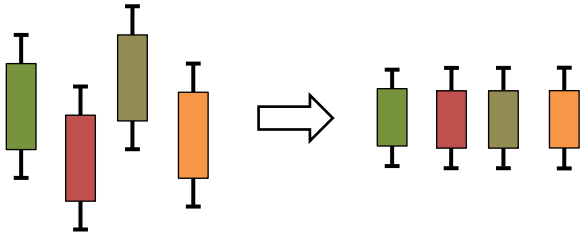
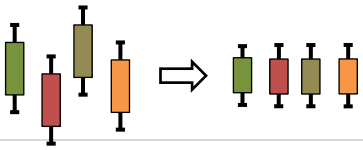


International Consortium for Harmonization of Clinical Laboratory Results

Operating Procedures

Updated: December 2019



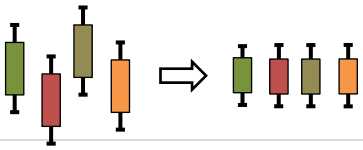
Background

Results from clinical laboratory measurement procedures should be equivalent irrespective of the laboratory, method or time when measurements are made. Equivalent results are necessary to allow meaningful interpretation of a patient's condition over time, to allow clinical practice guidelines to be implemented, to allow data from clinical research to be used to develop guidelines, and for results to be aggregated into electronic health records. Harmonization as used in this document means results for a measurand are equivalent among different measurement procedures irrespective of the technical approach used to achieve equivalence. Failure to recognize that results are not harmonized may lead to erroneous medical, financial, regulatory, or technical decisions.

The terms harmonization and standardization have been used in laboratory medicine with various meanings over the years. A revision of the standard ISO 17511, *In vitro diagnostic medical devices —requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples*, and a new standard ISO 21151, *In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for international harmonization protocols establishing metrological traceability of values assigned to calibrators and human samples*, have been approved, are being developed by TC 212 and are expected to be published in the near future. Based on the direction taken by ISO TC 212 in revising standard 17511 and the new standard 21151, definitions of standardization and harmonization are expected to be consistent with this paragraph. The term standardization is used to mean achieving equivalent results among different measurement procedures by having calibration traceable to higher order references. The term harmonization is used to refer to achieving standardization by having calibration traceable to an international harmonization protocol as the highest level of metrological traceability when there are no certified reference materials or reference measurement procedures for a given measurand.

Because the ICHCLR was created at a time when the terms harmonization and standardization were not clearly articulated, the term harmonization is retained in the name of the organization and is used with the same meaning as standardization, i.e. results for a measurand are equivalent among different measurement procedures irrespective of the technical approach used to achieve equivalence. Harmonization can also refer to the special case when a harmonization protocol is the technical approach to achieve standardization.

To address the problems of non-harmonized results, an international conference recommended that an international infrastructure be developed to provide: a systematic approach for prioritization of measurands to be harmonized based on medical importance and the technical feasibility to achieve harmonization; an information portal on global harmonization activities to coordinate work and avoid duplication of effort; and procedures to implement harmonization for measurands for which no reference measurement procedure or certified reference material was likely to be developed. (Roadmap for harmonization of clinical laboratory measurement procedures. *Clinical Chemistry* 2011; 57:1108-17.) The ICHCLR is the organization created to



provide the recommended international infrastructure. Implementation of the infrastructure requires the involvement and cooperation of international clinical laboratory and medical organizations, IVD manufacturers, metrology institutes, standard-setting organizations, public health organizations and regulatory agencies.

Abbreviations used in this document

HOG – Harmonization Oversight Group
ICHCLR – International Consortium for Harmonization of Clinical Laboratory Results
IFCC - International Federation of Clinical Chemistry and Laboratory Medicine
ISO – International Organization for Standardization
IVD – In-Vitro Diagnostics
JCTLM – Joint Committee for Traceability in Laboratory Medicine
SI – Système International d'Unités (International System of Units)
SPG – Strategic Partners Group
TC – Technical Committee (in the ISO process)

Mission of the ICHCLR
Provide a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results.

