

HARMONIZATION OF MEASUREMENT UNITS MISSION IMPOSSIBLE OR ETHICAL IMPERATIVE?

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ABSTRACT

Harmonization initiatives in laboratory medicine have a long history. Nevertheless, despite substantial efforts by international federations, scientific societies, and expert working groups, their implementation and widespread adoption remain incomplete, with many initiatives still at a relatively early stage of development. More recently, several initiatives have sought to identify scientifically sound yet pragmatic approaches to the harmonization of measurement units. To contribute to this debate, we invited experts from different disciplines of laboratory medicine, as well as a clinician, to provide their perspectives on the challenges, opportunities, and priorities for achieving greater harmonization. This Forum offers a unique opportunity to assess the current state of the art across multiple areas of laboratory medicine, including clinical chemistry, immunoassays, hematology, coagulation, molecular diagnostics, and serology. The contributions presented herein aim not only to highlight discipline-specific challenges but also to identify common principles and practical strategies that may guide future harmonization efforts. Although this paper does not propose a definitive roadmap for the harmonization of measurement units, its ultimate goal is to stimulate informed discussion and present a comprehensive spectrum of perspectives to international federations, national societies, regulatory authorities, and scientific journals. By doing so, it aims to support the identification of the most effective strategies for achieving greater consistency, comparability, and harmonization of laboratory reporting units worldwide.

KEYWORDS: harmonization; patient safety; SI units; measurement units; molar units

Preface

Mario Plebani

Harmonization initiatives in laboratory medicine have a long history; nevertheless, despite substantial efforts, their implementation and widespread adoption remain incomplete, with many initiatives still at a relatively early stage of development. Nevertheless, interest in harmonization projects has markedly increased in recent years, driven by the globalization of clinical laboratory activities, patients' expectations to receive interchangeable laboratory information, the need to reduce unjustified variability and improve patient safety, and the expanding exchange of laboratory data at local, national, and international levels. In particular, the COVID-19 pandemic has substantially increased awareness of the importance of harmonization not only among experts in laboratory medicine, but also among a broader range of stakeholders, including clinicians, patients, healthcare administrators, and policy makers [1]. Harmonization is now increasingly recognized as a critical prerequisite for ensuring healthcare quality, patient safety, comparability of data, and the sustainability of healthcare systems. Although early initiatives were mainly focused on the harmonization of analytical methods and procedures, accumulating evidence has highlighted the necessity of extending harmonization efforts to all phases and steps of the total testing process (TTP). Such an integrated approach is essential to provide a more comprehensive, clinically meaningful, and patient-centered framework – the so-called “complete picture” [2–4]. Although standardization and harmonization initiatives historically originated in clinical chemistry, the ongoing consolidation of clinical laboratories and the rapid expansion of several disciplines within laboratory medicine now require a broader and more integrated perspective. Harmonization should therefore encompass the entire field of laboratory medicine, including hematology, immunoassays, coagulation/hemostasis, microbiology, virology, molecular diagnostics, and genetics, overcoming the current fragmentation among disciplines and promoting a more integrated approach to diagnostics [5–7]. In this context, harmonization of measurement units plays a pivotal role, since every analytical result must necessarily be accompanied by a unit, representing one of the fundamental “comparators” required for correct interpretation of laboratory information. Misinterpretation of results expressed in different units has frequently been reported as a relevant patient safety issue, as clinicians may inadvertently assume the use of the units with which they are more familiar from another testing provider. In addition, lack of harmonization may lead physicians to request unnecessary repeat testing in another laboratory, resulting in increased healthcare costs, patient frustration, and further challenges to the sustainability of healthcare systems. Differences in measurement units remain common at local, regional, national, and international levels and, despite numerous harmonization initiatives, they continue to persist even within the scientific literature. In recent months, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Committee on Harmonization (C:H), following a survey aimed at better understanding the

current state of the art, has promoted a scientifically grounded yet pragmatic approach to the harmonization of measurement units [8, 9]. In parallel, the official journal of EFLM, *Clinical Chemistry and Laboratory Medicine* (CCLM), has published several relevant proposals from national scientific societies and dedicated working groups [10–13]. For this reason, we decided to organize a Forum for discussion by collecting the viewpoints of experts from different specialties within laboratory medicine, together with contributions from the Chair of the EFLM Committee on Exchange of Laboratory Data and from a clinician. The aim is to better understand how to effectively move towards harmonization, which should be grounded on a solid scientific foundation while also adopting a pragmatic approach capable of overcoming the current stagnation and impasse, often driven by one of the major enemies of progress: skepticism.

The need for systematic system for unity in units

Marc Thelen on behalf of the EFLM Division Quality, Standards and Regulations (D-QSR)

In the interpretation of laboratory test results, equivalence in interpretation hinges on equivalence in result. Whereas everybody can understand that harmonization of metrological traceability and the abandonment of methods with inferior selectivity requires long breath and decades to complete, it is hard to believe that the simple part of the harmonization, which is the harmonization of units, takes so long to complete. Indeed, lack of harmonization of units is, in some cases, the only remaining factor that still obstructs equivalence in results, after harmonization of the analytical procedures and even reference intervals. For a long time, this seemed mostly due to different regions in the world having a different tradition in the use of units, and all regions reason that harmonization should be achieved by the transition of other regions to their preferred units. However, starting from 1968 the International Federation of Clinical Chemistry (IFCC) began to recommend the use of SI units which has led to a guide with unit recommendation in 1987 [14]. Key points in that recommendation are the use of the mole to express the amount of substance, because of its functional metabolic relationship, instead of the use of mass, and the use of the liter to express volume in the denominator for concentrations. However, until today, harmonization of units is still far from complete, due to the lack of implementation of the existing recommendations. Moreover, the current recommendations leave room for choices that hamper harmonization. This mainly focusses on two aspects: (1) The possibility to use gravimetric units over the recommended molar units, and (2) the lack of rationale in the guidance on which thousand-fold to choose in the numerator of concentrations; mmol/L vs. μ mol/L. Existing published guidance by EFLM [9] or The German Society for Clinical Chemistry and Laboratory Medicine (DGKL) [10] recommends clear choices for SI based units respecting the IFCC recommendations, but doesn't rationalize which choices have been made between either molar or gravimetric units and for which thousand fold of the numerator has been chosen. Future guidance will have to focus on formulating such guidance. Already in the 1987 IFCC recommendations it was explained that for most measurands in laboratory medicine the molar concentration is related to the pathophysiological role of the particular measurand. For that reason, it is more functional to express the amount of substance in molar units

