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Understanding the key differences between ISO 15189:2022 and ISO 15189:2012 for an improved medical laboratory quality of service

Radu Ilinca[1,*], Ionuț A. Chiriac[1], Dan A. Luțescu[1], Ionela Ganea[2], Smaranda Hristodorescu-Grigore[3], Rucsandra-Elena Dănciulescu-Miulescu[4]

1. Medical Informatics and Biostatistics, "Carol Davila" University of Medicine and Pharmacy, Faculty of Dentistry, Romania
2. Modern Languages, "Carol Davila" University of Medicine and Pharmacy, Faculty of Medicine, Romania
3. Epidemiology Department, "Gr. T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Romania
4. Department of Endocrinology, " Carol Davila" University of Medicine and Pharmacy, Faculty of Dentistry, Romania

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Quality management systems offer several straightforward advantages for any laboratory. These advantages are both technical and commercial [1]. A very broad objective of the European Accreditation – an association of national accreditation bodies of the EU Member States and Associates "*accredited once, accepted everywhere*" [2] might not be that relevant for a medical laboratory. That is because this benefit brings more added value for testing/calibration laboratories or inspection bodies rather than medical laboratories. The main reason for this is that diagnostics and treatment decisions are not based just on laboratory results.

There are different types of referentials against which a laboratory might apply for accreditation. Relevent for this category are national standards [1, 3, 4] or private standards which means a set of requirements developed by a very specific community (either professional or geographical) having the objective of mutual results recognition. However, the most relevant standard is ISO 15189 due to the comprehensive nature of its requirements (management and technical) and also because it is a harmonized standard published in the Official Journal of the European Union [5]. It is the only standard applicable to medical laboratories that achieved this status. This should make it a preferred choice for the regulatory authorities and healthcare funding agencies as well. For example, France requires all the medical laboratories operating on the French market to be ISO 15189 – accredited [6].

Originally, medical laboratories were perceived as very similar to testing laboratories (including calibration) which were accredited against the ISO 17025 standard. It was then acknowledged that differences between a medical laboratory and a testing laboratory are significant enough that a specific standard should be developed. This is how ISO 15189 was developed and a robust version was published in 2007[7]. There are at least two major advantages of ISO-family standards namely continuous updates of the requirements based on the input from stakeholders and the market and endorsement by an international non-governmental organization which safeguards impartiality. In the case of ISO 15189:2007, a major revision was published in 2012[8]. The main difference between the two versions was the special requirements of the laboratory management information systems (LIMS) and automated results reporting. The rationale for revision was the rapid introduction of automated systems and computer software in the environment of a medical laboratory. High-throughput and ultra high-throuput analyzers started being commercially available many including automated modules for the preanalytical phase (sample sorting) which enabled processing of 1,000 samples / 8 hours [9]. These technological advancements generated challenges for laboratory staff in implementing the specific IT requirements which are in most cases beyond the technical competencies of a routine medical laboratory. Also, from the accreditation bodies' perspective, developing assessing tools to

* Correspondence to: Radu Ilinca, Medical Informatics and Biostatistics, "Carol Davila" University of Medicine and Pharmacy, Faculty of Dentistry, Romania. E-mail: radu.ilinca@umfcd.ro

determine conformity to these requirements was technically challenging.

By the end of 2022, an updated version of ISO 15189 was published by ISO[11]. This new version reflects the evolution of the medical laboratory market, addresses new topics (e.g. Point of Care Testing- POCT) and brings useful clarification of various concepts used in the 2012 version. Recent evolution from the business-model point of view at the international level has streamed the laboratory activity either towards ultra high-throuput laboratories, processing thousands of tests coming from a plethora of sampling points, most of the time with a large geographical distribution or local centres which have a very specific and limited activity. In the latter case, general requirements were not necessarily relevant, therefore specific requirements needed to be defined such that the technical competence can be established on an objective basis. Also, as ISO 17025[12] was reviewed and as it is a normative reference for ISO 15189, the review of the latter being mandatory. The 2012 edition of ISO 15189 had a limited approach (one reference) to POCT, therefore a comparison between the 2012 and 2022 versions of ISO 15189 is not relevant here.

The structure of the requirements of ISO 15189:2022 is aligned with the ones from ISO 17025:2017, which means that the management requirements are now at the end of the document. Also, there is an alignment with ISO 17043:2010[13] regarding proficiency testing providers which is a standard that might be of help for a medical laboratory, since ISO 15189 has detailed requirements for external quality assurance. That means the medical laboratory is required to give preference to 17043 – accredited proficiency testing providers.