Scope of the ICHCLR
Prioritize measurands requiring harmonization based on medical importance; provide an information portal on global harmonization activities; and support and develop procedures to implement harmonization. These services will optimize public health activities and patient care while eliminating duplication of effort and maximizing resource utilization. The scope includes:

- Applying a systematic process for prioritization and organization of work, on a global scale, for those measurands that are the most medically important and technically feasible for harmonization.

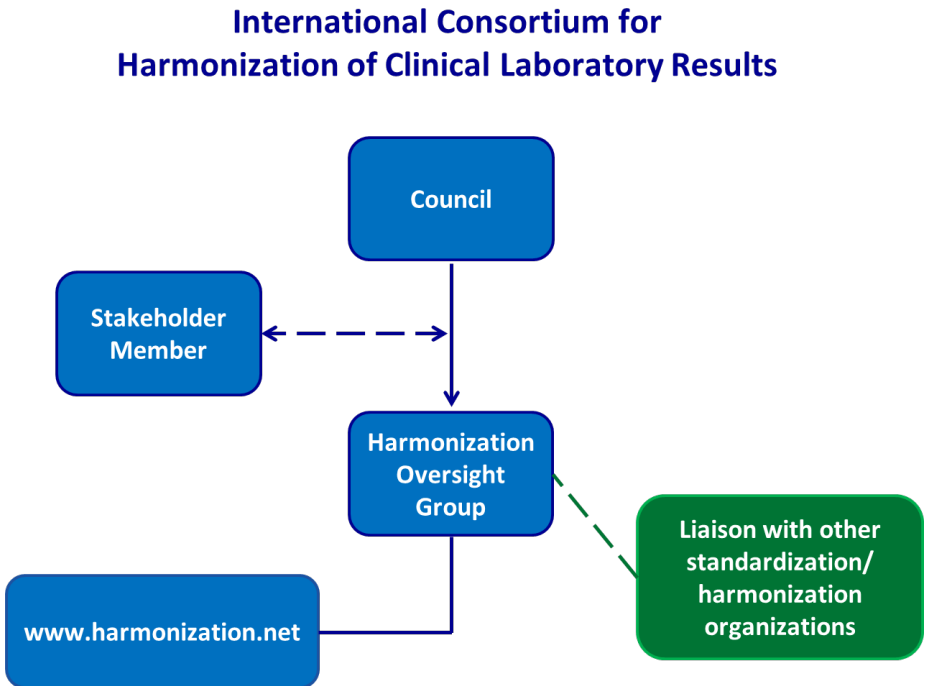
- Informing laboratory medicine stakeholders regarding global activities to harmonize clinical laboratory measurement procedures.

- Developing processes for harmonization of a measurand when no reference measurement procedure or certified reference material is available.

- Ensuring processes for harmonization are accepted by global organizations such as the Joint Committee for Traceability in Laboratory Medicine (JCTLM), IVD manufacturers, clinical laboratories and regulatory agencies in different countries.

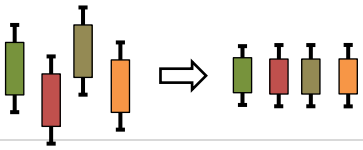
- Developing processes for assisting IVD manufacturers to meet regulatory requirements for implementing internationally agreed harmonization programs.

Structure and Operational Overview



The International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) is governed by a Council whose members are organizations that contribute at an annual financial level defined by the Council to support the core administrative functions of the program. The Council is responsible for the fiduciary and administrative oversight of the consortium. The Council is responsible for determining the scope of operations of the ICHCLR within a budget based on member annual participation fees.

The Harmonization Oversight Group (HOG) is the body responsible for operating the harmonization activites included in the scope of ICHCLR. The HOG proactively communicates with stakeholders to provide updates on harmonization activities and to solicit input from them on relevant activities in their organizations.The HOG cooperates with other international organizations to coordinate harmonization activities. The HOG maintains a web site to coordinate information about global harmonization activities.