rather than mass units. As a metaphor one could think of the situation of an attack by a herd of wild lions. Would you worry about their mass or about their number? In laboratory medicine, the purpose to quantify measurands is to quantify their relationship to a (patho)-physiological process, which for instance could be the risk for a certain pathophysiological status. In most cases the number of molecules is more relevant than their mass. For Lipoprotein a [Lp(a)] for instance, the molar concentration has a much better predictive value for cardiovascular risk than the mass of these molecules. This is because many variants of Lp(a) exist, which vary in the number of Kringle loops and with that in molar weight. The smallest Lp(a) variants with the lowest number of Kringle loops have the lowest molar weight and therefore the highest number of moles per kilogram. In our metaphor, the most dangerous lions to be chased by are the lean ones, not the obese, heavy ones. When you see lions, count their heads, not their weight. The same is true for Lp(a) molecules. Limiting factors of the use of molar units can be the availability of value assignment of calibrator in molar units. For measurands with a constant relationship between molar and gravimetric concentration, the (temporary) use of gravimetric units is acceptable. However, for measurands for which the molar concentration has a different relationship with the (patho)-physiological status of patients, development of metrological traceability in molar units should be prioritized. The other aspect of the unit that deserves a scientific rationale is the thousand-fold in which the result is expressed. With the liter and kilogram as only acceptable units for the denominator of concentrations, the thousand-fold is chosen by a pre-fix of the numerator. If future recommendations on units would present a rationale for the choice of the thousand-fold, that would increase acceptability of and compliance to such recommendations, as it decrease the risk that a future recommendation will change such choices.

The tasks of the EFLM committee: Harmonization

Martina Zaninotto, Lora Dukic on behalf of the EFLM Committee: Harmonisation

The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Committee for Harmonization (C:H) has published the results of a survey on the harmonization of measurement units, reference intervals, and terminology conducted in EU countries in 2023.

Analysis of the survey results, along with a comparison to a similar survey performed by the EFLM Working Group on Harmonization (WG-H) in 2016, indicated only minor progress toward harmonization – particularly regarding the use of recommended SI measurement units in laboratory reports – due to persistent use of non-SI units in specific countries that still use dL or mL as unit of volume, as well as of obsolete units, such as mEq/L, in reporting electrolytes results [8]. Such findings raised concerns about patient safety, especially in the context of implementing the European Health Data Space (EHDS) project. The strategy proposed by C:H to make the harmonization of measurement units sustainable and widely adopted, identifies some prerequisites that must to be considered: – the need for accessibility and exchange healthcare data; – the need to minimize the risk of patients' safety through the complete comparability in results reporting; – the need to adopt an operational approach taking into account the current situation in European

countries as evidenced by the survey results. Therefore, in an opinion paper recently published [9], the pragmatic approach proposed involves not only the adoption of International System (SI) units according to the rules from the international professional organization [15] but also the need to take into account specific parameters for which some concerns may arise reporting results in SI units, such as enzymes or drugs, being the final goal to assure the most widely shared approach. To achieve this goal, some formal and important key partners should be involved – institutional bodies; external quality assurance (EQA) providers; in vitro diagnostics (IVD) manufacturers; editors of the international scientific journals – with a view to establishing a network aimed at fostering dialogue and developing joint recommendations for the optimal use of SI units in every specific field and in every clinical setting [16]. Such recommended practice should be adopted not only by laboratory professionals but also by information technology (IT) specialists who develop coding systems tailored for the safe and reliable transfer of unambiguous laboratory data within the European Health Data Space (EHDS). By promoting harmonization, EFLM C:H has established intensive communication with EQA providers, in vitro diagnostics (IVD) manufacturers and professional organizations, like Biomed Alliance Europe, so that such constructive and open interaction resulted in the dissemination of the harmonization proposal. In the current healthcare and professional challenge, the harmonization of measurements units can no longer be an option and as members of the laboratory medicine scientific societies we need to make decisions, the first and most important of which may be to set out the timetable for adopting the liter (L) as the sole unit for expressing volume. Moreover, it is absolutely essential to shift the perspective on the harmonization and adoption of SI measurement units, from a purely technical consideration to ethical ones: – for the patients, in terms of justice that is the right to receive the laboratory data comparable across different healthcare settings and – as a part of the laboratory professional ethical duties, that include the stewardship for the correct test interpretation and for the comparability of laboratory information. According to this shared vision, the active involvement of the EFLM and IFCC inter-societies committees and task forces dealing with ethics in laboratory medicine will be a further crucial step.

Measurement units in immunoassays

Etienne Cavalier

Immunoassays are a particularly complex area for the harmonization of measurement units. Indeed, marked heterogeneity in reporting units is still observed between laboratories, sometimes even within the same country or the same city. Unfortunately, this adds to other well-known sources of variability of immunoassays, including incomplete standardization or harmonization, differences in assay design, antibody epitope recognition, calibration, matrix effects and analytical interferences. Clinicians may therefore be confronted with results for the same analyte expressed in different units, obtained with different methods, and interpreted against different reference intervals, decision limits or therapeutic thresholds. This can generate confusion, especially when patients are followed

across institutions, when results are exchanged electronically (cf. LOINC), or when guidelines and local laboratory reports do not use the same units.

The persistence of heterogeneous units is not only the responsibility of laboratories or manufacturers. Clinicians may also be reluctant to change units because they are used to historical numerical values and have developed clinical intuition around them. This is particularly true in endocrinology where interpretation often relies on familiar cut-offs, gray zones and longitudinal trends rather than on isolated values. A scientifically justified change may therefore be perceived as a loss of practical interpretability. There is also a very practical information-system issue. When a result is converted from one unit to another, the test may need to be renamed, remapped or treated as a different item by the laboratory or hospital software. This may interrupt graphical follow-up and make previous results less visible or less easily comparable in the patient record.

Administrative and financial constraints should not be underestimated either. Reimbursement rules, drug eligibility criteria, insurance requirements, national recommendations and therapeutic protocols may refer to a specific unit, which may differ from the unit used by the laboratory or from the unit that would be scientifically preferable. Laboratories may therefore be caught between metrological logic, clinical habits, software constraints and administrative requirements. Harmonization cannot be achieved by laboratories alone. It requires coordination between laboratory specialists, clinicians, manufacturers, EQA providers, health-information-system vendors, guideline developers, payers, insurers and regulatory authorities.

From a scientific perspective, harmonization of the units should not be confused with simple numerical conversion. For an immunoassay, expressing a result in SI units should not automatically mean converting pg/mL or ng/L into pmol/L. Such a conversion is meaningful only if the measurand is a clearly defined molecular entity and if the molar mass used for the conversion corresponds to the molecular form actually measured by the assay. This condition is relatively straightforward for small, chemically well-defined molecules. It is much less straightforward for many peptide and protein hormones. Also, many immunoassays do not measure a single molecular species. Depending on antibody specificity and assay design, they may detect intact hormones, fragments, prohormones, isoforms, glycosylated forms, complexes, macroforms or a mixture of immunoreactive species. A common unit may then create the appearance of harmonization without ensuring true comparability. A common unit should not be mistaken for a common measurand.

