How to Cite:
Alnihier, M. M. H., Alotaibi, A. T., & Alanzi, A. S. B. (2020). Standardizing units of measurement for medicinal biomarkers across healthcare systems and countries: Critical review. *Tennessee Research International of Social Sciences*, *2*(1), 25–36. Retrieved from https://triss.org/index.php/journal/article/view/41

Standardizing units of measurement for medicinal biomarkers across healthcare systems and countries: Critical review

Mohammed Mishal Hamoud Alnihier
KSA, National Guard Health Affairs
Email: AlniherMo@MNGHA.MED.SA

Ahmed Turki Alotaibi
KSA, National Guard Health Affairs
Email: A7mdoh85@gmail.com

Awad Shehab B Alanzi
KSA, National Guard Health Affairs

***Abstract*---**Background: In the field of laboratory medicine, the terms "standardization" and "harmonization" are often used interchangeably, as they both aim to achieve the same outcome: ensuring that measurement results from different routine measurement procedures are equivalent over time and space, in accordance with specific analytical and clinical quality requirements. However, these phrases delineate two separate but interconnected ideas grounded on the principles of traceability. Aim of Work: The aim of this review is to clarify the distinction between the concepts of standardization and harmonization in laboratory medicine, and to highlight the importance of these efforts in improving patient care. Methods: This review synthesizes the existing literature on the concepts of standardization and harmonization in laboratory medicine, their underlying principles, and their practical applications. Results: The term "standardization" refers to the process of ensuring that measurement results are comparable and can be traced back to the International System of Units (SI) using a high-quality primary reference material and/or a reference measurement method (RMP). The term "harmonization" is often used when there are no high-level main reference materials or reference measurement procedures available, but the results obtained are nonetheless comparable. Harmonization is a crucial element of quality in laboratory medicine since its main objective is to enhance patient outcomes by providing precise and practical laboratory

Tennessee research international of social sciences © 2020.
ISSN: 2766-7464 (Online)
Publisher: Smoky Mountain Publishing
Manuscript submitted: 27 Jan 2020, Manuscript revised: 09 Feb 2020, Accepted for publication: 15 March 2020

information. However, several laboratory test findings continue to exhibit significant variability and lack proper standardization and harmonization. Conclusion: In conclusion, laboratory experts should intensify their efforts to provide interchangeable and comparable laboratory data, with the ultimate goal of ensuring improved diagnosis and treatment in patient care.

***Keywords*---**Standardization, Harmonization, Laboratory medicine, Traceability, Quality assurance.

Introduction

The prevailing consensus is that quality in laboratory medicine should be defined as the assurance that every step in the whole testing process is executed accurately, hence providing sound decision-making and efficient patient care. The concept of the "brain-to-brain turnaround time loop" explains that the generation of any laboratory test result goes through multiple steps. These steps include ordering, collection, identification (at various stages), transportation, separation (or preparation), analysis, reporting, interpretation, and action. The ultimate objective is for the intervention performed on the patient, guided by laboratory data, to be precise, prompt, and secure. Harmonization is a crucial element of quality in laboratory medicine since its main objective is to enhance patient outcomes by providing precise and practical laboratory information. It is often believed by patients, physicians, and other healthcare professionals that clinical laboratory tests conducted by various labs on the same sample and specimen at different periods may be compared, and that the findings can be interpreted accurately and consistently [1-3].

Regrettably, this is not always true, as several laboratory test outcomes remain significantly inconsistent, inadequately standardized, and lacking harmonization. While the primary emphasis was initially on standardizing analytical processes and methods, the scope of harmonization extends to encompass all other elements of the total testing process (TTP), including terminology and units, report formats, reference intervals and decision limits, as well as tests and test profiles, requests, and criteria for interpretation. This notion has been described as "the comprehensive integration of all aspects of laboratory medicine, including the analytical phase as well as the pre- and post-analytical steps." [4-7]

According to the Clinical and Laboratory Standards Institute (CLSI), the definition of harmonization should be revised to encompass the process of acknowledging, comprehending, and elucidating disparities in all aspects of the Total Testing Process. This should be done while striving to establish consistency in laboratory information, or at the very least, a method of identifying and disseminating shared policies and procedures. The ultimate goal is to enable different groups to utilize data obtained from various laboratories interchangeably. The primary rationale for prioritizing a global perspective on harmonization is twofold: the inherent character of mistakes in laboratory medicine and the compelling data indicating significant error rates in both the pre-analytical and post-analytical phases [8,9]; the growing need to enhance the accuracy of test requests and

result interpretation; The presence of significant differences in terminology, units, and reference ranges; the necessity to shift from the notion of "normal" reference intervals to the longitudinal comparison of patient data across various technologies and laboratories; and the potential risks to patient safety associated with the aforementioned issues (a to c) [10]. Therefore, it is crucial for current and future initiatives to reflect the global perspective of harmonization and develop the most effective method to achieve enhancement.