Stakeholders Members are committed to supporting harmonization of clinical laboratory results (e.g. clinical laboratory and medical organizations, IVD manufacturers, metrology institutes, standard-setting organizations, public health organizations, regulatory agencies and individuals). Stakeholders support the ICHCLR by submitting measurands in need of harmonization, provide feedback on direction and activities of the ICHCLR, and receive all updates and reports on efforts by the ICHCLR to promote internationally the importance of and approaches for harmonization. Stakeholder members are assessed an annual fee defined by the Council to support harmonization activities of the ICHCLR.

The ICHCLR is hosted by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) which serves as the "Secretariat." As the Secretariat organization, the IFCC provides administrative, finance, accounting, and marketing services for a fee. The Secretariat also provides tax exempt status and liability protection and serves as the title-holding entity in all matters regarding the ICHCLR (intellectual property rights, copyrights, trademarks, patents, etc.).

The ICHCLR can establish a cooperative liaison relationship with other organizations that have activities for implementing harmonization for specific measurands. For example, the IFCC Scientific Division (SD) organizes harmonization/standardization projects for specific measurands. Prioritization of measurands and listing of current global harmonization activities by the ICHCLR is useful to the SD in its process to initiate specific projects.

Funding

Members of the Council fund the adminsitrative costs of the program with an annual contribution set by Council members each year for the following year. The Council also sets the annual fee to participate as an Organizationl Member or as a member of the Strategic Partners Group.

Detailed Operational Procedures for the Council

The ICHCLR is governed by a Council whose members are organizations with interest and experience in laboratory medicine (e.g. clinical laboratory and medical professional organizations, metrology institutes, standard-setting organizations). Council member organizations play an important role in providing a worldwide platform to promote and give international guidance on the importance of harmonization and its impact on accepted equivalence of measurement results in laboratory medicine.

Each Council member organization appoints one representative to serve on the governing Council. It is at the discretion of each Council member organization to determine the duration

of service for its representative. Council representatives select from among them one individual to serve as Council Chair. An individual must have a minimum of one year of service as a Council representative to be eligible to become Council Chair. The term of the Council Chair is three years, and an individual is eligible to serve two terms for a total of six years. In extraordinary situations, the Council may elect to extend the term of the Chair for one additional year (making a total of not more than seven years as Council Chair). Each Council member organization is entitled to appoint one member of the HOG, independent of and outside the scope of the Council duties outlined below.

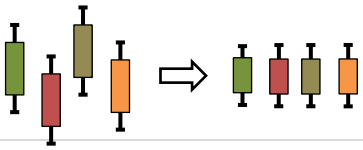
The responsibilities of the Council include:

- Determining the scope of operations of the ICHCLR within a budget based on annual participation fees of ICHCLR members.
- Establishing the annual funding level for Council members and other member categories to support the operation of the ICHCLR.
- Providing fiduciary and administrative oversight of the ICHCLR
- Identifying and appointing experts to serve on the HOG who cover a broad range of existing and emerging technologies and disciplines in laboratory medicine. The composition of the HOG should include members from industry, from non-industry organizations, from clinical laboratories and ad-hoc members based on expertise. Nominators must provide a Curriculum Vitae of the nominee and describe the expertise and experience of the individual with regard to harmonization development activities.
- Appointing the HOG Chair who must have a minimum of one year of service as a HOG member to be eligible to serve as HOG Chair. The term of the HOG Chair is three years, and an individual is eligible to serves two terms for a total of six years. In extraordinary situations the Council may elect to extend the term of the HOG Chair for one additional year (making a total of not more than seven years).
- Appointing the HOG vice-chair who serves in a deputy role but is not automatically in line to become the next chair. The term of the HOG Vice-Chair is three years, and an individual is eligible to serve two terms for a total of six years. In extraordinary situations the Council may elect to extend the term of the HOG vice-chair for one additional year (making a total of not more than seven years).

The Council meets face to face at least annually. Virtual meetings are preferred for most business, to minimize costs and to facilitate global participation.

Each Council representative shall disclose annually financial or other interests that may be perceived to have the potential to affect her/his ability to offer an unbiased view of matters that may come before the Council or the HOG.