Before changing units, several questions should be addressed. What does the assay actually measure? Is the molecular form sufficiently defined? Is the molar mass applicable to the species detected by the assay? Is the calibration traceable to a higher-order reference material or reference measurement procedure when available? Are reference materials commutable across methods? Will the existing reference intervals and decision limits remain valid after the change? These points are essential because between-method differences may persist even after adopting a common unit. If antibodies recognize different epitopes, if interferences differ, or if calibrators are not aligned, using the same unit will not make results truly harmonized.

A pragmatic approach is therefore needed. When the measurand is chemically well defined and a higher-order reference measurement system exists, SI units should be encouraged. This applies, for

example, to steroid hormones such as testosterone and estradiol, where molar units are scientifically meaningful and clinically usable. When the measurand is heterogeneous, method-dependent, or calibrated against biological international standards, forced conversion into molar units may be misleading. In such cases, mass concentration units or international units may remain more appropriate, provided that the method, calibrator, standardization status and decision limits are clearly documented. This may apply to several peptide or protein hormones measured by immunoassay, including thyroidstimulating hormone (TSH), prolactin, insulin-like growth factor 1 (IGF-1), parathyroid hormone (PTH) or growth hormone (GH), although the optimal solution will differ according to the degree of measurand definition and metrological traceability.

This pragmatic position should not be interpreted as accepting any historical unit. Even when strict amount-of-substance SI units are not appropriate, reporting should follow harmonized and practical conventions. The liter (L) should be used as the common denominator rather than the milliliter or deciliter, to facilitate comparison, electronic data exchange and implementation in laboratory information systems. The prefix should also be chosen to give clinically usable numbers, avoiding both unnecessary decimals and unnecessarily large values. C-terminal cross-linked telopeptide of type I collagen (CTX), for example, is much more convenient in ng/L than in $\mu\text{g/L}$. Other analytes may be better expressed in $\mu\text{g/L}$, nmol/L or pmol/L depending on their usual concentration range.

The objective is not to impose SI units in all circumstances, but to select the unit that provides the best balance between scientific validity, clinical interpretability and practical feasibility. For well-defined molecules with traceable reference measurement systems, SI units should be promoted. For immunoreactive mixtures, polymorphic hormones, glycoproteins, macroforms or analytes calibrated against international biological standards, retaining mass concentration units or international units may be more scientifically honest and clinically safer until the measurand and the traceability chain are sufficiently clarified. Ultimately, the unit chosen should reflect what is actually measured, not merely what is convenient or customary to report.

Harmonization of measurement units in nucleic acid (NA) analysis

Jim Huggett

The application of nucleic acid (molecular) analysis, which considers the detection and quantification of specific nucleic acid sequences and, in cases, their modifications, has grown over the last thirty years becoming integral to most areas of life science and clinical research. These techniques that detect specific sequences using targeted complementary methods and/or direct sequencing, are also increasingly applied as in vitro diagnostic tools. Associated measurement has also developed from the nineties where low throughput techniques detecting small numbers of sequences, occasionally considering quantity, were conducted, to today, where an array of high precision methods are available which, in cases, are capable of generating vast amounts of data.

Consequently, molecular analysis is increasingly becoming a high precision science. Despite this, harmonization of measurement units in this critical area of life science has not been a priority with differences in nomenclature abound, even when using the same technique for the same measurand.

As with biochemical analytes, units for nucleic acid analysis often rely on traceability to mass, often per unit volume, and the mole usually in solution as mol/m³; frequently described as molarity (M). In molecular diagnostics mass and mole tend to be used in the design and setup of the “IVD” and in monitoring the preparation and quality control of nucleic acids prior to analysis. Molarity is a popular choice for reporting concentrations of oligonucleotides, frequently used in the preparation and optimization of molecular procedures such as polymerase chain reaction (PCR) or next generation sequencing. Mass is typically used in the estimation of nucleic acid yield, such as post extraction or library preparation, or in supporting the value assignment of calibrators. Mass is typically estimated using spectrophotometry or fluorimetry. Spectrophotometry is known to be inaccurate, with estimates susceptible to interference from impurities or pH. Fluorimetry is generally considered to be more precise than spectrophotometry, but requires calibration, which will often depend on spectrophotometry. Mass estimations are often used to estimate ‘copies’ of nucleic acid sequence; however, this is usually calculated using estimates of molecular weight and predicted base pair size, which has the potential impact of confounding any bias associated with the initial mass-based estimation.

Unlike for chemical analysis, nucleic acid analytical results are frequently reported using copies, which is both useful given the large size, and potential size differences, of the sequence polymers and the fact they can be present within clinical samples at very low concentrations. Results are often reported relative to another ‘reference’ sequence(s) with results reported as a ratio or percentage. While this is a popular approach, as it is simpler from a calibration perspective, the resultant loss of magnitude may miss important clinical information. Furthermore, selection of reference sequence is frequently unvalidated which can lead to inaccuracies. Alternatively, number concentration is also used providing a measure of magnitude usually per unit volume. In this situation calibration is needed and in routine clinical quantification (for example for estimation of viral load) this is supported by WHO reference materials harmonized to the international unit (IU). Despite the frequent use of SI units, rigorous adherence to the SI system through metrological traceability with comprehensive uncertainty budgets is rare and the topic of interest of the Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) Nucleic Acid Analysis Working Group [17]. Nucleic acid analysis is an example where protagonists may also use machine specific outputs as units of measure. Possibly the most prominent example of this is the use of the real time quantitative PCR ‘quantification cycle’ (C_q), which is also termed ‘cycle threshold’ (C_t) and, historically, ‘crossing point’ (C_p). Use of this unit became popular during the COVID-19 pandemic as a surrogate for viral burden and potential severity [18]; however, this represented a bad choice, as interlaboratory error for uncalibrated assays was conservatively estimated to be >100 fold for a given C_q [19]. This represents a challenge for harmonization and standardization by many of nucleic acid analysis, especially for research which is exacerbated by the fact that nucleic acid sequences can vary in specimens by many orders of magnitude.

Harmonization of units of measurement in hematology

Barbara De La Salle

Harmonization of units of measurement in hematology has long been recognized as an important contribution to standardization of laboratory practice and patient safety. A lack of harmonization creates potential for confusion for clinicians, especially when patients' results may be shared between institutions, regions and countries. The International Council for Standardization in Hematology (ICSH) recommends the use of Système International (SI) units for the extended full blood count, with cell counts expressed per liter and the use of gram per liter as the preferred unit for the expression of hemoglobin concentration and related parameters [20]. Despite these recommendations, blood count parameters may still be reported in a variety of units in different regions. The continued use of diverse reporting units reflects the influences common to other pathology disciplines, including the inheritance of historical units and reference intervals and the need for international leadership to promote the change.

