Essential concepts and terms

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BIPM in Paris in 2022

This is a “living document”, version 2022-03-26. Suggestions for improvements are gratefully received.

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For clarity, this document adheres to the terminology detailed in the International Vocabulary of Metrology (VIM3) (1) and the VIN (2). Necessary terms are summarized in the glossary, which is provided as an appendix, and the essential concepts and terms for the present presentation are mentioned only briefly here.

Measurement is the objective determination of a quantity/amount. Quantities can be continuous or discrete, as exemplified by the absorbance of light at a specific wavelength and the counting of cells. Amongst the characteristics of quantities is that they can be logically compared mathematically as "less," "equal," or "more."

VIM 3 (1) defines measurement as "process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity" and notes that "Measurement implies comparison of quantities or counting of entities" and that "Measurement does not apply to nominal properties."

Measurements in Laboratory Medicine, for example, the concentration of medically relevant molecules, are rarely direct. Instead, measurements rely on chemical, immunochemical, and molecular biology *reactions* combined with the measurement of physical *quantities* that are sufficiently characteristic for the molecules intended to be measured to be fit for the intended use. Expressed in other words – measurements in Laboratory Medicine are commonly performed using *surrogate markers* (measurands) for the intended "analytes", where an "analyte" is your ideal concept of the molecule you wish to measure.

The concept "analyte" should be avoided in the metrology of Laboratory Medicine since it does not refer to a quantity. If the term "analyte" is used in the present text, it refers to the molecule/component the quantity of which (commonly concentration) is to be measured. Since the direct measurement of unique molecules is rarely possible, the quantity intended to be measured in practice is called a "measurand." The *measurand* refers to a quantity that can be measured in the practice (3-10).

The term *measurement procedure* refers to a *written* specification for performing a measurement, including a technical description of reagents, calibrators, equipment, instrument, and other details necessary to perform a measurement that implements those specifications. A *measuring system* is the entire *physical* in-vitro diagnostic system manufactured according to the specifications of the measurement procedure and used to perform measurements of measurands in patient samples to produce quantity values

that are used for diagnosis, monitoring of treatment effects, and for screening for risk factors and diseases. A measuring system comprises the physical instrument and includes calibrators, reagents, and any necessary auxiliary equipment.

Matrix effect is the influence of a property of the sample, independent of the presence of the analyte, on the measurement and thereby on the measured quantity value. Matrix effects are present both in native patient samples and in reference materials and are crucial for the commutability of reference materials. An essential difference between native patient samples on one hand and calibrators and control materials on the other, is that native patient samples are commutable by definition. *Commutability* is a nominal property (a material is either commutable or not commutable) of reference materials, demonstrated by the equivalence of the mathematical relationships among the results of different measuring systems for reference material and for representative samples of the patient samples intended to be measured. The conclusions reached regarding the commutability of a particular measuring system is that these conclusions are assumed to apply to all other measuring systems that are implementations of the same measurement procedure.

Equivalence is primarily a functional/clinical/medical concept "Agreement of measured values among different in vitro diagnostic measurement devices intended to measure the same measurand, where the differences in measured values on the same human samples do not affect clinical interpretation" (11). Still, limits also enter into the concept as follows "NOTE 1: A conclusion of equivalence of measured values for the same human samples among two or more measuring systems is based on the differences in measured values being within a pre-defined margin or limit (11).

Harmonization is "Achievement of equivalent measured quantity values (within clinically meaningful limits) for human samples examined for a stated measurand among two or more measuring systems by applying an *international consensus protocol* in their calibration hierarchies when fit-for-purpose higher-order reference materials or reference measuring systems are not available.

Note 1: Harmonization is one of the calibration hierarchy models described in ISO-17511:2020 (11) to achieve metrologically traceable quantity values for human samples.

Note 2: Harmonization is a special case of non-SI traceable standardization where the calibration of two or more measuring systems is traceable to an international harmonization protocol that defines the highest level of metrological traceability for the stated measurand but with no traceability to SI.