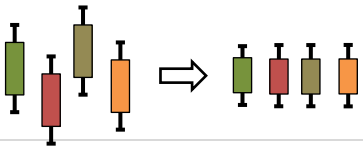
Detailed Operational Procedures for the Harmonization Oversight Group



The HOG is the body responsible for organization and coordination of the harmonization activities of the ICHCLR. HOG members should represent a mix of senior and junior scientists who have demonstrated expertise in harmonization activities, have experience in the consensus process, and can commit to the time necessary to fulfil responsibilities. There is no limit to the number of members on the HOG. The important consideration for the ICHCLR is to have a manageable number of HOG members who cover a broad range of existing and emerging technologies and disciplines in laboratory medicine. A HOG member's duty is to the HOG and not to be a representative of the particular organization making the appointment or the nomination. HOG members do not represent a specific industry or organization but ensure that the general perspective of "industry" and "organizations" is represented. HOG members can serve for two three-year terms for a total of six years. In order to maintain the needed expertise and consistency on the HOG, members can serve additional specified terms as recommended by the HOG Chair and approved by the Council.

The responsibilities of the HOG include:

- Soliciting submission of measurands for consideration
- Prioritizing the medical importance for harmonizing a measurand. The HOG reviews measurand submissions and determine a priority for harmonization based primarily on how the measurand is used for making medical decisions and the current guidelines for interpreting test results. The HOG may consider the technically feasibility for harmonization but bases priority primarily on medical importance.
- Reviewing evidence provided if an appeal for reconsideration of a measurand prioritization is made in writing to the HOG and responds to the submitting party within 60 days.
- Organizing and disseminating information on global activities for harmonization of clinical laboratory measurement procedures with a link to the organization addressing a measurand to promote coordination and to avoid duplication of effort
- Developing and coordinating collaborations and development of resources needed to support and promote harmonization in laboratory medicine.
- Working with stakeholders to ensure harmonization processes are accepted by global organizations such as the Joint Committee on Traceability in Laboratory Medicine (JCTLM) and by regulatory agencies in different countries
- Communicating harmonization issues and technical advances to regulatory bodies
- Assisting IVD manufacturers to meet regulatory requirements for implementing internationally agreed harmonization programs
- Maintaining the web site www.harmonization.net as a portal for information on global harmonization priorities and activities. The web site provides information on: the status of harmonization of measurands; organizations working to harmonize measurands; literature resources related to harmonization of measurement procedures; recommendations related to implementing harmonization of measurands, and other information of interest to stakeholders.



- Reviewing applications submitted to the ICHCLR for a harmonization project start-up funding and recommending funding or non-funding to the Council.

The HOG can recommend to Council to approve funding, if available, from ICHCLR financial resources to assist other organizations' committees or working groups with specific harmonization projects.

The HOG meets face to face at least annually. The HOG issues an annual report, posted on the web site, describing the status of its harmonization activities.

Each HOG member shall disclose annually financial or other interests that may be perceived to have the potential to impact their ability to offer an unbiased view of matters that may come before the HOG.

Revision of Operational Procedures for the Harmonization Oversight Group

Revisions to these Operational Procedures may be proposed by the HOG or the Council and accepted if approved by a majority vote of the Council.

Policies

Policy on transparency of proceedings and potential conflicts of interest

It is important that the International Consortium for Harmonization of Clinical Laboratory Results is open and transparent with its discussions and decisions on all matters relating to its harmonization activities. Such activities should not be inhibited by undeclared conflicts of interest.

Therefore, each participant in a harmonization activity of this organization shall be required to read and sign the conflict of interest policy and disclosure statement. The disclosure statement shall be signed annually by all members of the program's units or sub-units. A conflict of interest does not automatically exclude participation. However, since openness and transparency are important to the harmonization process, it is the duty of each individual to declare the possibility of any potential conflict of interest on each occasion when it may occur. If necessary, the HOG or the Council determines if a potential conflict is sufficient to preclude an individual from participation.