The most significant areas of variation have remained largely unchanged for many years: the reporting of white blood cell, red blood cell and platelet counts in units other than per liter, the use of different units for hemoglobin concentration and the reporting of manual, microscopic differential cell counts as percentage of the total white blood count rather than in absolute numbers. Similar inconsistencies occur in the expression of manual reticulocyte counts as percentage of red cells and nucleated red blood cells as per 100 white blood cells. Despite the efforts of bodies such as the ICSH, there remains a significant use of g/dL internationally for hemoglobin concentration. The ICSH has advised against the use of mmol/L for hemoglobin measurement on the grounds of possible confusion amongst healthcare workers in the interpretation of a fundamental screening test [21], although mmol/L is the recommended unit of measurement in some countries. The Joint Committee on Traceability in Laboratory Medicine (JCTLM) database hemoglobin reference method [22] expresses results in mass concentration (g/L), although the LOINC database includes two entries, which differ in measurement units (mass/volume and moles/volume respectively).

The UK Pathology Harmony initiative experience illustrates the challenges of harmonization of blood count units of measurement. The change from g/dL to g/L necessitated a year-long information campaign and the active engagement of professional bodies and other stakeholders to implement [23]. Even so, there is anecdotal evidence that g/dL is still used in some areas. A particular concern is in point of care testing (POCT), where results are being recorded and interpreted outside of the regulated central laboratory's sphere of influence and the remit of experienced laboratory professionals. For most blood count parameters conversion to SI units requires only the application of appropriate multiplication factors of 10 to account for the change in the volume denominator. However, although this variation may be evident as a matter of terminology to a human interpreter of laboratory results, it is a potential source of error and patient harm for the transfer of electronic data, or where a value is used in the calculation of another parameter. The case for harmonization remains strong.

Harmonization of measurement units for cells and subcellular particles

Eloise J. Busby

Methodologies for counting cells have evolved significantly over the last century. Early manual techniques, such as counting blood cells within a defined volume using a hemocytometer or enumerating viable microorganisms via limiting dilution [24], established foundational principles that remain in modern applications. However, as cell analysis in laboratory medicine advances, harmonization of measurement units across eukaryotic cells, prokaryotes, protozoa, and subcellular entities (often at the nm scale) becomes more challenging. Currently, a disharmony exists between international metrological standardization efforts and routine clinical application. The application of microbial enumeration is embedded within culture-based diagnostics. Clinical laboratories measure bacterial colony forming units (CFU)/mL to quantify viable microbial loads in patient samples, directly guiding diagnostic and treatment thresholds. For example, in urine cultures for a suspected urinary tract infection (UTI) 100,000 CFU/mL is considered indicative of bacteriuria in asymptomatic adults, while symptomatic catheterized patients may harbor bacterial burdens of 100 to 10,000 CFU/mL. Indicative thresholds based on CFU/mL are also applied to lower respiratory tract infections and bloodstream infections. In many situations molecular techniques have replaced culture for microbial number concentration estimation which is especially the case for viral analysis. However, quantitative culture approaches such as plaque assays (measuring plaque forming units) and tissue culture infectious dose 50 (TCID₅₀) remain important for confirming pathogen viability, testing antiviral susceptibility, and evaluating vaccine efficacy.

A challenge presented by traditional microbial culture is that it only measures culturable microbes, and is susceptible to bias through clumping or where a microbe is viable but does not culture. Microscopy is often used to estimate microbial burden such as sputum smear microscopy used to approximate *Mycobacterium tuberculosis* in clinical samples into standard categories (high, medium, low, or scanty). More precise quantitative precision may be achieved using genomic methods as surrogates for bacteria, that also provide estimates of characteristics such as resistance; however, routes for harmonization will be critical for these to be successfully used in this way [25]. Bias can also be introduced when quantifying latently infected cells where calibrators are poorly characterized leading to irreproducibility [26]. This is also relevant to the measurement of 'cell equivalents' or 'genomic equivalents' as an intermediary to cell number, where heterogeneous populations of cells may exist. In these situations, the definition of the measurand(s) and associated assumptions are important when comparing techniques. Clinical examples of human cell analysis continue along the theme of UTI diagnostics. Leukocytes in urine are primarily measured using a rapid chemical dipstick test, which changes color to detect leukocyte esterase. If this screening is positive, a laboratory performs microscopic analysis or automated flow cytometry on the urine sample to physically count the number of white blood cells per field of view. Another example of where enumeration of human cells is required is when obtaining a full blood count in the diagnosis of anemia, infection, or bleeding disorders, and is performed using an automated hematology

analyzer. In response to the increased use of automated approaches in clinical diagnostics, the International Council for Standardization in Hematology (ICSH) has established community standards for flow cytometry measurements of blood cell concentrations [20]. These efforts are further supported by specific diagnostic reference methods, such as Deutsches Institut für Normung (DIN) standards for erythrocytes [27], leukocytes [28], and platelets [29]. Conversely, academic and biomanufacturing sectors frequently lack this strict harmonization with diverse unit usage being employed. This highlights a disconnect in unit use between clinical standards and research practices.

Enumeration in parasitology relies on a combination of molecular, serological, and microscopy methods. For organisms like *Plasmodium* spp., quantitative metrics are essential to grade infections and monitor disease control. The WHO recommends reporting parasitemia via microscopy on thick/thin blood films as parasites/ μL based on white blood cell counts [30]. Quality assurance schemes help to harmonize these estimates, though variability in laboratory performance has been observed [31]. Nucleic acid amplification test (NAAT)-based schemes have increased in popularity in recent years, which have facilitated improvements in laboratory performance to further support the reliability of diagnostic tests [32]. Whilst precise molecular methods such as digital PCR are increasingly being explored, establishing the relationship between genomic copy number and parasite count is complex. Protozoa harbor multiple genomes depending on their life stage, and targeted multicopy genes are often compared against expert microscopy which can once again introduce bias [33].

As analytical technologies push the boundaries of detection, the harmonization of units must extend to the smallest biological scales. Subcellular entities including viruses, extracellular vesicles, exosomes, and lipid nanoparticles present new measurement hurdles such as signal to noise resolution owing to their small size. Furthermore, heterogeneity within a sample and an overlap in size makes dealing with sample purity challenging. Establishing consistent nomenclature and standardized measurement units for these nano-entities will be an important next step in ensuring that pre-clinical scientific research can be translated into clinical utility. As in other areas of bioanalytical science, measurements of entities such as viruses may be reported in international units (IU) to harmonize measurements of, for example, number of viral particles in blood (as viral load in IU/mL) with measurements often reported on a logarithmic scale. Log transformation allows for handling and contextualization of values across a broad dynamic range and assists with clinical interpretation where a standardized numerator or denominator is adopted.

