International Journal of Clinical Trials
Sanap SL et al. Int J Clin Trials. 2025 Aug;12(3):252-261
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20252204

Review Article

Steps and requirements of preparing trial master file and clinical trial manufacturing documentation

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Received: 11 April 2025
Accepted: 20 May 2025

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ABSTRACT

The preparation of a trial master file (TMF) and clinical trial manufacturing documentation is fundamental to ensuring regulatory compliance, maintaining data integrity and supporting the successful execution of clinical trials. A well-organized TMF serves as a key repository for essential documents that allow the conduct of a clinical trial to be reconstructed and evaluated, ensuring adherence to ICH-GCP (E6 R2), FDA, EMA and MHRA guidelines. With the increasing adoption of electronic trial master files (eTMF), sponsors and clinical research organizations (CROs) are transitioning towards centralized digital platforms to enhance data management, reduce compliance risks and facilitate real-time monitoring. This transition, however, presents challenges such as data migration complexities, system validation and maintaining audit readiness. Clinical trial manufacturing documentation plays a crucial role in ensuring the safety, quality and efficacy of investigational medicinal products (IMPs). Key documentation includes investigational medicinal product dossiers (IMPDs), master and batch manufacturing records (MBR/BMR), certificates of analysis (CoA), packaging and labelling records, stability reports and deviation/CAPA Reports. Compliance with good manufacturing practices (GMP), 21 CFR Part 211 and EU Annex 13 is essential to meet global regulatory expectations. Proper documentation ensures that clinical trial materials are manufactured, tested and distributed in accordance with predefined standards. This review outlines the stepwise process involved in preparing and managing a TMF and clinical trial manufacturing documentation. It highlights best practices for document organization, quality control and regulatory compliance, while also addressing challenges such as incomplete documentation, audit findings and evolving regulatory landscapes. Furthermore, the paper discusses the impact of digital transformation, including the role of artificial intelligence (AI) and blockchain in enhancing documentation security, efficiency and traceability.

Keywords: Clinical trial manufacturing, eTMF, Good clinical practices, Regulatory compliance, Trial master file

INTRODUCTION

Drug development causes and rising costs are problems plaguing the worldwide pharmaceutical business. Clinical trials are now conducted globally in developing nations due to the twin goals of time and cost savings. However, the third goal complying with global quality is challenging and demanding because to the disparities between industrialized and developing nations' regulatory procedures, ethical considerations, medical knowledge, clinical practice and health infrastructure. Outsourcing the clinical trial procedure has been the pharmaceutical industry's approach to managing such intricate multi-country clinical trials. The goal of attaining global quality has become challenging due to the outsourcing and globalization of clinical trials.

This article provides a concise overview of the developing situation with adherence to global clinical trial quality standards.[1] The discovery of novel medications, biologics and medical devices is greatly aided by the clinical research sector. In order to evaluate

the safety and effectiveness of novel therapeutic interventions while protecting patient rights and welfare, clinical trials are essential to this process. However, from start to finish, these studies produce a lot of documentation and are frequently costly and time-consuming.

The trial master file (TMF), which forms the basis for regulatory assessment and approval, is one of the most important sets of clinical trial documentation.[2] The TMF includes a number of crucial papers that offer an exhaustive record of trial conduct, guaranteeing adherence to regulatory requirements and good clinical practice (GCP).

To support regulatory filings and show the integrity of the trial data, the TMF must be properly prepared, maintained and organized. To guarantee openness and compliance with legal requirements, the documentation process consists of a number of crucial processes, including document creation, collecting, review, approval and archiving.[3] The clinical trials transformation initiative (CTTI) has developed best-practice recommendations for the structure, functioning and communication processes of DMCs in an effort to better understand and apply.[4]

Over time, the function of contract research organizations (CROs) has also changed. After initially concentrating on particular facets of clinical trials, CROs have grown into full-service organizations that oversee data administration, safety monitoring, regulatory compliance, investigator selection and patient recruiting. CROs must manage the strict regulations set by federal agencies, international guidelines and industry standards as they take on more responsibility for regulatory and ethical monitoring. Their compliance with these rules guarantees data integrity, human subject protection and the general success of clinical trials.[5]

A crucial step in the regulatory review procedure is the creation of the TMF and clinical trial manufacturing paperwork. The integrity, effectiveness and compliance of clinical trials depend on the integration of RBM, efficient DMC operations, careful site selection and strong CRO management. In addition to offering insights into best practices and regulatory issues in clinical research, this article will examine the necessary procedures and requirements for creating the TMF and clinical trial manufacturing documentation.[6]

DEFINITION AND IMPORTANCE OF TMF

Definition of TMF

A set of crucial records that enable the reconstruction and assessment of a clinical trial's conduct is known as a TMF. Records that show adherence to regulatory requirements and Good Clinical Practice (GCP) are centrally stored there. Clinical research is made transparent and accountable via the TMF, which contains records created prior to, during and following a clinical study (ICH E6(R2,2016(1,2).