Note 3: Harmonized is the condition in which harmonization (equivalence among quantity values) is achieved among two or more measuring systems." (11).

Since the publication of ISO-17511:2020 (11) and ISO-21151:2020 (12), harmonization should no longer be regarded as an alternative to standardization but rather as one of the tools for reaching standardization used in calibration hierarchies #3 to #6 (11).

The qualitative concept measurement *trueness* is the "closeness of agreement between the *average* of an infinite number of replicates of measured quantity values and a reference quantity value" (Figures 2 and 3). Trueness is quantitatively expressed as *bias*. Another qualitative concept, measurement *accuracy* describes the closeness of agreement between a single measured quantity value and a true quantity value of a measurand. Accuracy includes both systematic and random error components. Measurement *error* is a quantitative expression of accuracy.

Precision is expressed quantitatively as its opposite – *imprecision* using the standard deviation unit.

There are three types of imprecision:

1. *Repeatability imprecision* (13, 14): "Conditions where independent test results obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals". In Laboratory Medicine, repeated measurement results using aliquots of the same sample obtained during a single day by the same analyst using the same measuring system reflect repeatability imprecision.
2. *Reproducibility imprecision* (13, 14): "Conditions where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment." In Laboratory Medicine, repeated measurement results using aliquots of the same sample obtained several days by different analysts using different measuring systems, different lots of reagents, and calibrations reflect repeatability imprecision. The conditions used when determining reproducibility imprecision must be detailed.
3. *Intermediate imprecision* (13, 14): is imprecision somewhere in between repeatability and reproducibility imprecision. The conditions used when determining reproducibility imprecision must be detailed.

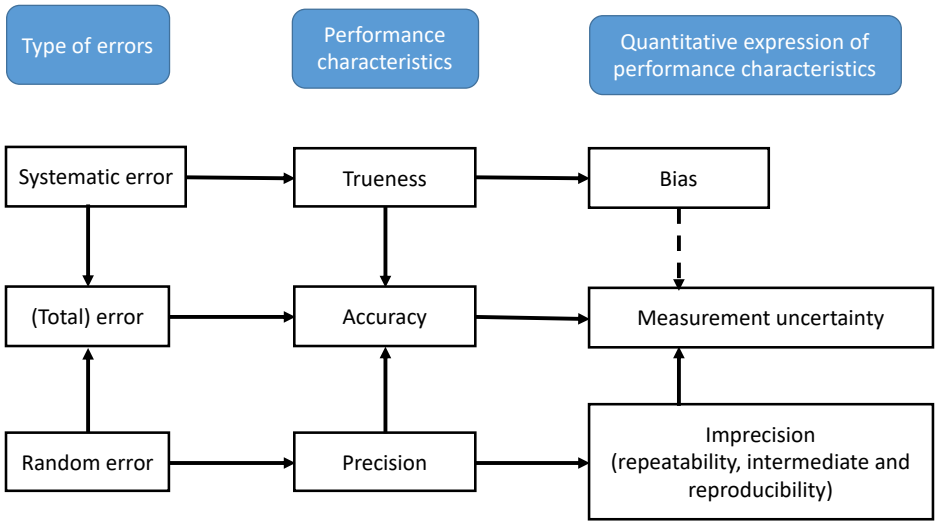

Figure 1: Concept diagram, adapted from Menditto et al. (15), explaining the relations between concepts describing random and systematic errors as well as measurement uncertainty. The dotted line from bias to measurement uncertainty indicates that it should be eliminated if bias can be estimated.

A more *accurate* result has a more minor *measurement error*. It is on average more *true* when the *bias* is small and more *precise* when the *random error* is small.

A weakness in the concept diagram in figure 1 is that *accuracy* has a double meaning – a qualitative- and a quantitative sense. The qualitative purpose expresses whether a *single* measurement result from measuring system A is likely to be more or less accurate than a measurement result from measuring system B. The accuracy of a single measurement result in a quantitative meaning is the difference between the sum of the random and systematic error minus a reference measurement result.

