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A Comparative Review of ICMR, WHO, and EMA Guidelines for Good Clinical Laboratory Practices

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Abstract

With the advancement of clinical research and the increased burden on laboratory services, there is an unmet need for guidelines regarding proper laboratory functioning and reliable data generation. Several organizations from all over the world have published guidelines for these clinical and research laboratories. Good Clinical Laboratory Practices (GCLP) are stepwise procedures aimed at strengthening the quality of test results produced by all clinical laboratories engaged in human sample analysis. In this article, we attempt a comparison of the GCLP guidelines recently issued by the Indian Council of Medical Research with the guidelines released by the World Health Organization and the European Medicines Agency. Also, we have included and discussed several suggestions that, if included, will lead to the strengthening of the laboratory practices used for both research and patient care for overall improvement in the Indian healthcare system.

Keywords
- clinical laboratory
- Good Clinical Laboratory Practices
- guidelines
- healthcare system

Introduction

The regulatory environment regarding laboratory services continues to evolve because of their rising importance in healthcare services and medical research. According to Organization for Economic Co-operation and Development (OECD), there should be better quality of data being generated from research/tests being conducted at different laboratories handling chemicals including industrial chemicals, pesticides, food additives, biotechnology products, and pharmaceuticals. OECD mandates good laboratory practice (GLP) to be followed for the enhanced validity and mutual acceptance of test data that will ensure the optimal use of resources and laboratory animals. Similarly, laboratories handling human samples are the backbone of the healthcare system and they include laboratories involved in patient care, diagnosis, treatment, prevention, and clinical research. There is a need for uniformity and standardization in human

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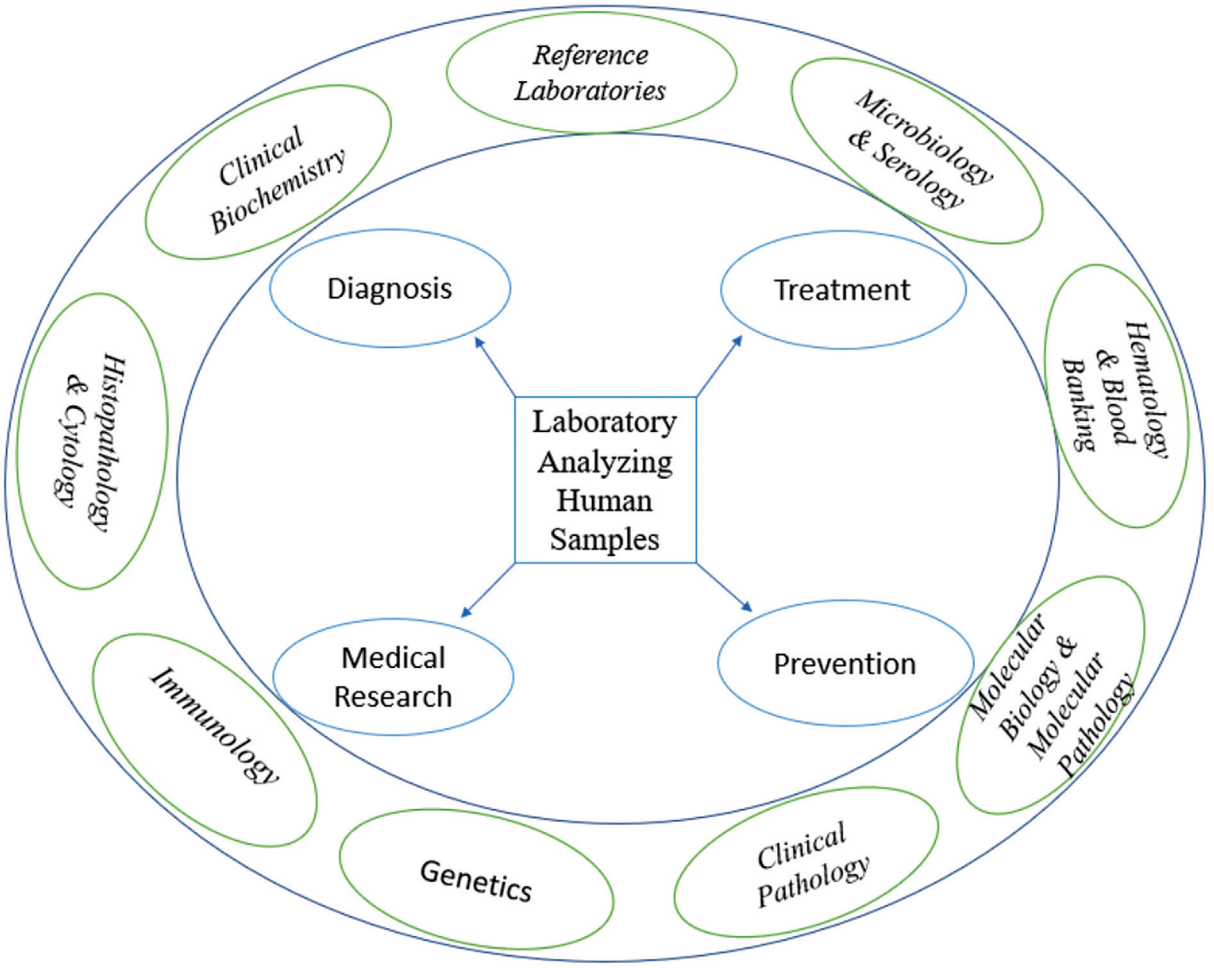