Harmonization of hemostasis testing and reporting

Emmanuel Favaloro

The field of hemostasis is complicated by the substantial variation in possible measurement units for the many markers and analytes potentially assessed by testing laboratories (Table 1). The disharmony in units is particularly problematic for some analytes, for example D-dimer and factor

assays. For D-dimer, including consideration of secondary units and possible age range adjustment, 28 different combinations of units of measurement were reported overall by respondents to one survey [34]. This leads to much error and confusion, as previously detailed [34–37]. For factor assays, percent (%) of normal was historically used, but remains present today; alternatives are U/dL or U/mL, or if linked to an international standard IU/dL or IU/mL. Again, this leads to confusion and may lead to inappropriate therapies. There are many ongoing initiatives attempting to improve harmonization of hemostasis reporting [38]. However, strict adoption of SI units (e.g. g/L) will likely not occur. First, most analytes in Table 1 represent functional activities, with many examples of type 2 discordance in antigen vs. activity (i.e., reporting a factor VIII level in g/L may misreport a level as being normal, but this detected protein may not express any functional activity, so will misrepresent reality). Second, most hemostasis analytes are complex proteins with variable structural species. At the moment, clinicians are in general broadly familiar with ‘normal reference ranges’ (which tend to be close to 50–200 U/dL for most analytes), as well as pathological cut-offs (usually close to 50 U/dL, or else defined by international consensus – e.g., 10 U/dL for ADAMTS-13 to define thrombotic thrombocytopenia purpura). If each analyte was to be reported in g/L or mol/L or equivalents, then separate, difficult to recall reference ranges or pathological cut-offs would arise for each analyte. Third, clinically useful reporting in hemostasis includes the use of assay ratios, in particular for a complex protein like von Willebrand factor (VWF), which has a multitude of activities or functions, and multiple molecular weight species based on multimerization of a core protein structure. Currently, the ‘normal reference range’ and pathological cut-off for these ratios is represented by ~0.7–2.0 and 0.7, respectively. It is difficult to envisage how these ratios will be calculated and used if SI units were universally adopted. In summary, the complexity and variability of hemostasis analytes, the presence of multiple species or variants of the same protein, and the different functional activities that some proteins express, has led to a situation in which pragmatic adoption of other ‘harmonized’ units has dominated; these will likely dominate for some time to come. Indeed, for the only analyte routinely reported in g/L (fibrinogen), given the complexity of the presenting protein species in dysfibrinogenemia or in disease, a strong case can be argued to convert reporting from g/L to the more classical or common % or U/dL.

Harmonization of measurement units – infectious disease serology perspective

Wayne Dimech

Unlike other medical pathology disciplines, the standardization of infectious disease serology results has been problematic for decades. Several attempts have been undertaken to create reference standards for infectious disease serology, but generally these have proven unsuccessful in aligning the quantitative results of different commercial immunoassays that test for antibodies for the same organism. The reasons harmonization of units for infectious disease serology has proven difficult has been detailed previously [39, 40]. It is important to first understand the clinical use of

serology testing. The detection of antibodies to antigen(s) specific to an organism is used as an indicator that the individual has been exposed to the organism through a wild-type infection or vaccination. The presence of antibodies is used to predict a person's immunity to future infection (e.g., anti-HBs or anti-rubella antibodies), or as a surrogate for predicting infection (e.g., anti-HIV or antitreponemal antibodies). Another use of infectious disease serology results is to predict the stage or prognosis of disease. For example, the presence of anti-EBV EBNA antibodies indicates a past EBV infection, whereas anti-EA IgG or anti-VCA IgM indicates a recent infection. The many hepatitis B serology markers can predict the stage of disease – acute or chronic infection, or clearance of infection with immunity [41]. The clinical interpretation relies of the presence or absence of antibodies. It rarely, if ever, uses a quantitative assessment for clinical interpretation [42]. The main reason for the difficulty in harmonizing serology results is that each test detects different measurands [43]. An anti-HIV test could detect an antibody response to one or more of up to 15 different antigens. These antigens frequently mutate. An infected individual may develop different subclasses of antibodies to various HIV antigens which come and go over time. Antigens used by the test kit manufacturer may be disrupted, inactivated whole organism, purified native antigen or recombinant antigen. The conjugate used in each test will differ and could be produced from a range of species (mouse, rabbit), be antibody fragments, polyclonal or monoclonal in nature [44]. The test could be designed to disrupt antibody-antigen complexes or just detect free, circulating antigens or antibodies. Some tests utilize signal amplification to increase analytical sensitivity. So, even if an assay detects anti-HIV, each assay is detecting different measurands, so harmonization of the reported results between tests is fraught. The most accepted “quantitative” serology test is for the detection of anti-rubella IgG. The current WHO International standard was developed by the Staten Serum Institut (Copenhagen, Denmark) in the 1970s and designated RUB-1-94. It was introduced as the WHO International Standard in 1995 [45]. Therefore, the same standard has been used to calibrate all commercial anti-rubella IgG assays for more than 30 years. However numerous publications throughout the standard's history have noted the poor standardization of anti-rubella IgG results [46–53], even though rubella virus has only three antigens. Following a publication from a multi-institute expert review of standardization of anti-rubella IgG, including representatives from WHO, USA CDC, USA FDA, Paul Ehrlich Institute, National Serology Reference Laboratory, Australia and National Institute for Biological Standards and Control (NIBSC) [46], the WHO Expert Committee on Biological Standards concluded stakeholders “*should be encouraged to reconsider the appropriateness of quantitative anti-rubella measurement for the determination of immune status and use of 10 IU/mL as a cut-off point for assessing immune protection*” [54]. The International Standard instruction for use (IFU) was modified to include a statement “*IVD manufacturers, regulators and assay users should be made aware of RUBI-1-94 potential lack of commutability when used as a calibrant*” [55]. Other international standards also have disclaimers for use as calibrants. The 3rd International Standard for Anti-Measles (code: 97/648) claims “*This preparation has not been calibrated for use in ELISA assays and/or a unitage assigned for this use*” as it was originally developed for the quantification of antibodies using the plaque neutralization test (PNT) for vaccine potency [56].

Table 1: Disharmony in hemostasis testing and reporting.