Aim of Work

In this article, we aim to clarify the distinction between the concepts of standardization and harmonization in laboratory medicine, and to highlight the importance of these efforts in improving patient care.

Factors influencing the process of harmonization

The primary factors motivating the need for harmonization in laboratory medicine may be classified into two broad categories: patient-centered and organization-centered.

Ensuring the Well-Being and Protection of Patients

The evidence presented shows that not only inconsistent findings, but also variations in terminology, units, and reference ranges may lead to misunderstanding of laboratory information, incorrect treatment, and negative patient outcomes [11,12]. The primary motivation for harmonization is the need to minimize patient risk arising from variations in laboratory practices and findings. This imperative is considered an ethical obligation for laboratory personnel.

Application of Guidelines

Scientific and professional groups are creating and publishing guidelines to help with the ordering and interpretation of laboratory tests. These guidelines are based on evidence and aim to promote best practices. The recommendations are formulated to optimize clinical outcomes for patients and ensure efficient use of resources, regardless of the location where patients are examined and treated [13,14]. Practice guidelines sometimes rely on fixed decision values for laboratory tests. However, the absence of harmonization amongst clinical labs in terms of measuring processes and outcomes might lead to incorrect interpretation and treatment choices. When a test employed in a recommendation is not harmonized, the test findings cannot be matched with the thresholds and interpretation criteria. This may mislead clinicians and undermine their efforts to comply with the guidelines [15,16].

Accessing and Using Several Laboratories

Patients should no longer be obligated to use the same laboratory consistently in order to get consistent findings. In order to accommodate factors such as work, family, and travel schedules, it is important to allow patients to get consistent test results from labs located in various places. Whether individuals plan to travel

domestically or internationally, it is illogical to mandate their use of a certain clinical laboratory based on the argument that findings from multiple labs lack consistency and comparability. The implementation of a patient-centered service should be modified in order to facilitate the comparison of data across various providers and geographical regions [17].

Electronic Medical Records

With the recent advancements in information technology, it is now feasible to combine electronically dispersed data from several labs. It is vital to recognize that the requirement for harmonization has risen due to the implementation of electronic health recording (EHR). Berg and Lane argue that the transition to complete electronic reporting of pathology findings highlights the hindrance caused by variations in test nomenclature, reference intervals, and units of measurement. While the laboratory often facilitates the transmission of test results, healthcare services frequently want to integrate external test data and maybe even the findings of at-home or point-of-care testing into the patient record [12]. Currently, this fair criterion often requires the laboratory to do duplicate tests.

Frequently, the presentation of data in electronic health records lacks clarity regarding the source of the result. Furthermore, it is concerning that clinicians are often unaware of the potential discrepancies that can arise when a sample or specimen is tested using different methods or interpreted by different pathologists. This is particularly relevant in cases involving tumor markers or endocrine tests, where there is a significant level of variability between different methods. The variations in laboratory results prevent the comparability and interchangeability of data, and can even alter the patient's "natural history" that is based on data collected over time and by different laboratories. This can lead to misinterpretation and improper decision making, treatment, and monitoring [18,19].

Official Recognition or Certification That an Organization or Program Meets Certain Standards or Qualifications

ISO 15189, the International Standard for clinical laboratory accreditation, mandates that laboratories must calculate the measurement uncertainty for each measurement method and document the accuracy and metrological traceability. The International Standard (5.6.4) explicitly requires examination findings to be similar, stating that "comparability applies to both identical and different procedures, equipment, several locations, and any combination of these elements. Furthermore, it is necessary for the laboratory to inform users about any disparities in the comparability of findings and to explain the potential impact on clinical practice when measuring devices provide varying measurement intervals for the same measurand and when examination procedures are altered [20].