Fig. 1 Scopes of Good Clinical Laboratory Practice (GCLP).

biological sample analysis all over the country. Good Clinical Laboratory Practices (GCLP) are the stepwise procedures aimed at strengthening the quality of test results produced by all clinical laboratories engaged in human sample analysis. Therefore, implementation of the principles of GCLP is of paramount importance to ensure the reliability and integrity of data generated by laboratories. GCLP guidelines were first published by Research Quality Association (formerly called as British Association of Research Quality Assurance) in 2003.[1] These guidelines served as the foundation for several other GCLP guidelines formulated by different organizations like the World Health Organization (WHO), the Indian Council of Medical Research (ICMR), and the European Medical Association (EMA). In 2009, WHO published GCLP guidelines[1]. Similarly, EMA released a "Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples" in 2012.[2] In addition to it, recently, in 2021, ICMR revised the 2008 GCLP guidelines to formulate the ICMR GCLP 2021 guidelines that are applicable for samples collected from both clinical trials and patient care purposes to be analyzed in clinical laboratories to generate timely and accurate data.[3,4] The scopes of GCLP extend to all clinical laboratories engaged in human sample analysis for patient treatment, diagnosis, prevention, and clinical research such as microbiology and infectious disease serology, hematology and blood banking, molecular biology and molecular pathology, clinical pathology, clinical biochemistry, histology, cytology, and genetics (►**Fig. 1**). GCLP encourages good practices to be followed during patient preparation, sampling, sampling, laboratory functioning, documentation, and test data management. The versatile benefits of GCLP include better infrastructure development following right and accurate procedures, optimal resource utilization, data and quality management, and improved patient care that are depicted in detail in ►**Fig. 2**.

