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Review Article

Ensuring Quality in Clinical Research: The Impact of Quality Assurance and Quality Control in the Field of Good Clinical Practice

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Good Clinical Practice (GCP) compliance delivers assurance that the study participants' safety is protected and that the obtained data are legitimate and credible. One of the tools to obtain quality in clinical research is to assure robust quality assurance and quality control as part of the quality management system. This is considered essential for sponsors to assure that the data from the clinical trial have integrity and reliability. One of the purposes of this article was to provide information to allow clinical research, quality assurance professionals, academics, and members of ethics committees to stay up to date with clinical research and good practice developments. This article investigates the enormous value of quality assurance and control in clinical trials, highlighting their pivotal role in ensuring the integrity, safety, and efficacy of research findings.

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Key messages

- Updates with the new International Guideline on Good Clinical Practice in providing reliable and robust data from clinical trials
- Highlights the Investigator's responsibilities according to ICH GCP R3
- Quality assurance, often forgotten, presents a pivotal role in ensuring the integrity, safety, and efficacy of research findings
- Overview of inspection findings from major regulatory agencies

1. Introduction

Good Clinical Practice (GCP) in our country, North Macedonia, was first introduced in 2009 as an 'Instruction on the working basis of the Good Clinical Practice' by the Ministry of Health and based on the Law for Medicines and Medical Devices issued in 2007.[1][2] In this document, the basic principles of the

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then-issued ICH GCP E6 (R1) were covered.[3] Namely, the document discussed the international ethical and scientific quality standards in terms of planning, implementation, monitoring, and reporting of clinical trials conducted on humans; the tasks and responsibilities of the Ethical Committee (known as the Institutional Review Board) in approving clinical trials; further, the principal investigator's responsibilities in the clinical trial; the plan for the trial conduct, potential changes and amendments, the Informed Consent Form as a 'must' document for a participant to be enrolled, the Investigator's brochure, and the basic documents for conducting the clinical trial.

GCP compliance delivers assurance that the study participants' safety is protected and that the obtained data are legitimate and credible. The Declaration of Helsinki, first published in 1964, is the basis of the principles presented in the Guideline, concentrating on the safety, rights, and well-being of the study participants.[4] In general, the principal investigators are quite aware of the safety of the participants and the training procedures that one investigator must possess in their curriculum vitae. Investigators are aware that clinical research plays a crucial role in advancing knowledge, the availability of new therapies, and finally improving patient outcomes. What has always been challenging to understand and address by the principal investigators is the field of the quality of data. It has already been required in the first version of ICH GCP that the Quality Control (QC) activities must be performed during clinical trial conduct as a tool that significantly supports the Quality Assurance (QA) system, with their mutual aim to assure overall quality in the trial. Moreover, Annex 5a issued by the World Health Organization (WHO) in 2016 entitled **"Guidance on good data and record management practices" has been replaced in 2021 by Annex 4 or the "Guideline on data integrity"** with the following structure: Introduction and background, Scope, Glossary, Data governance, Quality risk management, Management review, Outsourcing, Training, Data, data transfer and data processing, Good documentation practices, Computerized systems, Data review and approval, Corrective and preventive actions, References, Further reading, and Appendix 1 - Examples in data integrity management.[5][6]

Clinical research positions are at the forefront of biomedical developments and the growth of novel therapies and treatments. To establish firm trust in the results, studies must be conducted with rigid attention to detail. In this regard, quality assurance and quality control occur as essential pillars, safeguarding the delivery of the highest quality and most reliable data.

Briefly, this article focuses on the enormous value of quality assurance and control in clinical trials, highlighting their pivotal role in ensuring the integrity, safety, and efficacy of research findings. We would like to emphasize and give special focus to the question of why principal investigators must understand the importance of data quality generated during clinical research/trials, especially because data integrity avoids or at least reduces the problems that might occur during the monitoring process of the study and, more importantly, avoids major audit/inspection findings from a regulatory point of view.