The pre-examination processes, such as providing information to patients and users, collecting and handling primary samples, and filling out request forms, as well as the post-examination processes, including reporting results, specifying report attributes and content, and revising reports, should establish a foundation

for standardizing these procedures. However, according to the International Standard, harmonization is also a necessary condition for accreditation. Currently, several national organizations are maintaining a rigid approach to laboratory certification. As per the recommendations of the European Co-operation for Accreditation (EA), ISO 15189 scopes can be either fixed, where each test included in the accreditation is documented, or flexible, where all combinations of medical field, examination type, and materials that the laboratory is competent in are mentioned. Currently, national accrediting organizations maintain the practice of using set scopes due to both inertia and the concern that a more flexible scope might result in an excessive assessment of labs' competency. The majority of nations exclusively use fixed scopes. EA encourages the utilization of adaptable scopes, since it facilitates innovation and enhances the quality of laboratory medicine. The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has officially approved and provided support for this technique [21,22].

Integration and Interconnection

Tate et al. [23] have emphasized that clinical laboratory testing has become a worldwide endeavor, with labs no longer operating independently. Globalization issues, such as the implementation of shared guidelines and protocols, adherence to International Standards for accreditation, and the rise of medical tourism, all impact the provision of laboratory services [23]. Consequently, these factors promote the standardization of laboratory operations across different countries. The growing movement towards consolidation and networking of clinical labs necessitates the need for laboratory findings to be comparable and interchangeable as a logical foundation. While it is often assumed that using the same methodologies and diagnostic platforms would provide equal findings, data from external quality evaluation systems reveal significant discrepancies across laboratories using the same techniques and approaches. Harmonization and standardization cannot be attained by just increasing the workload and sample size. These processes rely on a solid scientific and professional foundation, rather than being dependent on large quantities [24].

Clinical Governance

The variations between different labs lead to uncertainty for individual patients and the wider community, resulting in increased vulnerability for clinical laboratories and a decrease in the credibility of the profession [25]. Clinical laboratory practice must constantly consider the factors of clinical efficacy, quality, and patient safety. Harmonization is a common problem in Clinical Governance, aimed at preventing cost-cutting measures and prioritizing clinical efficacy, quality, and patient safety in the provision of laboratory services [26].

Present Endeavors and Efforts Towards Coordination And Standardization

The number of harmonization activities is growing, and the increased recognition of the significance of the global perspective has prompted several efforts to enhance the different stages of the TTP, not just in clinical chemistry but also in the broader area of laboratory medicine.

Performance Metrics

As per the Institute of Medicine's (IOM) approach to healthcare quality, it is important to identify trustworthy Quality Indicators (QIs) in order to measure the quality of a specific component of treatment by comparing it to a set standard. A quality indicator is an objective measure that has the potential to evaluate all critical care domains defined by the IOM, including patient safety, effectiveness, equity, patient-centeredness, timeliness, and efficiency. It is based on evidence associated with these domains and can be implemented consistently and comparably across different settings and over time [27].

The establishment, execution, and supervision of useful analytical quality requirements have been pivotal in enhancing the quality of laboratory services and decreasing the occurrence of analytical mistakes. Nevertheless, there is a substantial amount of research that illustrates the significance of the extra-analytical phases, namely the pre-analytical stages, their susceptibility, and their influence on the overall quality of laboratory information. The discovery and implementation of relevant Quality Indicators (QIs) is a potential approach to gather data on quality in the TTP. It is especially beneficial for spotting errors in the different phases of the process, giving important information for quality improvement programs [28]. Furthermore, Quality Indicators (QIs) are an essential need for the certification of clinical labs in accordance with the International Standard ISO 1518919. While some nations have built intriguing programs on indicators in the TTP, there is currently no agreement on creating unified recommendations for the implementation of universal QIs and standardized language [29].

In 2013, a preliminary agreement was reached during a Consensus Conference held in Padua. This agreement was the result of a review of the model of quality indicators (MQI) developed by the Working Group on 'Laboratory Errors and Patient Safety' of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). The list of Quality Indicators (QIs), which is widely agreed upon and considers both their significance and relevance, may be evaluated by any clinical labs that are possibly interested. This evaluation aims to find further measures in the harmonization process. Figure 1 depicts the correlation between the worldwide harmonization and the use of Quality Indicators (QIs) for monitoring and enhancing the quality of every stage of the testing process [30].

Overview and Plan for Achieving Consistency and Standardization

Significant advancements have been achieved in the field of harmonization in laboratory medicine. There is a widespread understanding that harmonization should include not just the analytical phase, but all stages of the TTP, which involves "the request, the sample, the measurement, and the report". Harmonization attempts should not only focus on clinical chemistry tests, but also include the whole area of laboratory medicine, including measurements conducted in research and translational medicine projects [31,32]. Furthermore, there is a consensus that due to the intricate nature of the procedures involved in achieving harmonization, a methodical approach is necessary. The foundation of

this should rely on "a system with clearly established protocols, open and accountable functioning, efficient communication with all parties involved, global participation, and a collaborative approach to working together" [33].