Modifications in the New ICMR GCLP Guideline 2021 as Compared to the 2008 Guideline

The new (2021) ICMR GCLP guideline has taken over the old (2008) GCLP guideline without major alteration/changes and deletions in the factual descriptions, except for the addition of some new aspects. The salient additional features of the GCLP, 2021 by ICMR as compared to GCLP, 2008 guidelines are as follows:[3,4]

1. As compared to the old guideline, the new guideline has classified laboratories into different levels like small, medium, large, very large, and multiple location

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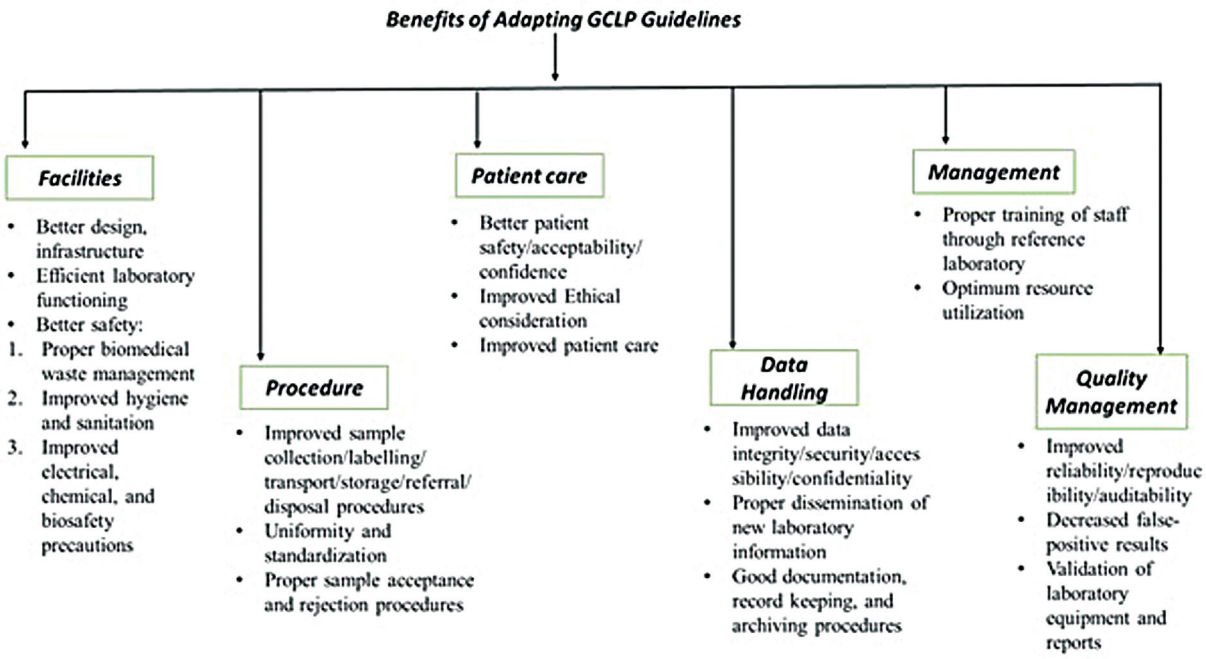

Fig. 2 Summary of beneficial outcomes of adapting Good Clinical Laboratory Practice (GCLP) guidelines in day-to-day practice.

laboratories based on samples from the number of patients/participants per day. The guidelines are outlined in a detail regarding the requirement of location, size, design of laboratories, various facilities required for the proper functioning of the laboratories, and the storage of sample/reagents/consumables/records that play a pivotal role in the organization and functioning of laboratories.