Laboratory test/analyte/marker	Methodology	Possible units
Routine assays		
Prothrombin time (PT)	Clotting assay	s, ratio, %
International normalized ratio	Clotting assay/calculation	Ratio (none)
Activated partial thromboplastin time (APTT)	Clotting assay	s, ratio
Thrombin time (TT)	Clotting assay	s
D-dimer ^a	Latex immunoassay (LIA)	µg/L, µg/mL, mg/L, ng/mL, (others; g/L minimally used)
Fibrinogen	Clotting assay	g/L; mg/dL; %
Specialized assays		
Factor assays (II, V, VII, VIII, IX, X, XI, XII)	Clotting assays; some chromogenic (FVIII, FIX)	%, U/dL, IU/dL, U/mL, IU/mL; VWF also reported as ratio of functional activity to antigen
Factor XIII	Functional, LIA (clot solubility)	
von Willebrand factor (VWF) antigen and activity assays	LIA, ELISA, CLIA, platelet agglutination	
ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, 13)	LIA, ELISA, CLIA	
Protein C, Protein S, Antithrombin	Functional, LIA	
Lupus anticoagulant (LA)	Clotting assays	Ratio, normalized ratio, ICA (formula/calculations)
Anti-phospholipid antibodies (anti-cardiolipin [aCL], anti-b2glycoprotein I [ab2GPI], etc.)	ELISA, CLIA, MFI, other	U/mL, GPL or MPL units
Heparin induced thrombocytopenia (HIT) antibodies	ELISA, CLIA, LIA, LFA, functional assays	U/mL, OD
Heparin and heparin-like anticoagulant drug levels	APTT or anti-factor Xa chromogenic assays	U/mL
Direct oral anticoagulant drug levels	Clotting or anti-factor Xa chromogenic assays	ng/mL

CLIA, chemiluminescence immunoassay; ELISA, enzyme linked immunosorbent assay; ICA, index of circulating anticoagulant (Rosner Index); LFA, lateralflow assay; LIA, latex immunoassay; MFI, multiplex flow immunoassay; OD, optical density. ^a Also has secondary units: fibrinogen equivalent units (FEU) vs. D-dimer units (DDU).

Recently, a concerted effort was made to develop a standard for anti-SARS-CoV-2 antibodies [57, 58]. The design of this standard differed to that of previous standards, as it took into consideration the variability of the viral antigens. The report demonstrated a degree of harmonization if results of binding antibody units (BAU) to different antigens (receptor binding domain [RBD], spike subunit 1 [S1], or spike) were taken into account, depending on the assay's target antigen. They concluded BAU results in IU/mL could “*successfully be compared across a range of well validated commercial assays with different designs and formats*” [58]. They suggested that both the antigen and analyte should be specified when reporting the results of binding antibody assays (e.g., BAU_{RBD}-IgG/mL or BAU_{RBD}-Ig/mL). However, others questioned this position [58, 59] or have reported that the standardization of anti-SARS-CoV-2 assays was not successful [60, 61]. Irrespective of the lack of standardization of infectious disease serology units using international standards as a calibrant for binding immunoassays over a 30-year period, it is important to note that serology does not “measure the amount” of an analyte. The signal to cut-off ratio (S/Co) or the IU/mL is not quantifying the amount of antibodies present. It detects the amount of binding between the antibodies in the patient's sample and the antigen(s) on the solid phase of the assay [39]. Finally, there is no clinical need for quantitative serology assays. A person with low-level anti-HIV is still managed the same as a person with high levels. It has been demonstrated that low levels of antirubella IgG (below the

suggested 10 IU/mL level for immunity) are protective [62]. This is because, even though an individual's immune response may wain, subsequent exposure to the antigen will cause a secondary immune response supported by the pre-existing cellular immunity. The quest to harmonize infectious disease serology results using international standards as calibrants has been unsuccessful and has created clinical issues through the over-reliance on a quantitative value. Of note is anti-rubella IgG testing. It has been noted on many occasions that there is little harmonization of low-level anti-rubella IgG test results across assays. This situation leads to clinicians falsely identifying seroconversions in pregnant women [46, 63, 64]. This misdiagnosis could result in an unnecessary termination of pregnancy or a congenitally infected baby. WHO international standards play an important role in harmonizing biological assays such as PNT used in vaccine potency studies but should not be used as calibrants for binding immunoassays for infectious disease serology testing.

From structure to standard, together – towards a unified laboratory language

R. L. Smeets on behalf of the EFLM Committee on Exchange of Laboratory Data

As laboratory specialists we are responsible for the correct analysis of samples, providing proper and trustable results as a solid basis for medical decision making. Our profession has been subject to change over the years, in which the analytical process was automated and the order placement and result reporting rapidly digitalized. We now enter a new phase in the transition of our profession laboratory medicine which is defined by cross-enterprise exchange of diagnostic data. The European Health and Data Space regulation enforces the exchange and usage of medical information for primary care and secondary use (e.g. research) and includes diagnostic data exchange in the near future. Although, laboratory data is structured, it is not uniform. Furthermore, there is a plethora of diagnostic data available, there is a huge amount of human instigated variation in description of diagnostic data, diversity in analytical methods, which hampers comparability and interpretability of results, and our systems have been configured for internal communication. Our internal, local focus does not support external, (inter)national communication of diagnostic information.

This brings us to the problem which we need to solve... we should stop dealing in diversity. The FAIR principle, in which data should be findable, accessible, interpretable and reusable, also holds true for diagnostic data. We therefore need to transform our data. We need to unify in vision, harmonize on units and methods and start with semantic standardization of result communication. This will bring true value to diagnostic data and is a new form of postanalytical quality, which we should care for, govern and control. This will make a difference; this will add value to laboratory medicine. This makes data, reusable, interpretable information. But which steps should we follow and how do we achieve unity? First we need to define our common goal, our vision on diagnostic data exchange and reusability. Diagnostic data that we generate has an intended use for primary care and research purposes as has also been defined in the European Health Data Space (EHDS) regulation. Our data

must therefore be exchangeable, interpretable and reusable, guaranteeing not only men – but also machine readability. Therefore, we need to organize our diagnostic data, semantically standardize our data, unify on units of measurands and define the methods based on equivalence, comparability and interpretability. By stratifying our diagnostic data based on a data complexity matrix (Figure 1) we can group diagnostic tests based on exchangeability and interpretability into 3 clusters; simple – results of tests which are comparable, equivalent and can be semantically standardized using same LOINC and Unified Code for Units of Measure (UCUM) or Nomenclature, Properties and Units (NPU) units. This first step will help us to define the rules for correct semantic standardization as a basis for correct exchange of diagnostic information. Furthermore, this datadriven approach can guide harmonization efforts within our scientific community and harmonize the use of result reporting units. The second step – complicated tests: the conventional semantic standards do not correctly standardize the data and interpretation of results and reuse of information is at risk. For this category we need to do a fitgap analysis and start a discussion on the current data model for lab data exchange and define the lacking elements which need to be added or evaluated in order to achieve correctness of data and interpretation of results. This second step will help us to evolve the current data model for diagnostic data exchange and can help us to identify missing meta data elements, like method or calibrator (traceability) for primary and secondary use. The last category is complex data; the use of conventional semantic standards is not recommended due to the complexity of reporting and the risk of misinterpretation. For this category we need to define the correct protocol for exchange (e.g. flow cytometry reports or metabolic profiles).