A proposal has been made to establish the Harmonization Oversight Group, which would be responsible for managing various aspects of the process. This includes receiving proposed candidate measurands for evaluation, prioritizing measurands, overseeing the implementation of harmonization schemes for different measurands, and communicating with all stakeholders involved. Clinical and laboratory organizations, in vitro diagnostic (IVD) manufacturers, government or regulatory bodies, journal editors, and research groups provide their expertise on measurands and other relevant information to facilitate harmonization efforts. The organizers of external quality assessment (EQA) and proficiency testing (PT) programs should have a crucial role in maintaining and highlighting the importance of a higher level of harmonization. This can be achieved by using control materials that can be compared across different laboratories, target values assigned by reference laboratories with approved reference systems or designated comparison methods, and reliable statistical analysis of the collected data [34,35].

Cobbaert et al. emphasize that the level of interchangeability or test equivalence and the effectiveness of standardization/harmonization initiatives may be assessed by EQA schemes, sometimes referred to as PT programs. An instance of successful implementation of harmonization on a worldwide scale may be seen in the initiative focused on bone turnover indicators, which was jointly pushed by the International Osteoporosis Foundation (IOF) and the IFCC. During the pre-analytical phase, the project determined the suggested bone indicators, namely the serum C-terminal telopeptide of type 1 collagen for bone resorption and the serum procollagen type 1 N propeptide for bone production, from a comprehensive list of possible laboratory tests. Furthermore, a meticulous assessment of pre-analytical factors that contribute to variance has been conducted, and suggestions for minimizing this variation by standardizing all methods have been provided. During the analytical phase, the standardization initiatives have been carefully designed and a temporary harmonization procedure has been carried out by evaluating commercially available assays. During the post-analytical phase, reference ranges have been determined for both young and older healthy adult populations, as shown by studies [36-39]. Harmonization projects, therefore, the strategy should be built on a three-tier framework: (a) at the local level, in addition to adopting international and national recommendations and guidelines, practical steps should be implemented to temporarily standardize laboratory procedures regarding measurement units, reference ranges, and decision limits. These temporary remedies should be used until a consensus is reached both domestically and globally. Furthermore, it is crucial for the clinical laboratory to ensure the accurate implementation of a particular guideline within the local population. Additionally, on a national level, the dissemination of internationally developed guidelines should be accompanied by the adoption of standardized terms, units, and communication of results, including critical findings. Lastly, at an international level, efforts should be made to pursue standardization and harmonization projects, as well as the release of practice guidelines that encompass all aspects of the testing process, from test requesting to result interpretation.

Conclusion

It is often believed by patients, physicians, and other healthcare professionals that clinical laboratory tests conducted by several laboratories at different times on the same sample and specimen may be compared, and that the findings can be interpreted accurately and consistently. Regrettably, these assumptions are not consistently based on solid evidence as laboratory test results often exhibit significant variability. Furthermore, the global laboratory information system introduces even more variability due to issues pertaining to the quality of the biological sample and interpretation criteria. From a patient-centric perspective, harmonization in the field of laboratory medicine refers to the requirement that the information provided should be comparable, regardless of the specific measurement procedure employed or the location and timing of the measurement. This aspect serves as the primary motivation for the implementation of harmonization initiatives. Recently, additional factors have heightened the need and significance of initiatives to standardize laboratory information. Most notably, it has been shown that discrepancies in laboratory information not only lead to confusion but also pose significant risks. There is compelling evidence that mistakes in laboratory medicine have a significant impact on patient outcomes and patient safety [9].

Additional factors contribute to the growing need for the development and execution of more effective harmonization activities. There have been two significant developments in this field. Firstly, it has been recognized that harmonization should not only focus on the analytical phase, but also encompass all stages of the TTP (the request, the sample, the measurement, and the report). Secondly, it has been acknowledged that achieving harmonization is a complex process, requiring a systematic approach. The latter should be established on a robust infrastructure that includes well defined processes, transparent operations, efficient communication with all parties involved, and a collaborative attitude to cooperation. Additional accomplishments include acknowledging the need of implementing the principles of harmonization and standardization not just in clinical chemistry testing, but also in the broader area of laboratory medicine, including research measures and translational medicine programs [40].