2. The selection of appropriate laboratory personnel is also essential for the functioning of the laboratory. ICMR GCLP 2021 has focused on training (induction training and on-the-job training) and periodic assessments of laboratory personnel.
3. Various reagents, kits, and materials are used for performing tests in laboratories. Information about preparation of working solutions, disposal of unusable/expired reagents, medical disposables, and radioactive materials handling are mentioned in a detail in the new guideline.
4. For the collection of a clinical sample in a proper manner, the prerequisites like pre-examination processes including patient preparation, and arrangement of devices for sample collection have been objectively outlined. Also, sample labelling, proper documentation, and transportation to the site of testing are critical and the ICMR GCLP 2021 guidelines include detailed information on these procedures that were not mentioned in ICMR GCLP 2008 guidelines.
5. All samples should be checked for their fitness for analysis when received in the laboratory and if a sample is not fit, it should be rejected. The ICMR GCLP guidelines 2021 mention the different parameters to be checked for fitness including container type, sample quantity, temperature and quality of the sample, and any leakage. Similarly, the detailed criteria for sample rejection are also mentioned.
6. ICMR GCLP 2008 guidelines mentioned test result reporting, whereas the ICMR GCLP 2021 guidelines provide procedures for the release of test results with the primary requisites including patient identification, the timing of sample collection and analysis, laboratory contact details, and authorized signatory.
7. Information on sample/chemical/e-waste disposal and procedures of equipment disposal and condemnation is of utmost importance for the proper functioning of the laboratory and are included in ICMR GCLP 2021 guidelines in a separate heading as compared to ICMR GCLP guidelines 2008.
8. ICMR GCLP 2008 guidelines mentioned safety in the laboratory under the headings of general safety and biosafety measures, whereas ICMR GCLP 2021 guidelines included extra measures like chemical and electrical safety and laboratory and personal hygiene.

Comparison with GCLP Guidelines from Other Organizations

The WHO published the GCLP guidelines in 2009. Similarly, the EMA published a reflection paper in February 2012 for laboratories that perform the analysis or evaluation of clinical trial samples. In this review, we have compared the important areas concerning GCLP in the different guidelines provided by ICMR, WHO, and EMA. These comparative features are highlighted in ►**Table 1**.[1,2,4]

1. Inclusion of laboratories: The guidelines laid by both the WHO and EMA included the laboratories performing tests on samples from clinical trials only. However, the ICMR GCLP guidelines have broader scope and include laboratories those process samples not only from clinical

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Table 1 Comparison of GCLP in the guidelines provided by ICMR, WHO, and EMA

	ICMR GCLP, 2021	WHO GCLP, 2009	EMA reflection paper, 2012	Remarks/comments
Scope	All clinical laboratories wherein human samples are processed for diagnosis, patient care, disease control, and clinical research	Organizations that analyze samples generated by a clinical trial	Laboratories involved in analyses of samples generated by a clinical trial	ICMR GCLP has broader scope whereas the other two focuses only on Clinical Trials
Infrastructure	The basic requirement in concordance with local authorities like: 1. Signage within or outside the facility 2. Essential health and safety regulations 3. Emergency and disaster management 4. Power and water supply 5. Ventilation, environmental control (temperature, humidity, and light) 6. Communication with a referral center 7. Sample collection and analysis area 8. Area for radioactive substances 9. Storage and archiving areas 10. Waste management	Minimum requirements are specified like availability of: 1. Adequate number of qualified personnel 2. Appropriate facilities: size, construction, location, design 3. SOP 4. Analytical project manager for the overall conduct of analysis 5. Well-trained trial staff 6. Archiving facility for storage of samples, specimens, data, and reports 7. Waste disposal	Information about 1. Suitable size, construction, and location 2. Appropriate storage conditions for sample integrity 3. Waste storage, collection, and disposal 4. Provides detailed information about maintenance of instruments during pandemics like COVID-19	ICMR provides detailed and comprehensive GCLP guidelines covering laboratories handling samples from research and routine health care
Pre-examination process	Information regarding 1. Patient preparation: ❖ As per prescription or requirement ❖ Timing of sample collection 2. Primary sample collection ❖ As per SOP 3. Sample labelling and documentation 4. Requisition forms 5. Transport of samples 6. Acceptance and rejection criteria	1. The trial protocol should be followed for patient preparation 2. Also, this section is with a reference to the WHO handbook of laboratory management for the details	1. Sample labelling and transport: Cold chain for maintaining the integrity of samples 2. Assessment for the integrity of samples at the time of reception of samples 3. Maintaining records for sample reception 4. Protocol for proper storage of samples	ICMR guidelines are more comprehensive; however, the EMA reflection paper suggests in-depth guidelines to preserve the integrity
Patients	1. No specified information for patients' safety 2. The requisition form should contain consent for sample collection and testing	1. Trial protocol for safety and confidentiality of patients 2. Consent for sample collection and testing	Policies for: 1. Safety of patients 2. Reporting of unexpected or out-of-range results 3. Coding of samples to maintain confidentiality 4. Consent for sample collection and for all tests to be conducted	EMA reflection paper focuses more on patients' safety and confidentiality