2. The meaning of quality in clinical research and its origins

The importance of voluntary participation in medical experiments and the protection of the participants has its roots in the Nuremberg Code (1947), but the document issued in 1964, known as the Helsinki Declaration (World Medical

Association), has integrated details such as informed consent, prospective research design, data integrity, confidentiality, and independent protocol review. Data quality and data integrity were introduced much later in the 20th century, when scientific evaluation was based on statistically valid designs and not just on case-by-case individual opinions by the physician in charge.[2][7] As expected, the Food and Drug Administration (FDA) installed a set of new regulations, i.e., investigational new drug (NDA) regulations, from which the ICH GCP principle for quality has been extended in terms of data integrity. As such, data integrity has become integral in avoiding biased results, whether they are detected out of quality-related issues or are the results of fraud. Hence, the quality in the ICH GCP is a space that starts with the design of the study, followed by the study conduct phase, data recording, and until the reporting phase.

Therefore, a deficiency in the quality of the protocol or a case report form (CRF) would increase the number of monitoring findings and data queries addressed by the monitor/auditor/inspector. Compliance with the GCP as a quality standard during the clinical trial offers assurance that the reported data and results are accurate, credible, and that the rights, integrity, confidentiality, and wellbeing of the trial subjects are protected.

3. Importance of source documents

The principal investigator, or investigator as it is now referred to in the ICH GCP R3 in section 2, is responsible for diverse activities that are associated with the clinical trial.[8] The responsibilities for the investigator according to the ICH GCP R3 from May 2023 are given in **Table 1**. Investigators are ultimately responsible for the design/creation and the management of source documents at the investigator's site. These documents must be retained in order to confirm the existence of the subjects and to speak about the integrity of the study.

No	Responsibility	Comment
1	Qualification and training	Investigators must maintain credentials, i.e., keep accurate, up-to-date CVs for themselves and for the rest of the team; they should be acknowledged with the IB and/or SmPC of the investigational product provided by the Sponsor.
2	Resources	The investigator should be able to demonstrate a potential for recruiting the proposed number of eligible participants within the recruitment period as agreed with the sponsor.
3	Responsibilities	The restriction of qualified physicians and dentists to be solely responsible for trial-related medical care and decisions has been eased to allow other qualified healthcare professionals, in line with normal clinical activities and local regulatory requirements, to be involved.
4	Communication with IRB/IEC	Obtain study approval, informed consent approval, notification in case of SAE, and notifications of significant news/protocol amendments.
5	Compliance with protocol	The investigator should follow the protocol and deviate only where necessary to eliminate immediate hazard(s) to trial participants. In case of deviations undertaken to eliminate immediate hazard to trial participants, the investigator should inform the sponsor, IRB/IEC, and/or regulatory authorities promptly.
6	Premature termination or suspension of a trial	Trial participant withdrawal has been expanded, most probably with the idea to reduce dropouts from clinical trials, as this can have an impact on trial quality and the reliability of results. The changes cover and expand reasons for withdrawal by the participant and determining if there would be some way to address a participant concern. The guidance now considers different types of withdrawal and that there should be follow-up measures to avoid data loss.
7	Participant medical care and safety reporting	The sponsor is responsible for the ongoing safety evaluation of the investigational product(s). Safety Information and Adverse Drug Reaction Reporting have been significant additions contained in this new section of Safety Assessment and Reporting.
8	Informed consent of trial participants	Use an approved informed consent form, and conduct and/or supervise the consent process. New additions address that the time for consideration of participation may be reduced where justified, e.g., in emergency situations. Investigators are asked to ensure that participants are informed how their data will be handled, including if they withdraw from the trial prematurely, and that the participants should have access to the trial results and the treatment they have received if they wish to do so. There is new text on informing participants of the trial results and details of the treatment that they received when they participated in the trial.
9	End of participation in a clinical trial	The investigator should also have a plan in place for the ongoing care of the subjects after the end of the trial, especially if the subjects have experienced adverse events during the trial. This plan should also be demonstrated to the

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No	Responsibility	Comment
		participants and should be part of the informed consent process.
10	Investigational product management	Maintain accurate, complete documentation of the shipment, storage of the product, as well as appropriate dispensation, administration, and accountability.
11	Randomization procedures and unblinding	The investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, emergency unblinding to protect a trial participant, unblinding due to an SAE) of the investigational product(s).
12	Records	Overall, the guidance can be summarized that in terms of generating, recording, and reporting trial data, the investigator should ensure the integrity of data under their responsibility, irrespective of the media used.
13	Clinical trial/study reports	In accordance with ICH E3 Structure and Content of Clinical Study Reports.