Importance of TMF

Clinical trials must adhere to regulatory requirements, which include maintaining a comprehensive and organized TMF as required by regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[3] The TMF enables regulators to assess the trial's integrity and data quality while guaranteeing compliance with ICH-GCP principles (EMA, 2018). Furthermore, by offering a clear record of trial-related decisions, processes and activities, a well-maintained TMF supports risk-based monitoring approaches and improves audit and inspection preparation by enabling regulatory agency audits and inspections (MHRA, 2021).[2]

From the standpoint of operations and data management, the TMF serves as a central repository that facilitates effective document management by clinical trial teams and enhances cooperation between sponsors, investigators and contract research organizations (CROs) to guarantee trial integrity and continuity (Gartner, 2020).[4] Additionally, by providing recorded evidence that clinical trials were carried out ethically and protecting the rights and welfare of participants, the TMF is an essential instrument for legal and ethical protection. The TMF also serves as a legal record in situations of disagreements or court cases pertaining to trial conduct (WHO 2019).[5]

KEY COMPONENTS OF TMF

Essential documents before, during and after the TMF

An extensive collection of crucial papers known as a TMF makes it possible to assess how well a clinical trial was conducted and the Caliber of the data generated. These documents are divided into three categories according to the trial phase in which they are produced: prior to the clinical phase, during the clinical conduct and following the study's conclusion.[7]

Important documents guarantee ethical compliance and appropriate execution prior to the start of a clinical research. The investigator's brochure helps investigators make well-informed judgments by giving them the most recent scientific facts about the product. Consistency is ensured by recording trial procedures and amendments in the signed protocol and amendments document. Before consenting, individuals are guaranteed to comprehend the goals, hazards and advantages of the study thanks to the informed consent form (ICF).

Transparency is ensured by financial agreements that specify financing, resource allocation and researcher remuneration. The Insurance Statement attests to the participants' risk coverage. These records uphold openness, protect participant rights and guarantee financial responsibility, ethical standards and regulatory compliance in clinical research.

Important documentation guarantee corrects execution and compliance throughout the clinical phase. Records of delegation, training logs and employee credentials are all included in investigator files. Licenses and approvals are contained in regulatory submissions. Monitoring documents document visits and contacts between investigators and sponsors. While subject enrolment logs record screened and enrolled subjects, accountability records record research medication and device use, guaranteeing openness and protocol compliance.[8]

Important documentation guarantee appropriate closure and compliance following the conclusion or termination of a clinical research. A final record of product usage is provided by the investigational product(s) accountability at site. Participants can be identified for follow-up using the subject identification code list. The clinical study report provides a summary of the trial's processes and outcomes, while the audit certificate attests to the audit and its conclusion.[9]

Investigator files

To record the credentials and duties of the clinical trial team, investigator files are crucial. The investigator's credentials are summarized in the Curriculum Vitae (CV), staff qualifications are verified by the Professional Licenses, allocated trial tasks are tracked in the Delegation of Authority Log and procedure, GCP and pertinent instruction are documented in the Training Records.[10]

Regulatory submissions

Authorizations from the institutional review board (IRB) or independent ethics committee (IEC) record alterations, approvals of research protocols and informed consent forms. Regulatory authority approvals also contain any contact with regulatory bodies and ethical committees, as well as national or regional approvals.[11]

Monitoring documents

Monitoring Visit Reports Keep track of site visit results to make sure rules and procedures are followed. While Follow-up Letters provide a summary of visit outcomes and specify necessary activities, Monitoring Logs keep account of all correspondence between the investigator and the sponsor.[12]

Planning and setup: TMF and document management

With an emphasis on compliance and appropriate structuring throughout the clinical trial process, the european medicines agency (EMA) offers a thorough guideline, content, management and archiving of the clinical trial master file (paper and/or electronic), that describes best practices for TMF management.

Furthermore, a defined taxonomy for classifying TMF material is provided by the DIA TMF reference model. This paradigm ensures effective documentation and supervision while assisting sponsors, contract research organizations (CROs) and stakeholders in maintaining uniformity and regulatory compliance in TMF administration.[10]

Effective management of the TMF involves several key considerations

When assigning tasks, sponsors need to keep an eye on Contract Research Organizations (CROs) and make sure that TMF sections are available via electronic systems (eTMF) or frequent document transfers. Only authorized staff may access sensitive data, including randomization codes and unblinded adverse event reports, thanks to role-based access constrains.[13]

TMF management elements

Sponsors, CROs and investigators should have explicit agreements about the assignment of TMF tasks. Change control, eTMF system administration, access protocols, TMF structure and indexing norms are important components. It is necessary to set up appropriate training, document retention SOPs, correspondence management and regulatory access methods. Furthermore, following the conclusion of the trial, TMF archiving, oversight methods, data preservation plans and backup strategies guarantee compliance and continuity.[14]

Internal audits in quality assurance

Structured assessments of an organization's internal controls, risk management and regulatory compliance are known as "internal audits." They are essential in locating non-conformities, inefficiencies and places in need of development. Process improvement is a primary goal, where audits aid in streamlining processes, cutting waste and improving overall effectiveness.