As previously mentioned, the activity of medical laboratory has become truly interdisciplinary requiring not only medical knowledge but also IT, metrology, legal and quality assurance, which are more enforced in management system certification standards (e.g. ISO 9001). Therefore, enhancing and consolidating term definitions were introduced. This will minimize the risk of possible misinterpretation errors since a term might have a different meaning in the metrology world than in the medical world. Up to now, term definitions were to be found in other documents, far less popular in the medical laboratory libraries: International Vocabulary of Metrology [10] or Guide of Uncertainty Measurement GUM [14]. Therefore, an efficient implementation of the new ISO 15189[11] should always start with understanding the terms and their definitions now available in the document. Changes in this respect focus mainly on the data interpretation (bias, measurement bias, measurement accuracy/accuracy of measurement/accuracy measurement uncertainty (MU), trueness/measurement trueness). There are also new definitions of terms which apparently might be straightforward to understand but can easily have legal implications given their potentially different meanings (laboratory user, patient, complaint, consultant, impartiality). A particularly important definition is that of "external quality assessment" since in the previous version of the ISO 15189[8], external quality assessment was more or less equivalent to proficiency testing schemes participation with a singular requirement. In the case of the new version, the definition is more conceptual and allows the laboratory to use a wide range of techniques other than classical participation in the proficiency testing schemes (e.g., participation in sample exchanges with other laboratories). Commutability of reference materials is another key concept introduced in ISO 15189:2022[11] and it emphasizes the importance of this property of reference materials when used for both internal and external quality assurance procedures. This is especially important in proficiency testing when the organizer should make sure its samples match the stated equipment by the laboratory. Not using commutable samples by a proficiency testing provider severely increases the risk of issuing inaccurate results for the participant laboratory. This can generate negative consequences for the laboratory in relation to its customers, authorities and accreditation body. Overall, the new version of the standard introduces 15 new definitions which should be carefully taken into account when implementing the requirements of the standard especially since they are not that straightforward to understand by most laboratory professionals.

The way the requirements are defined in ISO 15189:2022[11] has also been changed in the sense that more emphasis is placed on risk analysis in contrast with the previous version of the standard. This means that the new version is less prescriptive than the previous one. A careful reader will notice that there are five requirements concerning risk analysis rather than one in the previous version. The first reason for this approach is to align the standard with the view of ISO 9001:2015 where risk analysis plays an important role in developing the quality management system. This alignment is also useful because the reality in the market shows that companies that run a medical laboratory have also implemented the requirements of ISO 9001. This alignment allows easier development of a single, unitary quality

management system within the entire company not just at the level of the laboratory. ISO 15189 has been, at least in the past years, the referential of choice for medical laboratories throughout the world and not all the requirements were compatible with local legislation as the medical laboratory legal framework is heavily regulated. Since legal requirements can vary from country to country at the international level or at the regional level, even in integrated economies, [15,16] defining the requirements with notes either "when/where applicable" or "where appropriate" coupled with the risk analysis requirements, enable the laboratory to develop more effective documentation and are easier to align with other sets of requirements.

Usually, one of the fundamental documents of any quality management system is the quality manual. Traditionally, its existence has been so far a basic specific requirement. However, the new version of ISO 15189[11] does not hold this mandatory requirement anymore, just like ISO 9001:2015, offering increased flexibility for the laboratory in developing the quality management system. This flexibility should be understood as all requirements of the standard are defined at the minimum needed to be addressed to prove competence rather than maximum. Therefore, it should be noted that no *expressis verbis* requirement for a quality manual does not mean that the information contained here is not relevant anymore. Also, concerning the quality management, the new version does not require the appointment of a quality manager anymore. Instead, it is newly required that activities are managed by personnel (not necessarily a single one) with authority and resources. By implementation of this change, a concept of shared but clear responsibilities is encouraged since the definition of who is responsible can, if needed, be also accountable for nonconformal activities.

The requirements definition in the new version is patient-focused, starting from the definition. The laboratory has to consider harm to the patient and improvements to the patient. All the processes have to consider "potential risk to the patient". This approach is unitary throughout the phases of the laboratory activity, starting from examination requests to post-examination processes. For example, the new version of ISO 15189[11] distinguishes a case when an oral examination request can be accepted and processed (Clause 7.2.3.2).

Regarding an important part of the laboratory activity – internal quality control, its importance is reflected in the level of detail for the requirements. Development of an internal quality control programme based on risk assessment using the Sigma tools has already been introduced with promising technical results but also complying with regulatory documents[17]. In the new standard, the main focus is on the "validity pertinent to clinical decision making" thus strengthening the link between the laboratory activity and the clinician. Several criteria are defined for selecting the internal quality control which enables the laboratory to also use third-party materials. Frequency of running the internal control procedure is also governed by a risk analysis of the patient harm rather than a simple prescriptive approach.