Collaboration among laboratory experts, doctors, IVD producers, accreditation, and regulatory authorities is essential for accomplishing these objectives. The organizers of extEQA and PT programs should have a crucial role in maintaining and highlighting the importance of enhanced harmonization. This can be achieved by using commutable control materials, target values assigned by reference laboratories with approved reference systems or designated comparison methods, and reliable statistical analysis of collected data. Harmonization activities are a responsibility and ethical requirement for laboratory personnel and scientific institutions.

References

1. Plebani M. Quality indicators to detect pre-analytical errors in laboratory testing. Clin Biochem Rev 2012;33:85–8.
2. Lundberg GD. Acting on significant laboratory results [editorial] JAMA 1981;245:1762–3.
3. Plebani M, Laposata M, Lundberg GD. The brain-to-brain loop concept for laboratory testing 40 years after its introduction. Am J Clin Pathol 2011;136:829–33.
4. Aarsand AK, Sandberg S. How to achieve harmonisation of laboratory testing-The complete picture. Clin Chim Acta 2014; 432:8–14.
5. Panteghini M. Implementation of standardization in clinical practice: not always an easy task. Clin Chem Lab Med 2012;50: 1237–41.
6. Plebani M. Harmonization in laboratory medicine: the complete picture. Clin Chem Lab Med 2013;51:741–51.
7. Tate JR, Johnson R, Sikaris K. Harmonisation of laboratory testing. Clin Biochem Rev 2012;33:121–2.
8. Plebani M. The detection and prevention of errors in laboratory medicine. Ann Clin Biochem 2010;47:101–10.
9. Plebani M. The CCLM contribution to improvements in quality and patient safety. Clin Chem Lab Med 2013;51:39–46.
10. De la Salle B . Pathology harmony moves on: progress on implementation in haematology. Br J Haematol 2012;158:804–5.
11. McLawhon RW. Patient safety and clinical effectiveness as imperatives for achieving harmonization inside and outside the clinical laboratory. Clin Chem 2011;57:936–8.
12. Berg J, Lane V. Pathology harmony: a pragmatic and scientific approach to unfounded variation in the clinical laboratory. Ann Clin Biochem 2011;48:195–7.
13. Bossuyt X, Louche C, Wiik A. Standardisation in clinical laboratory medicine: an ethical reflection. Ann Rheum Dis 2008; 67:1061–3.
14. Sturgeon CM. Common decision limits -the need for harmonised immunoassays. Clin Chim Acta 2014;432:122–6.
15. Miller WG, Tate JR, Barth JH, Jones GRD. Harmonization: the sample, the measurement, and the report. Ann Lab Med 2014;34: 187–97.
16. American Association for Clinical Chemistry. The need to Harmonize Clinical Laboratory Test Result. A White paper of the American Association for Clinical Chemistry, July 2015. Available from: https://www.google.it/search?q The+need+ to+Harmonize+Clinical+Laboratory+Test+Result+A+White+p- aper+of+the+American+Association+for+Clinical+Chemistr- y&ie utf-8&oe utf8&gws_rd cr&ei T6jRVfCIA8m6UdzZg- gE [last accessed 15 Aug 2015].
17. Plebani M. Laboratory medicine: value for patients is the goal. Clin Chem 2007;53:1873–4.
18. Castellani WJ, Sinard JH, Wilkerson ML, et al. Accreditation and regulatory implications of electronic health records for laboratory reporting. Arch Pathol Lab Med 2015;139:328–31.