Additionally, they guarantee regulatory compliance by confirming that laws and regulations are being followed. Additionally, by evaluating internal controls and keeping an eye on financial activity, audits help with fraud detection and prevention. Risk management is another essential role, where audits assess operational vulnerabilities and suggest ways to mitigate them. Internal audits improve corporate integrity by documenting evidence, creating remedial action plans and conducting ongoing monitoring.[15]

Methodologies for internal audits

Based on risk assessment, TMF audits rank important documents, including regulatory approvals, informed consent forms and monitoring reports. In accordance with ICH GCP E6(R2) Section 5.0 (Risk-Based Quality

Management), they concentrate on high-risk areas such as GCP compliance, safety reporting and protocol deviations. Performance audits evaluate the effectiveness of the TMF process, guaranteeing timely, accurate and comprehensive documentation while confirming adherence to sponsor requirements, SOPs and regulations. ISO 9001 audits review document control, process standardization, CAPA implementation and continuous improvement in TMF management to make sure that ISO 9001:2015 Quality Management System (QMS) requirements are followed.[6,16]

COMPLIANCE REVIEW FRAMEWORKS

ISO 9001

Regardless of whether you offer services or goods, it is applicable to and can be used by any organization in any industry.[16]

ISO 14001

It lays down crucial specifications to assist you in recognizing, managing and keeping an eye on the environmental effects your company has. Additionally, ISO 14001 offers a framework to help you determine legal compliance, cut down on waste and pollution and continuously improve.[16]

ISO45001: It was created in response to industry need for a standardized, externally recognized health and safety management system standard. Although ISO 45001 is not required by law, it does help organizations find relevant laws, manage risks and enhance performance.[16]

ISO 27001

Comprehensive information security management is the main goal of, which covers important topics including security policies, asset management, access control, cryptography and secure communications. In addition to addressing incident response, business continuity and legal compliance to preserve information integrity, it guarantees human resource security, physical and environmental protection, secure operations and supplier management.[16]

Regulatory audits in TMF

Ethical approvals, informed consent forms and protocols, as well as sponsor and investigator record such as delegation logs and monitoring reports, are essential clinical trial documents. Compliance and transparency are guaranteed via version control logs, safety reports, site and subject records, data management files and regulation submissions (INDs, CTAs, IRB/EC approvals).[17]

ELECTRONIC TMF CONSIDERATIONS: DIGITAL SYSTEMS AND VALIDATION

Introduction to electronic trial master file

A computerized system called an Electronic Trial Master File (eTMF) is used to track, organize and preserve important clinical trial information. It improves accessibility, efficiency and compliance by taking the role of conventional paper-based TMFs.

Key considerations for eTMF implementation.[11]

Data security and regulatory compliance are guaranteed by adherence to FDA 21 CFR Part 11, GCP ICH E6 (R2), EMA eTMF Guidelines, MHRA expectations and HIPAA/GDPR.

When selecting an eTMF system, consider on-premises vs. cloud-based options, compatibility with clinical systems like EDC and CTMS, metadata tagging for document classification, audit trail capabilities for compliance and role-based access controls for security.

Standardized indexing, naming practices and version tracking are necessary for version control and document management in order to preserve integrity. Automated alerts, ALCOA+compliance and making sure that documents are legible, attributable, reliable and accessible improve accuracy and regulatory compliance.

Verification of eTMF mechanisms.[18]

Utilizing a risk-based validation approach for regulatory compliance, computer system validation (CSV) adheres to GAMP5 standards, which include user acceptance testing (UAT), operational qualification (OQ) and performance qualification (PQ).

Advantages and difficulties of adoption of eTMF

Implementing an eTMF system comes with high initial costs, requiring user training and change management. Data migration from legacy systems is crucial, along with ensuring long-term system sustainability for continued efficiency and compliance.

Clinical trial manufacturing

Maintaining quality control, guaranteeing regulatory compliance and protecting the integrity of investigational pharmaceuticals (IMPs) all depend on clinical trial manufacturing documentation. This study, which is backed up by citations to reliable sources, looks at important facets of clinical trial manufacturing paperwork, regulatory requirements and best practices.

