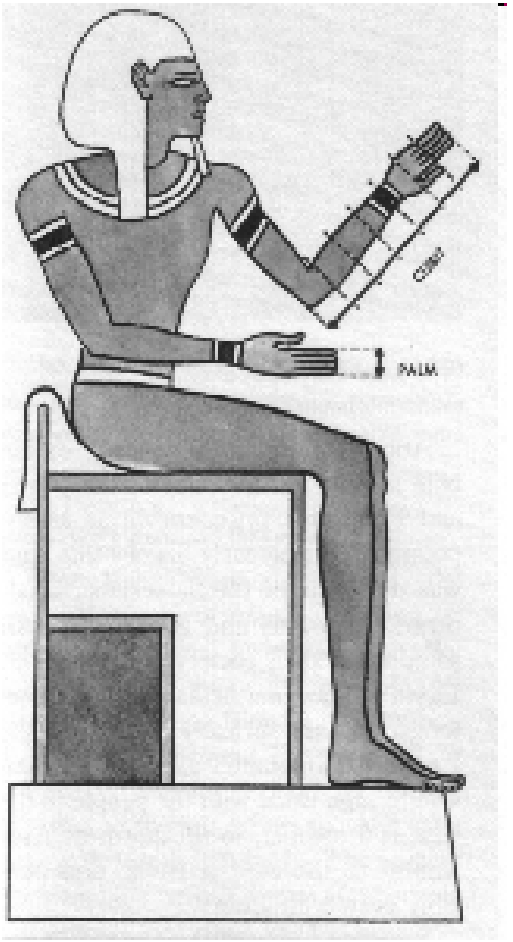



*Diagram of Egyptian definitions of cubit and palm*

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Accurate results for patient care

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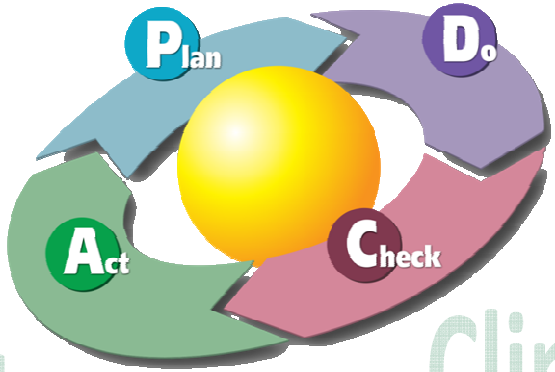
Laboratory profession




IVD manufacturers

MedTech Europe
from diagnosis to cure

All stakeholders

Clinical laboratories

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not: Please Do not Change Anything

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Supported by an unconditional grant by
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