19. Watson ID, Siodmiak J, Oosterhuis WP, et al. European views on patients directly obtaining their laboratory test results. Clin Chem Lab Med 2015;53:1961–6.
20. International Organization for Standardization (ISO). Medical laboratories - particular requirements for quality and competence. ISO 15189:2012.
21. Plebani M, Sciacovelli L, Chiozza ML, Panteghini M. Once upon a time: a tale of ISO 15189 accreditation. Clin Chem Lab Med 2015;53:1127–9.
22. Thelen MH, Vanstapel FJ, Kroupis C, et al. Flexible scope for ISO 15189 accreditation: a guidance prepared by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group Accreditation and ISO/CEN standards (WG-A/ISO). Clin Chem Lab Med 2015;53:1173–80.
23. Tate JR, Johnson R, Barth JH, Panteghini M. Harmonization of laboratory testing - a global activity. Clin Chim Acta 2014;432: 1–3.
24. Plebani M. Clinical laboratories: production industry or medical services? Clin Chem Lab Med 2015;53:995–1004.
25. Trenti T, Canali C, Scognamiglio A. Clinical governance and evidence-based laboratory medicine. Clin Chem Lab Med 2006; 44:724–32.
26. Chiozza ML, Plebani M. Clinical governance: from clinical risk management to continuous quality improvement. Clin Chem Lab Med 2006;44:694–8.
27. Shahangian S, Snyder SR. Laboratory medicine quality indicators: a review of the literature. Am J Clin Pathol 2009;131:418–31.
28. Plebani M, Sciacovelli L, Aita A, et al. Performance criteria and quality indicators for the pre-analytical phase. Clin Chem Lab Med 2015;53:943–8.
29. Sikaris K. Performance criteria of the post-analytical phase. Clin Chem Lab Med 2015;53:949–58.
30. Plebani M, Astion ML, Barth JH, et al. Harmonization of quality indicators in laboratory medicine. A preliminary consensus. Clin Chem Lab Med 2014;52:951–8.
31. Plebani M. Evaluating laboratory diagnostic tests and translational research. Clin Chem Lab Med 2010;48:983–8.
32. Plebani M, Marincola FM. Research translation: a new frontier for clinical laboratories. Clin Chem Lab Med 2006; 44:1303–12.
33. Miller WG, Myers GL, Gantzer ML, et al. Roadmap for harmonization of clinical laboratory measurement procedures. Clin Chem 2011;57:1108–17.
34. Braga F, Panteghini M. Verification of in vitro medical diagnos- tics (IVD) metrological traceability: responsibilities and strate- gies. Clin Chim Acta 2014;432:55–61.
35. Jones DGR. Analytical performance specifications for EQA schemes - need for harmonisation. Clin Chem Lab Med 2015; 53:919–24.
36. Cobbaert C, Weykamp C, Franck P, et al. Systematic monitoring of standardization and harmonization status with commutable EQA-samples - five year experience from the Netherlands. Clin Chim Acta 2012;414:234–40.
37. Miller WG, Jones GR, Horowitz GL, Weykamp C. Proficiency testing/external quality assessment: current challenges and future directions. Clin Chem 2011;57:1670–80.
38. Bauer D, Krege J, Lane N, et al. National Bone Health Alliance Bone Turnover Marker Project: current practices and the need for US harmonization, standardization, and common reference ranges. Osteoporos Int 2012;23:2425–33.

39. Vasikaran S, Eastell R, Bruye`re O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int 2011;22:391–420.
40. Vasikaran S, Cooper C, Eastell R, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. Clin Chem Lab Med 2011;49:1271–4.

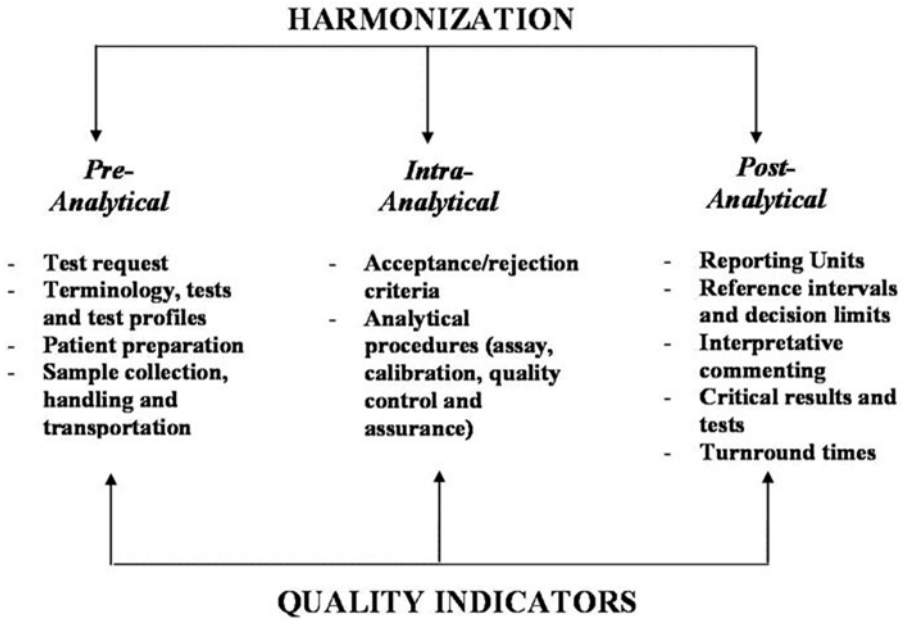

Figure 1. The correlation between harmonization and quality indicators plays a crucial role in enhancing overall quality in the testing process