Complementary to internal quality control, external quality control requirements are expanded in the new version of ISO 15189[11]. While in the previous version of the standard, external quality control was more or less equivalent to proficiency testing participation, the new version allows seven alternative approaches. The use of alternative approaches may also be employed when an external quality programme is "not suitable" not just "not available" like in the previous version of the standard. However, the decision for alternative approaches should be justified and objectively proven effective. Regarding the selection of a proficiency testing provider, the new version places a strong focus on the fulfilment of requirements of ISO 17043 by the provider. This new requirement should be seen as a constraint to the previous version of the standard since more and more accreditation bodies accept in their policies for proficiency testing participation only results released by ISO 17043-accredited providers when available. Proficiency testing schemes can be grouped by the way the target value is defined. The new version of ISO 15189[11] lists the types of acceptable methods of defining the target value ranking first the strategy of using a target value independently set by a reference method. This ranking available in [11] is not random since proficiency testing schemes that set the target value this way are known to provide the most relevant results concerning the performance of the laboratory. Whenever the external quality control is not satisfactory, a risk analysis should be performed on the patient's results with appropriate measures to be taken, which may also include reviewing the patient report. This risk analysis should be performed based on the "clinical significance" of the results.

Regarding the LIMS, since the previous versions of the standard of 2012, there has been much evolution in the market, not only in the medical laboratory world. New challenges and risks also generated a new legal framework. At least in the European Union, two normative documents have been enforced [18,19] which apply also

to any medical laboratory. This is reflected also in the new version of ISO 15189[11]. Perhaps, the most significant new risk for LIMS is related to cybersecurity. Clause 7.6.3 c) explicitly requires taking into account cybersecurity when implementing an information system. Data in a medical laboratory are always a target since a wealth of information can be extracted and illegally exploited, like patient personal data, patient personal medical history, patient current medical condition, patient population medical condition, and laboratory internal procedures and methods. Even though a large majority of medical laboratories use off-the-shelf LIMS, the laboratory is "ultimately responsible" for its LIMS and is required to verify the correct functionality before introduction and any changes (including configurations which usually require minimum modification) have to be validated before implementation. Since modern medical laboratories use advanced information systems and given the risks associated with these systems, careful attention should be paid when selecting, implementing and upgrading such a system.

Throughout the new version of ISO 15189[11], the word "occurs" 86 times in contrast to the 2012 version where it occurs 12 times. Requirements for risk analysis were detailed at the level of key requirements. However, the new version of the standard does not specify how a risk analysis should be performed. There is a myriad of ways such a task can be achieved. A mere suggestion is to use the framework provided by [20]. This approach essentially answers two fundamental questions: i) How often can something go wrong?; ii) What are the consequences of that wrong? A 5x5 matrix may be defined as follows (Table 1):

The main task is to correctly quantify the terms to the associated activity since the quantifiers are usually subjective. Tentatively, the following definitions can be used: almost certain – continuously expected, probable – occurs frequently, possible – will occur several times, unlikely – it might happen occasionally, improbable – unlikely to occur but not possible. As for quantification of the risk, the new version of ISO 15189 focus should be on patient harm. The range should also be aligned with the laboratory activity. A typical output for Catastrophic impact might be a release of false-negative results or a release of tampered results which are almost certainly released. An example for Negligible impact might be a minor delayed release of a report which does not include critical results which are improbable to be released.

This paper explored the various types of quality assurance standards and outlined the key differences between the 2022 and 2012 versions of ISO 15189. While the technical requirements are not substantially changed, clarifications in terminology and increased flexibility while reducing prescriptiveness offer the medical laboratory the possibility to better tailor its quality management system to better answer the patient needs. Detailed requirements for internal quality assurance, external quality assurance and information systems have been discussed and a simple but effective method of developing a risk analysis was provided. As the entire focus is patient based, the 2022 version of ISO 15189 [11] is expected to be better suited for integration with the clinical side of the healthcare system, thus contributing to the ultimate goal of any healthcare system – increase the overall population health status. This updated version might become the standard of choice for any laboratory implementing a quality management system since it is strictly focused on the primary beneficiary of the activity – the patient.

AUTHORS' CONTRIBUTION

Authors declare equal contribution in all regards.

CONFLICT OF INTEREST

None to declare.

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Table 1. Risk Assesment Matrix

Likelihood	Consequence				
	Neglegible (1)	Minor (2)	Moderate (3)	Critical 4)	Catastrophic (5)
Almost Certain					
Probable					
Possible					
Unlikely					
Improbable					

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