Table 1. Investigator responsibilities according to ICH GCP R3

According to the ICH GCP R3, section 2.12, source records should be attributable, legible, contemporaneous, original, accurate, and complete (ALCOA-C). Any changes to them should also be traceable, should not obscure the original entry, and should be explained, with digital systems having an audit trail for this purpose. The investigator should define what is considered to be a source record(s), the methods of data capture, and their location prior to starting the trial and should update this definition when needed. The European Agency for Medicines and its compliance working group points to the medical record as a crucial element of study subject care. It ensures that an ongoing record of information relating to the study subject, visit and test records, medical history, diagnoses, treatments, etc., is available to the treating physician/investigator and his or her colleagues who may intervene in the care of the study participant or take over that care, if necessary. Any information that would routinely be expected to appear in a medical record should continue to appear there during the study to ensure the care of the study subject is maintained. The fact that the study subject is in a clinical trial, its identity, and any specific information over and above the routine that impacts on the study subject's care should also appear, or be clearly referenced and readily available to the caregiver. The medical record may also be the first place in which trial-related data is recorded and, as such, becomes by definition the source document for that data. It may also be the main point of information on medical history for the purposes of the study, even if that information was originally recorded elsewhere.

The medical record should provide sufficient baseline information to permit the investigator to enroll the study subject in the trial with due recognition of the needs of medical care and in compliance with the protocol. The medical record is also the common point of confirmation of study subject identity and demographics.[9][10]

4. Auditors in the evaluation of the QC and QA activities

The overall responsibility for ensuring quality and GCP compliance in clinical research lies with the principal investigator. Additionally, auditing is the independent method for confirmation of the clinical trial's compliance with the relevant local and international laws and regulations.[10][11][12] In broad terms, an audit is a systematic monitoring method that is applied to control that the documents and clinical activities used are effectively obtained according to the study protocol, GCP, and regulatory requirements. However, auditing presents a time-consuming and laborious activity, and that is why the auditor must be well-trained in the relevant regulations and the study's protocol and all related procedures for study conduct. Traditional QA practices rely heavily on audits to detect sites or studies with quality issues (9–12). Current site monitoring strategies, which rely on on-site visits with source data verification (SDV) and on risk-based approaches, are also attempting to mitigate the risk of occurrence of clinical quality issues.[13][14] In the past several years, especially during the COVID-19 pandemic, audits have become more effective in several ways by including remote technologies, in terms of accelerating the decrease of traditionally conducted audits and inspections. Starting from the cost-effective auditing system introduced by Califf et al.[15], towards the available guidelines for a risk-based approach to monitoring by the FDA in 2013. More recently, Park et al. [16] introduced the quality assurance tool 'Screening audit," which is generally presented as a questionnaire that includes 20 questions that summarize the results in five categories of audit findings. They analyzed 462 studies retrospectively and compared the results with those obtained by previous regulatory assessments. On one side, this tool can be used as an effective method for overseeing and controlling the GCP environment in one institution, and on the other side, it can be used by Sponsors for site qualification or during a routine audit. In an article published by Ménard et al.[17], all QA activities for the COVACTA study (treatment of Covid-19 pneumonia) were performed by using 100% analytics, with a main focus on patient safety in terms of assessing the risk for Adverse Events (AE) under-reporting (including Serious Adverse Events (SAE) and Adverse Events of Special Interests (AESI)) and ensuring proper dosing of the patients with tocilizumab. Individual investigator sites have been monitored for potential AE underreporting, using descriptive analytics, complemented by a machine learning approach in real time with early detection of quality issues.[18]