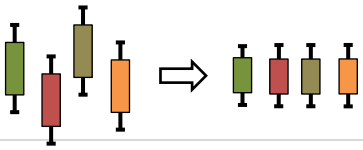
Policy on cooperation with other organizations

The ICHCLR recognizes that global harmonization of results cannot be accomplished by a single organization. Consequently, our policy is to foster cooperative working relationships with all

interested stakeholders, and thus avoid duplicative activities and enable optimal use of available resources to achieve the goal of harmonized clinical laboratory results.

Policy on confidential or proprietary information

Confidentiality agreements may be executed if needed to consider confidential or proprietary information relevant to a measurand's evaluation for medical importance or technical feasibility, or to implement a harmonization activity.



Appendix

Definitions

A. Essential terms:

Because the ICHCLR was created at a time when the terms harmonization and standardization were not clearly articulated, the term harmonization is retained in the name of the organization and is used with the same meaning as standardization, i.e. results for a measurand are equivalent among different measurement procedures irrespective of the technical approach used to achieve equivalence. The following definitions are from draft revisions to ISO 17511 and may be edited in the final version

Harmonization – achievement of equivalent measured quantity values (within clinically meaningful limits) for human samples examined for a stated measurand among two or more IVD medical devices by applying an international consensus protocol for calibration traceability when higher order reference materials or suitable reference measurement procedures are not available. The resulting measured quantity values (for all IVD medical devices harmonized according to the consensus protocol) are not traceable to SI.

NOTE 1: Harmonization is one of several calibration traceability models described in ISO 17511 to achieve metrologically traceable quantity values for human samples.

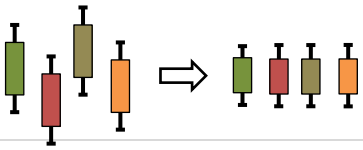
NOTE 2: Harmonization is a special case of non-SI traceable standardization where the calibration of two or more IVD medical devices is traceable to an international harmonization protocol that defines the highest level of metrological traceability for the stated measurand, but with no traceability to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

NOTE 3: Harmonized is the condition in which harmonization (equivalence among quantity values) is achieved among two or more IVD medical devices.

Standardization - achievement of equivalent measured quantity values (within clinically meaningful limits) for human samples examined for a stated measurand among two or more IVD medical devices, where each “standardized” IVD medical device is calibrated according to a defined hierarchy of relationships to higher order references (materials and/or measurement procedures).

NOTE 1: Standardization of an IVD medical device is achieved preferably by implementation of a calibration system that is traceable to higher order references, ideally with traceability to SI.

NOTE 2: Not all standardization approaches result in traceability of final measured values to SI, but may be the best available means for achieving equivalent results for human samples among



different IVD medical devices. Such standardization approaches should be replaced when an approach becomes available that provides traceability to SI.

NOTE 3: Standardized is the condition in which standardization of results for human samples is achieved among two or more IVD medical devices.

B. Other terms:

Higher-order reference measurement procedure – a measurement procedure that is highly specific for a measurand, thoroughly validated, and whose calibration is directly traceable to SI using a primary reference material or the measurement procedure itself defines the SI.

IVD Industry - an organization that manufactures and/or distributes materials used in clinical laboratory testing. For example, industry includes manufacturers or distributors of instruments, reagents, cell lines, calibrators, controls, reference materials, proficiency testing or external quality assessment programs. Note that reference materials may also be provided by metrology organizations and proficiency testing or external quality assessment programs and may also be provided by public health or professional organizations.

Measurand – the quantity intended to be measured. Specification of a measurand includes the specific molecular form or species that is measured as well as the matrix in which that molecule is contained. Note the term analyte (component represented in the name of a measurable quantity) is sometimes used when measurand is intended.

Primary reference material – a pure substance with a certificate of analysis that describes its purity and the molecular form of the substance.

Secondary reference material – a material, frequently in the matrix of the clinical samples intended to be measured, which has its value assigned by measurement or by a consensus process.

Stakeholder - any individual or entity with an interest in harmonization of clinical laboratory results including: clinical practice groups, laboratory practice groups, in-vitro diagnostics manufacturers, public health organizations, metrology institutes, standards development organizations, regulatory organizations, proficiency testing or external quality assessment providers.