This step-up approach will define the needs and necessities for further diagnostic data structurization and will guide us towards the needed standardization which will be the basis for correct use of diagnostic data and therefore maximizing care value.

A scientific basis for choosing laboratory units

Young Bae Hansen, Chair of IFCC Committee on Nomenclature, Properties and Units (C-NPU)

Dybæk and Jørgensen wrote in 1967: “To state that the mass concentration of hemoglobin in a blood sample is 25 is essentially meaningless. If the unit g/L is assumed, the patient is considered anemic. If the unit g/dL is assumed, the patient is considered to be polycythaemic” [65]. Any laboratories can choose a unit for a given quantity with reasonable and sound arguments, whether scientific, cultural, or traditional. This may work perfectly at that given hospital/laboratory. However, when laboratory results must be shared across organizational, geographical, IT system and time borders, commuting clinicians and patients are faced with increasing uncertainty of interpreting the values due to presentation of several units for the same quantity. They cannot tell if a value change means the patient is improving or just reflects a different unit. This is a valid and current concern, especially when clinicians and patients are moving between different health care sectors and even country borders. Also, collecting results from different laboratories creates heterogeneous data. This requires difficult management to make the data uniform before it can be analyzed. Studies on treatment or lab trials are often published in different units. Evaluation of

treatment or laboratory trials at a hospital is being published with different units that the readers may not use and have to convert to different units that they are familiar with, using an arbitrary conversion factor. Thus, comparison of results may be difficult.

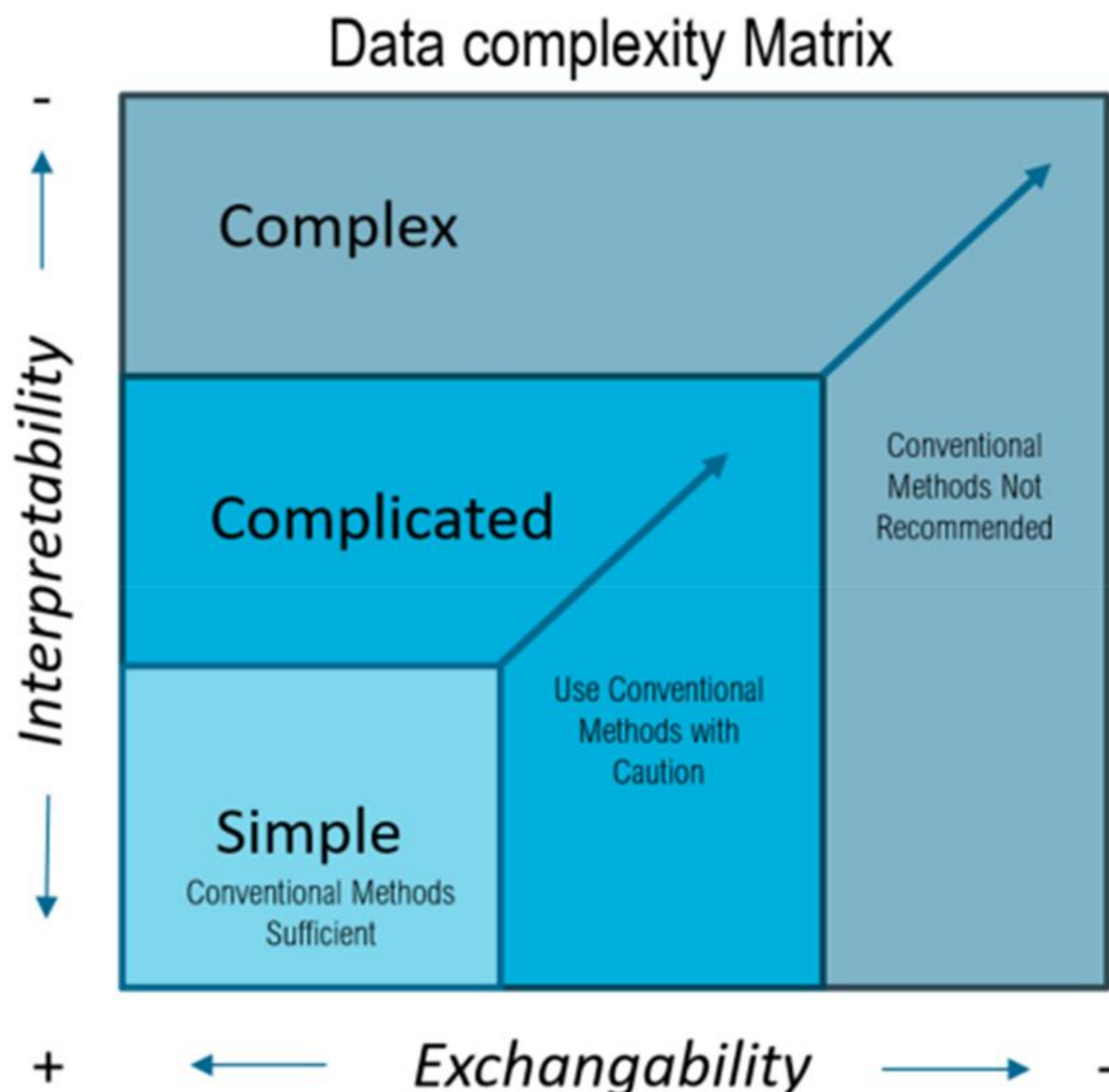


Figure 1: Proposed data complexity matrix for stratification of diagnostic data exchangeability.

Thus, the demand of having the same unit for a quantity increases. Whether standardization or harmonization efforts are taken, the efforts and discussions lie in the choice of unit. The question remains: how do we select the same unit, and what arguments should guide this choice? First, the choice must be objective, consistent, stable, reproducible, traceable, and transparent. This ensures future generations do not face the same debates that may lead to major changes. Second, while many sound arguments exist – cultural, traditional, laboratory fields, patient safety, scientific, medical treatment, technology, or based on surveys (opinionable), – only the scientific argument meets the above criteria. The other listed arguments struggle in meeting these criteria. The scientific argument relies on either evidence or logical reasoning. Evidence is the preferable and logical

reasoning being the next preferable, but as it may be difficult to perform studies in the pursue of evidence, the logical reasoning is the most practical approach. The argument of patient safety is valid and essential; however, it should be a part of the definition of the scientific argument.