5. Staying informed and deficiencies identified during inspections in 2020-2022

The environment of clinical research is a dynamic, evolving place; hence, to be and stay informed in terms of regulatory changes, ethics, and technical novelties is not just challenging but crucial. One way to stay informed is to use proactivity, which means being alert for any new updates to the valid versions of the latest guidelines. The steps to be undertaken include participating in or being a member of specific organizations where one receives newsletters. Very practical and informative mediums are relevant online forums and, of course, conferences and workshops. Being aware of the enormous pool of data available on the worldwide internet, applying the really simple syndication feed (RSS) allows one

to get updates related to regulatory news without accessing the websites of the EMA or FDA (eliminating the need to search for it on a weekly or monthly basis. [19][20][21][22][23][24][25] The website of MALMED contains the regulations just for North Macedonia, without any connection link to the worldwide regulatory agencies. Hence, to be sure, if one wants to be up to date with the latest regulatory and safety information, one must access the globally recognized regulatory pages, i.e., the Center for Drug Evaluation and Research and MHRA news. One of the cost-effective approaches is to learn how to avoid mistakes that have already been identified by the major regulatory agencies.[19] **Table 2** gives a brief overview of the inspection findings from the FDA and EMA. According to the Annual Report of the Good Clinical Practice (GCP) Inspectors' Working Group, a total of 36 GCP inspections were conducted (26 routine and ten triggered) in 2022, with a note that some of them, due to the COVID-19 pandemic, were conducted remotely.[20] Most of the inspections were conducted in North America (44.4%), followed by the EU/EEA (36.1%) and non-EU Western Europe (8.3%), with none in non-EU Eastern Europe. Most of them were conducted at the clinical investigator site (20 inspections), Sponsor (four inspections), and CRO (two inspections). A total of 470 deficiencies (17 critical, 260 major, and 193 minor) were recorded, which presents an average of 13 findings per inspection. Some of the findings, in addition to **Table 2**, include the following, namely as a finding in relation to study contracts/agreements:

- The contracts and/or master service agreements with third-party vendors and/or service providers that were inspected in detail did not (or did not adequately) address the legal right for representatives of regulatory agencies (inspectors) to inspect those third parties, their activities, and systems on site.
- The contract for the long-term archiving of the site documents, including the investigator site file, did not adequately address specific GCP requirements for these documents (e.g., period for archiving conditions, etc.).
- There were no separate written agreements with different hospital departments that provided study-specific services for the principal investigator.

Facilities and equipment:

- During the pharmacy visit, the inspectors observed that the available space was globally insufficient to store the IMP of ongoing studies and did not allow for the allocation of specific areas for product quarantine or expired products, which increased the risk of human error.
- Equipment standardization and documentation of certification were insufficient. This indicated a lack of risk assessment given the relevance to the primary endpoint.

Qualification and Training:

- Lack of training of CRAs on sponsor Standard Operating Procedures (SOPs)/guidance documents and GCP.
- Missing CVs for a substantial part of the personnel involved in the study; CVs were not signed.
- The periodic medical examinations specified in the study protocol were performed by an investigator, but no GCP training was available for him in the trial master file.

Monitoring:

- The process in place to allow for remote monitoring visits to be performed by the CRA was not GCP compliant as the protection of the privacy of the trial participants was insufficiently ensured.
- Lack of a monitoring plan.
- There was no evidence provided to inspectors that the monitoring issues identified at the site were escalated in a timely manner. There was no evidence of continuous and effective medical monitoring activities.

The number of inspections in the United Kingdom (UK) that were undertaken by the MHRA GCP Inspectorate in total was also 36 for 2019-2020. In addition to these, the MHRA Laboratories compliance team performed ten inspections in facilities that perform clinical trial sample analysis and four inspections for non-UK bioequivalence studies. In this period, a total of seven sponsors were inspected (six systemic and one triggered inspection), and in four of them, at least one critical finding was identified, and all had at least one major finding. Briefly, in a total of 55 findings at the sponsors' sites, four were critical, 17 major, and 34 classified as other. The four identified critical findings in four different organizations were related to pharmacovigilance, namely a breach of UK Statutory Instrument 2004/1031 and several regulations, followed by a failure to implement CAPA for previous major inspection findings, which can have a significant impact on safety reporting to the regulatory authorities.[21] In regard to the CROs, the MHRA inspected a total of five organizations, including vendors of electronic systems and niche providers of services used in the conduct of the clinical trial. A total of 70 findings were identified, with four critical, 25 major, and 41 classified as other. The four major findings were related to the control process of data integrity, IMP management, data integrity, and protocol compliance. A more comprehensive overview is shown in **Table 2**. The MHRA inspected 12 investigator sites, and all of them were associated with a sponsor/CRO. None had a critical finding, and ten had at least one major finding, with a total of 81 identified findings.