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Table 1 (*Continued*)

	ICMR GCLP, 2021	WHO GCLP, 2009	EMA reflection paper, 2012	Remarks/comments
Equipment	Information about 1. Selection/use/maintenance 2. Qualification for installation, operation, and performance should be checked before use 3. Logbook and SOP for all equipment 4. Calibration and verification using reference material 5. Disposal and condemnation	Information about 1. Use/cleaning and maintenance/ periodic inspection 2. Out-of-service equipment: identified and documented	Information about 1. Operation/ maintenance/ cleaning/ and calibration 2. Use of the suitable computerized system	All guidelines have mentioned facts regarding equipment for GCLP in detail, though ICMR guideline puts extra criteria for qualification of instruments before use
Reagents, kits, and materials	1. Description of reagents, kits, and materials in terms of batch no., cat. no., manufacture date, expiry date, storage conditions 2. Preparation of stock solution 3. Disposal of reagents	1. Suitably labelled 2. Preparation date and expiry date 3. Specific storage and stability instructions	1. Reagents and materials should be suitable for use	ICMR guidelines mentioned the labelling of reagents, kits, and materials with detailed parameters
Quality management	1. IQC for quantitative and qualitative tests 2. External quality assessment/ proficiency testing 3. Internal audit 4. Technical audit checklist 5. Quality indicators	1. Quality control: test facilities should subscribe to membership of external accreditation/ performance/proficiency schemes to demonstrate the competency of the work performed 2. Quality audit	1. QA processes: ensuring patient safety and confidentiality 2. QC 3. SOPs and facility policies	ICMR guideline has separately mentioned IQC for quantitative and qualitative tests. Though SOP and logbooks requirements are mentioned separately in different headings in ICMR guideline, it is not being captured under quality management
Data	1. Data integrity 2. Data Confidentiality 3. Data security ❖ Hardware security ❖ Network security ❖ Application security ❖ Personnel security 4. Data integrity audits	1. Data record 2. Computer systems to receive, capture, process, or report data should be acquired, developed, tested, released, used, maintained, and retired according to established guidelines or laws. 3. Restricted/authorized personnel access	1. Data recording 2. Data reporting 3. Computerized system	ICMR guidelines mentioned data security in separate headings like hardware, network, application, and personnel; however, other guidelines did not mention such details. WHO and EMA focuses digitalization of data management systems, and in ICMR guideline it has not been mentioned separately

Abbreviations: ICMR, Indian Council of Medical Research; EMA, European Medicines Agency; COVID-19, coronavirus disease 2019; GCLP, Good Clinical Laboratory Practices; IQC, internal quality control; QA, quality assurance; QC, quality control; SOP, standard operating procedure; WHO, World Health Organization.

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research but also from patients for diagnosis and disease control.

2. Procedures included: The ICMR GCLP guidelines focus more on clinical samples from healthcare sectors and include details of pre-examination processes like consent, patients' preparation, primary sample collection, and primary sample collection devices. Also, it provides information about requisition, labelling, documentation, transport, acceptance and rejection criteria, and storage of samples. The WHO GCLP guidelines and the EMA reflection paper focus more on patients' safety, sample storage, retrieval, and chain of custody of samples and the criteria to expedite the reporting of results and reporting of any deviations from standard operating procedures.
3. Infrastructure: All three guidelines provide detailed information about instrument selection, use, and maintenance. The EMA reflection paper also provides guidelines to prevent the use of out-of-service instruments.