If the laboratory and medical communities agree on these or some of the criteria, a major step forward has been achieved. The most essential next step is to critically establish and validate these criteria across all laboratory disciplines. A final comment, the unit is an integrated part of a quantity and is only meaningful when the other elements are included such as the system (the patient or part of the patient), component (chemical/molecular entities or biological processes) and the kind-of-quantity (e.g., mass ratio, substance concentration, etc.).

The clinician's perspective

Paolo Simioni

Laboratory medicine is a cornerstone of modern healthcare, providing objective information for risk assessment, diagnosis, treatment selection, patient monitoring, and follow-up. Accordingly, both the complexity of laboratory testing and the time required for test ordering and result interpretation have substantially increased. Studies evaluating physician workflow have shown that reviewing laboratory and imaging results represents a considerable proportion of clinicians' daily activities, contributing significantly to cognitive and administrative workload [66]. For laboratory information to generate clinical value, test results must be reported in a clear, understandable, and readily interpretable manner. Laboratory reports should enable comparison of results across institutions, align with clinical guidelines, minimize the risk of misinterpretation, and support continuity of care. These requirements are particularly important in an era of increased patient mobility, globalization of healthcare, and growing patient access to laboratory services from different providers, both nationally and internationally. Therefore, harmonization of laboratory reporting practices – including measurement units, reference intervals, and decision limits – is essential to ensure consistent interpretation of results and optimal patient management, regardless of where testing is performed. When identical analyte concentrations are reported using different measurement units, clinicians may experience uncertainty and confusion. Moreover, the increasing practice of providing laboratory reports directly to patients, particularly in outpatient settings, introduces an additional risk of misinterpretation. Abnormal or borderline results may generate unnecessary anxiety and concern, prompting patients to seek clarification from their primary care physician or other specialists. This may result in additional consultations, inappropriate repeat testing, increased healthcare costs, inefficient use of resources, and delays in clinical decision-making. Lack of uniformity may therefore lead to misinterpretation, diagnostic errors, inappropriate clinical decisions, or suboptimal patient management. From a clinical perspective, harmonization of measurement units is not merely a technical or analytical issue, but a fundamental patient-safety and healthcare-quality imperative. Non-uniform units may also lead to unnecessary repeat testing, hinder longitudinal comparison of results generated by different laboratories, and create barriers to interoperable electronic health records, health information exchange networks, and clinical

decision support systems. Harmonized measurement units are therefore a prerequisite for safe, efficient, and patient-centered healthcare delivery. Although harmonization must be grounded in robust scientific evidence, its ultimate purpose extends beyond scientific uniformity. Its primary goal is to improve clinical interpretation, support informed decision-making, enhance patient safety, and ultimately improve patient outcomes. As clinical specialist in coagulation and thrombosis disorders, I have long supported the approach adopted for the introduction of the International Normalized Ratio (INR) for reporting prothrombin time results. Although initially debated and resisted, the INR has become one of the most successful examples of harmonization in laboratory medicine. It has enabled comparability of results generated by different laboratories, using different reagents and instruments, across countries and healthcare systems. Most importantly, it has substantially contributed to the safe and effective management of patients receiving oral anticoagulant therapy by ensuring that clinical decisions are based on results that are consistent, reliable, and universally interpretable [67]. Another critical requirement for successful implementation is education and training. The transition to harmonized units requires targeted educational initiatives for healthcare professionals, laboratory staff, students, and trainees to ensure correct understanding and interpretation of results. The temporary coexistence of conventional and harmonized units may increase uncertainty and create opportunities for error. Since clinicians often have long-standing familiarity with conventional units, the introduction of new reporting systems may initially generate concern, resistance to change, and perceived risk of misinterpretation. Greater efforts are also needed to harmonize measurement units in scientific publications, which are essential tools for updating and disseminating medical knowledge. Successful implementation therefore requires a carefully planned change-management strategy, including educational programs, clear communication, dual reporting where appropriate, and close collaboration between laboratory professionals and clinicians. These measures are essential to facilitate adoption, maintain patient safety, and ensure that the benefits of harmonization are fully realized. In conclusion, from a physician's perspective, harmonization of measurement units is fundamentally a clinical issue rather than a purely technical laboratory matter. Uniform reporting enhances patient safety, improves communication among healthcare professionals, facilitates continuity of care, supports evidence-based clinical practice, and enables the full potential of digital health technologies, including electronic health records and clinical decision support systems. Although implementation may require substantial effort, investment, and coordinated educational initiatives, the benefits for patients, healthcare professionals, and healthcare systems are undeniable. In an increasingly interconnected and mobile world, harmonized measurement units should no longer be regarded as an aspirational goal, but as an ethical responsibility and a prerequisite for high-quality, patient-centered healthcare. The central question is therefore no longer whether harmonization is desirable, but how rapidly and effectively it can be achieved. The challenge now is to translate scientific consensus into coordinated action, engaging laboratory professionals, clinicians, educators, scientific societies, regulatory bodies, healthcare organizations, and policymakers in a shared commitment to improving patient care through harmonization.

Conclusions

Mario Plebani

The collection of viewpoints on the harmonization of measurement units presented in this Forum, contributed by experts from different fields of laboratory medicine, is not intended to provide definitive recommendations. Rather, its purpose is to stimulate discussion and highlight the opportunities, challenges, and potential strategies for achieving greater consistency in laboratory reporting worldwide. The opinions expressed reflect the individual perspectives of the contributors, and no attempt has been made to develop a consensus-based or cross-disciplinary position. The formulation of formal recommendations should remain the responsibility of international scientific and professional organizations, including the IFCC, EFLM, ICSH, and other relevant bodies. These organizations are uniquely positioned to critically evaluate the available evidence, build consensus among stakeholders, and issue authoritative guidance. Nevertheless, it was consistently emphasized that harmonization should be actively pursued at all levels – local, regional, national, and international – as it represents not only a scientific and professional objective but also an ethical responsibility toward patients and healthcare systems.

Over the past few months, the Journal has published a series of articles addressing this important topic. It therefore appears timely to provide readers and other stakeholders with an updated overview of the current state of harmonization across the various disciplines of laboratory medicine, while also presenting the perspectives of experts with diverse professional backgrounds and experiences. We believe that this Forum should be brought to the attention of the aforementioned scientific and professional organizations for careful consideration. It is our hope that the viewpoints collected herein will contribute to the development and eventual endorsement of a shared international position, thereby fostering greater consistency in laboratory reporting and helping to overcome the current fragmentation in the adoption and use of measurement units.

Ultimately, harmonization should be recognized as a fundamental component of high-quality laboratory medicine, contributing to clearer communication among healthcare professionals and with patients, improved comparability of results across institutions and countries, enhanced patient safety, and greater continuity of care in an increasingly interconnected healthcare environment.

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