Regulatory Agency	Findings	Source
European Agency for medicines (EMA)	• Lack of communication plan between sponsor and CRO; • Lack of audit clause and retention time of data recording in clinical trial agreement between the sponsor, site, and Principal Investigator (PI); • Internal SOPs not adhered to; • Performance of subcontracted activities before signature of a valid contract; • Documents missing in the Trial Master File (TMF)/Investigator Site File (ISF), or misplaced, or stored in another location without a note to file or filed with delay; • TMF table of contents not granular enough to allow knowing which documents are located in each section; • The investigator site file (regulatory binder) and a third of the trial participant binders could not be located by the site during the inspection, making it difficult for inspectors to reconstruct and validate the data from the study for these trial participants and recreate the study. Without the knowledge of the staff at the site, the investigator site file, and the missing trial participant source documents, inspectors could not validate the data of these trial participants • Relevant access to source data was not in compliance with GCP for a number of clinical sites. This impacted both source data verification by clinical research associates (CRAs) and conduct of the inspection by the inspectors. In addition, at the site inspected, an unvalidated process was used to generate certified copies. There was no robust process for CRAs or inspectors to verify the completeness and correctness of the printouts of electronic systems/repositories • Deletion of documents allowed without the need for a quality check and not traceable; • Late provision of updated Investigator's Brochures (IBs) to sites; • Late completion of GCP [ICH] E6 R2 training or refresher; • Late training in updated IBs and protocol amendments; self-training is not deemed adequate for significant amendments; • Lack of procedure for periodic review of user accesses. • Lack of an audit trail to reconstruct the course of events; • Deficiencies in/late provision of access to electronic systems for relevant team members (PI, monitors); • Lack of risk assessment of the computer system;	Annual Report of the Good Clinical Practice (GCP) Inspectors Working Group (IWG) 2021 and 2022

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Regulatory Agency	Findings	Source
	• Lack of procedure for validation of computerized systems; • Lack of testing documentation and conduct • Security issues for the remote internet access to the system (no encrypted channel). • Lack of periodic reviews of firewalls protecting the system. • Lack of record of security incidents. • Lack of deployment of critical patches. • Reporting of serious adverse events not done within the 24-hour timeline • Several potential adverse events collected by the clinical nurses or by oncologist residents in the electronic medical records were not collected, assessed, or reported in the trial eCRF	
FDA (Food and Drug Administration)	• Failure to prepare or maintain adequate, accurate case histories with respect to observations and data pertinent to the investigation and informed consent; • An investigation was not conducted in accordance with the signed statement of investigator and investigational plan; • Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects • Failure to report non-serious adverse events to the sponsor in accordance with the study protocol timetable for reporting. • Minutes of IRB meetings have not been prepared, maintained in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on actions, including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research • The general requirements for informed consent were not met in that the information given was not in language understandable to the subject or the subject's representative • The quality assurance unit failed to periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken • The quality assurance unit failed to prepare and sign a statement to be included with the final study report which specified the dates inspections were made and findings reported to management and to the study director • The phlebotomy site is not prepared by a method that gives maximum assurance of a sterile container of Whole Blood • Failure to maintain facilities in a clean and orderly manner • Source documents are missing	FDA Enforcement actions; warning letters; Sellers JW et al.[19]

Regulatory Agency	Findings	Source
	• Medical history does not support protocol-required documentation of failure • Transcribed laboratory results in the medical record differ from values in reports • Delegation log not kept up to date • Visits noted in CRF but not on source documents	
MHRA (Medicines and Healthcare products Regulatory Agency)	Pharmacovigilance: • The inspection findings in relation to the major finding for pharmacovigilance from the last MHRA GCP inspection had not been addressed with a robust CAPA in a timely manner, and there was evidence that implemented actions had been ineffective. • There were more adverse reaction terms considered expected in the safety database used for SAR case assessment than contained in the RSI that had been approved by the MHRA in the Clinical Trial Authorization (CTA). • A conservative approach was not applied where the investigator's causality assessment was missing on an SAE report submitted from the investigator site. Instead, the assigned company causality would drive reporting requirements as stated in company operating procedures. This resulted in delayed reporting of SUSARs and had the potential for underreporting of SUSARs. • Inconsistencies between the clinical database and safety database were identified • There was a significant lack of follow-up of pregnancy reports; reviewed cases were not followed up in a timely manner in line with company procedures • A number of events had been reported late as SUSARs due to an incorrect expectedness assessment upon the event becoming Fatal/Life Threatening. This demonstrated that the RSI was not being applied correctly to all cases upon initial receipt. • A discrepancy was identified in the reconciliation of trial events which compared safety data reported in the clinical and safety databases • Unreported SUSARs were still found due to investigator causality of 'unknown' or 'not assessable' and a non-conservative approach taken Data integrity and data integrity control process: • There was insufficient documentation available to demonstrate when database pages were frozen, unfrozen, and re-frozen between database locks in order to verify what data had been changed and by whom or when	GCP Inspectorate GCP inspection metrics Report issued April 2023