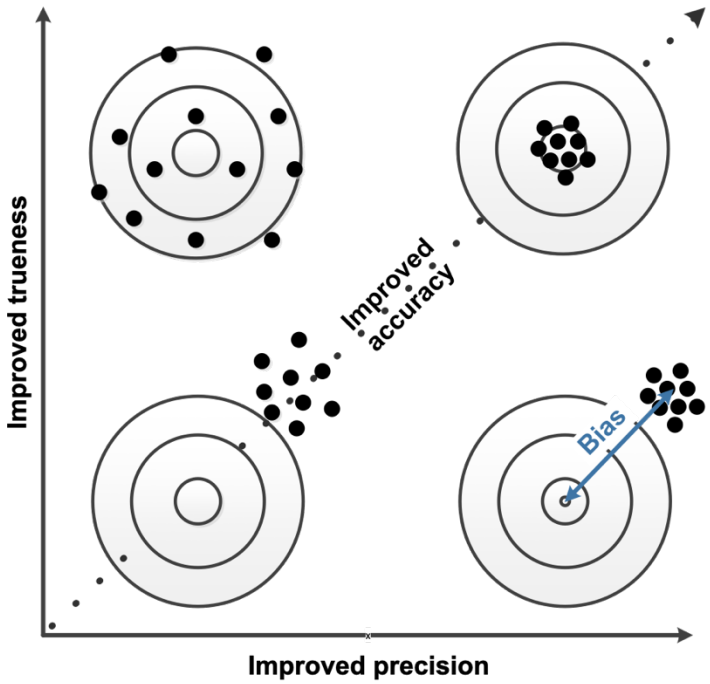

Figure 2: A graphical illustration of the meaning of trueness, precision, and their combination – accuracy.

Accuracy includes both random and systematic components that can be present to any relative extent.

Measurement results are expressed on four "*measurement levels*"; *nominal*, *ordinal*, *interval,* and *ratio*. Each level of measurement specifies how the numbers that are assigned to the measurands relate to the basic characteristics of the measurand determined by noting the presence or absence of four parts: 1) distinctiveness, 2) ordering in magnitude, 3) equal intervals, and the presence of 4) absolute zero. A measurand has the characteristic of *distinctiveness* if measurement results can be expressed as different numbers, characters, or strings of characters. For example, persons have other names, blood groups have different characters or strings of characters making the distinctive regarding naming. Measurement results can also indicate an *ordering in magnitude*, with more significant numbers representing more of the measurand being measured than smaller numbers. For example, a urinary dipstick of +2 indicates a higher concentration of urine albumin than +1, even if this does not necessarily mean that +2 in this context means twice the concentration compared to +1. *Equal intervals* are obtained if equivalent differences between measurements represent the same quantity being measured. For example, if a two-point difference between the hemoglobin concentrations of 130 and 145 means the same difference in concentrations as the two-point difference between 115 and 130, the measurement has equal intervals. A measurement has an absolute zero when a measurement of zero represents an

absence of the property being measured. For example, a concentration of 0 means the absence of the molecules in question in the solution used for measuring. An obvious example is the Centigrade and Kelvin temperature scales. The Kelvin scale starts with 0 - the temperature when no molecules move.

In contrast, the Centigrade (Celcius, ^{o}C) scale does not mean the absence of temperature (movement of molecules). The four characteristics of measurement just described determining the four major levels of measurement: nominal, ordinal, interval, and ratio.

Characteristic	Nominal	Ordinal	Interval	Ratio
Distinctiveness	yes	yes	yes	yes
Ordering in magnitude	no	yes	yes	yes
Equal intervals	no	no	yes	yes
Absolute zero	no	no	no	yes

Table 1: Characteristics of the four levels of measurement (16).

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