Prospect for Robust ICMR GCLP Guidelines

The following points can be considered to make the ICMR GCLP guideline more robust.

1. The scope can be extended to include analysis to be done on the subject himself, rather than on any biological samples drawn from the subject, the tests like pulmonary function test, neuropsychiatric evaluation, electrocardiography, ultrasound examination, X-ray, and CT scan. This will help to ensure the viability and integrity of such data generated apart from the testing of biological samples. Also, the use of next-generation sequencing for patient management has gained immense popularity in the current era. Hence, the addition of guidelines for such modern investigations needs to be considered for the betterment of healthcare in India.
2. Prepreparation of patients helps in obtaining proper samples. So, standard operating procedures will help to guide and ease the process of pre-preparation. Although personnel training has been mentioned in the ICMR GCLP, it needs to highlight the critical areas where training and skill development needs to be reinforced so that the proper samples would be collected and subjected to undergo proper testing. Such areas include patient preparation (e.g., time of visit, food intake, clothing, and prior physical activity), instrument/reagents preparation (e.g., type of needle and syringe, anticoagulants, different color coding of sample collection tubes, place or sitting arrangement while the collection of samples), specimen collection (e.g., the number of pricks for blood sample collection, volume to be drawn, the way the nasal swab to be inserted), sample storage, analysis, and reporting recording.[5,6]
3. The integrity and stability of a test sample depend on storage conditions including appropriate temperature. Also, plasma/serum separation before storage helps to maintain the integrity of the sample for a longer duration and helps in removing the discrepancies in analysis caused by cellular fractions. So, it is important to include criteria like the maximum time for which a sample can be kept before plasma/serum separation and transport procedures. Categorization with color-coded transport bags to distinguish the samples to be frozen from those to be processed immediately may help to preserve the integrity and stability of samples during transport to the site of testing. The transport system like the vehicle and cold chain system should be periodically checked and validated. The collection vial is also very crucial for the analysis of biochemical, hematological, and coagulation test parameters. Appropriate considerations for the sample collection tubes may also be considered for inclusion. In the absence of a disposable vial or required transport bag in an emergency, the type of container used should have proper labelling adhering to the standard operating procedure being followed.[6]
4. After the tests are conducted, proper disposal of leftover samples according to the rules of biomedical waste disposal is indispensable. The duration for which the leftover sample is to be stored considering the integrity and stability of different parameters, if included in the guidelines, will help in repeat analysis on the same sample wherever required. It will also help clinical laboratories that use the leftover sample for clinical research.
5. Any deviation from standard operating procedures during the conduction of a test or data analysis will result in anomalous results that will be detrimental if not corrected. The inclusion of systems to report such deviations and the requirement of the retest in cases of serious deviations will help in generating good results and future corrections.[1,2]
6. In case of incomplete/improper labelling, and processing of samples, the guideline has mentioned rejecting the sample. However, the policy of quarantine may be a better option for the samples/results before rejection. In cases, where there is a risk of compromise of sample integrity during the time taken for confirmation of the identity of the sample, the test should be conducted, and the result should be kept on hold. The result should be rejected if the identity of the sample cannot be confirmed. This will help to reduce the requisition of new samples in cases of discrepancies in the identities of patients.[2]
7. Critical values of any parameter represent a life-threatening pathophysiological state that mandates prompt action on the patient. Therefore, the critical values for various parameters should be defined and guidelines should include expediting the reporting of critical values so that timely corrective actions can be taken.[7,8]
8. The turnaround time (TAT), defined as the time interval between the specimens received in the laboratory to the time of dispatch of verified reports, is considered one of the key indicators for laboratory performance. Hence, the inclusion of guidelines on TAT will help in monitoring the performance of laboratories.[9,10]