	Regulatory Agency	Findings	Source
		• From database records, it was not possible to verify if any data changes made to the primary endpoint data had been confirmed by the PI prior to analysis. • The audit trail provided from the eCRF system was not in a suitable format to aid review at a system level to identify what data changes were made, by whom, and when in order to verify if the changes were authorized. • There was a lack of documentation to demonstrate that the eCRF audit trail had been reviewed between database locks by data management or reviewed during the trial to verify what changes were being made in the eCRF by data management staff. • It was found that the audit trail was unreliable as it had not documented accurately the data changes made for primary endpoint data. IMP management: • There was a lack of overall accountability of IMP received, dispensed, and returned, as well as compliance checks to verify if patients took the required amount of medication. • The Certificates of Conformance (CoC) for the respective batches did not specify what the dose was for that batch (each kit could contain more than one strength of the tablet). • The shipment records and consignment reports accompanying the shipments did not state what dose the kits supplied were but did state the batch number. • A PI at the site informed inspectors that they had raised concerns with regards to the packaging of IMP in blister wallets which were not clearly labelled to state when each dose should be taken or what the strength of each tablet was. The initial stock of IMP contained no labelled inside wallets to indicate when the dose should be taken. Whilst the inspected site took steps to protect trial patients from dosing errors by educating the parents/carers of all the trial participants and by halting recruitment at this site, there was no urgent safety measure or potential serious breach submitted by the Sponsor/ CRO to ensure that trial participants did not come to any harm due to the lack of adequate labelling. Furthermore, the PI's concerns were not reflected in the monitoring visit reports. • The patient information leaflet was not updated following the update to packaging in light of the issue outlined above Protocol compliance:	

Regulatory Agency	Findings	Source
	• There was a lack of a robust process in place for ensuring protocol compliance with dose reductions required by the selected trial protocol. • There was evidence of a participant not receiving the required dose reduction as mandated by the protocol but instead having their dose increased. • It was found that there was a delay in action being taken when changes in safety blood measures from baseline (required to inform any dose reduction) could not be calculated due to missing baseline data. The lack of action was unacceptable, as CRO personnel failed to ascertain the impact of a missing baseline value on the safety of the trial patient. This demonstrated a lack of understanding of the trial protocol by the pharmacovigilance representative. • There were no timelines specified in the Medical Monitoring Plan for actioning an alert received from the Central Laboratory or IRT system by the Pharmacovigilance team. As a result, there was a delay in actioning an alert for a patient who required a dose reduction	

Table 2. Inspection findings from FDA Warning Letters, MHRA, and EMA

6. Conclusion

By incorporating quality into every part of the clinical trial process, organizations can gain significant benefits, ensuring regulatory compliance, enhancing efficiency, and safeguarding patient safety. Moreover, with the increased application of technological advancements in clinical trials, quality assurance and control challenges are sure to rise. Therefore, clinical researchers/investigators are encouraged to implement robust quality assurance and quality control actions to guarantee the accuracy, reliability, and validity of the data collected and analyzed.

Statements and Declarations

Data Availability

All data discussed in this review are sourced from publicly available materials, including regulatory guidelines, official reports, and published articles cited in the reference list. No new primary data were generated or analyzed in this study. Further inquiries can be directed to the corresponding author.

Author Contributions

Conceptualization: M.P.; Methodology: M.P., E.A., D.Z.; Writing–original draft preparation: M.P.; Writing – review and editing: M.P., E.A., D.Z.; Supervision: M.P. All authors have read and agreed to the published version of the manuscript.

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