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9. Many instruments used in our country are not validated for patient diagnostic use, rather they are meant for research use only. Proper guidelines should be framed regarding when and how research use equipment can be used for patient sample analysis and reporting.
10. The ICMR GCLP guideline has mentioned in detail the data management. Additionally, there should be the provision of data backup for any untoward incidence of data loss from any site. The archive facility is mentioned for records and data. Additional archive facility/guidance for biological samples, slides, tissue blocks, and specimens will facilitate to review of the results if needed. Storage of data should be proper and computerized systems can be used to improve the ease of storage according to established guidelines like the Organization for Economic Co-operation and Development (OECD) Monograph "The application of GLP Principles to computerized systems," the Food and Drug Administration 21CFR Part 11 for electronic records and electronic signatures.[1] Moreover, guidelines for reflex and addon testing on stored samples within defined time frames may be evolved to decrease time-to-diagnosis.
11. An interoperable healthcare system based on safe laboratory patient data sharing is urgently needed for better patient care, as evidenced by the severe acute respiratory syndrome coronavirus 2 pandemic. This will minimize repeat testing by providing rapid access to the subject's complete medical record, thereby allowing any underlying issues to be addressed and it will save time, resources, and manpower, as well as improve patient outcomes. This can be accomplished by building databases or using presently available public databases such as ClinVar and DECIPHER, which allow laboratories, physicians, researchers, and patients to submit data. Therefore, if guidelines for data sharing are included, the process of data sharing will be streamlined, and access to such data would be made easier.[11,12]
12. Regular maintenance and calibration are important for the proper functioning of the instruments. However, during pandemics like coronavirus disease 2019 (COVID-19) or natural disasters, maintenance, and calibration by a physical visit of the designated technician is difficult. So, guidance for calibration and maintenance of instruments through video calling or some other possible methods will help in the proper functioning of instruments during pandemics like COVID-19. In this regard, recently MHRA has released "Guidance for manufacturers and GLP on exceptional flexibilities for maintenance and calibration during the COVID-19 outbreak" in 2020.[13]
13. GLPs are a system used for achieving the objectives of mutual acceptance of data across the OECD members and associated countries. National GLP Compliance Monitoring Authority is the committee under the Department of Science and Technology, Government of India that monitors the compliance of laboratories functioning in India adhering to OECD principles.[14] Currently, there are 52 GLP-certified laboratories in India (by 22 June 2022).[15] In a similar view, there can be a certification/registration or accreditation of clinical laboratories adhering to GCLP principles, which will promote uniformity and standardization in human biological sample analysis all over the country

Conclusion

India has become a major contributor to healthcare as evident in the recent pandemic. The handling of the immense workload by laboratory facilities due to the increased number of cases during the pandemic in a developing country (India) of more than 1.4 billion population is only possible because of substantial growth in the healthcare sector. Similarly, the current revision of GCLP guidelines in India is a welcome step that will lead to the strengthening of clinical laboratories and ultimately better healthcare. This review has compared currently available international GCLP guidelines with Indian guidelines and highlighted the potential areas for development. Consideration of the suggestions mentioned in this review will lead to further strengthening the clinical laboratory practice for the improvement in the Indian healthcare system.

Abbreviations

CRO, Contract Research Organization; EMA, European Medical Association; FDA, Food and Drug Administration; GCLP, Good Clinical Laboratory Practice; GLP, good laboratory practices; ICMR, Indian Council of Medical Research; NGCMA, National GLP Compliance Monitoring Authority; OECD, Organization for Economic Co-operation and Development; RQA, Research Quality Association; SOP, standard operating procedure; TAT, turnaround time; WHO, World Health Organization.

Authors' Contributions

Rajat Kumar Joshi was involved in planning, designing, data collection, manuscript writing, reviewing, and editing. Sudhir Chandra Sarangi was involved in planning, designing, data collection, manuscript writing, reviewing, and editing.

Soumya Ranjan Mallick, Sarita Mohapatra, and Sudip Kumar Datta wrote, reviewed, and edited the manuscript.

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Conflict of Interest

None declared.

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