For the integrity and safety of experimental pharmaceuticals, clinical trial production must adhere to good production practices (GMP). GMP regulations offer

a structure to guarantee that goods are continuously manufactured and managed in compliance with quality requirements. Following these rules is crucial for the manufacturing procedure and related paperwork, such as the TMF, in the context of clinical trials.[19]

Compliance with good manufacturing practices[20]

Maintaining a clean manufacturing area, preventing cross-contamination by controlling the environment, defining and validating production processes, enforcing stringent documentation, providing adequate staff training, guaranteeing record-keeping and traceability and putting in place systems for product recall and complaint resolution are all highlighted in GMP standards.

Investigational medicinal product dossier overview

The Investigational Medicinal Product Dossier (IMPD) is a critical document submitted to regulatory agencies in the European Union (EU) before conducting clinical trials. It provides comprehensive data on the quality, safety and efficacy of the IMP. The attributes, stability data, production controls, composition and structure of the drug substance (API) are all included.[21]

Dosage form, content, formulation rationale, pharmaceutical development, storage conditions, labelling and packaging are all included in the drug product (Formulated IMP).[21]

Nonclinical data (preclinical studies)[6]

Nonclinical studies use laboratory and animal research to evaluate pharmacology and safety prior to human trials. These consist of pharmacokinetics, which studies ADME and pharmacodynamics, which analyses medication effects and processes. Acute and chronic toxicity, carcinogenicity, genotoxicity and developmental and reproductive toxicity are all covered in toxicology assessments.

Clinical information (earlier human research)[19]

If available, data from previous clinical studies are included in this section to bolster the suggested investigation.

Phase 1 studies

Preliminary human studies evaluating dosage and safety.

Phase 2 research

Initial patient efficacy trials.

Phase 3 studies

Extensive research verifying effectiveness and tracking adverse effects.

Clinical trial design

A protocol detailing the goals, outcomes and selection criteria for the research

ANALYSIS CERTIFICATE[21]

For document control and to reassure the client that every page of the COA is there, it is crucial that each page be numbered and indicate the total number of pages. A sample COA can be found in Annex.[1]

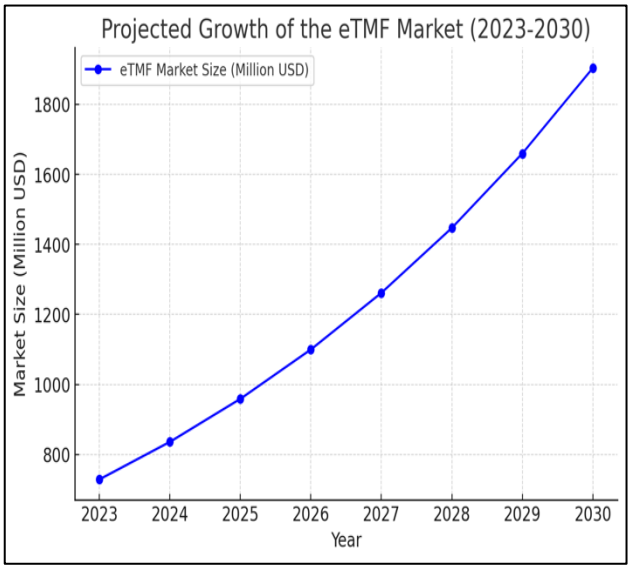

Figure 1: Graphical representation of the projected growth of the eTMF market from 2023 to 2030, based on the given CAGR of 14.7%. Let me know if you need any modifications.

The body

The original production site's name and address are listed on the certificate of analysis (COA). If not from the manufacturer, a list of the accountable party that provided the COA, together with their contact information, must be included.

It includes the excipient specification identification (e.g., USP, NF, Ph. Eur.), grade, trade name, batch number, production date and chemical or compendial name, as well as the compendial designation (if applicable). For sensitive items, stability statements, storage requirements and expiration or retest dates are provided. Excipient quality compliance and traceability are guaranteed by comprehensive characteristics, test protocols, acceptance criteria, analysis outcomes, alternative test results and retest intervals (where appropriate).

Statements of certification of compliance[21]

Along with other conformance declarations and pertinent standards, GMP standards such as IPEC-PQG Excipient

GMP and EXCIPACT are adhered to. Other pharmacopoeia compliance is evaluated. In addition to customer-provided information for quality assurance, the grade and composition of the ingredients (if a mix) are mentioned.

***Permission*[21]**

Identification of the authorized person for approval or a statement with an electronic signature that may be tracked back to the signatory, Manufacturing date, Number of Pages.

LIBELLING AND PACKAGING SPECIFICATIONS[22]

Packaging of the kit

Selecting the best packing materials for the medication or product under test is a step in the kit design process.

For instance, an injectable drug would need vials, autoinjector pens or pre-filled syringes, whereas an oral prescription might come in a bottle or blister pack. To prevent damage, some items need to be shipped via cold chain, have sophisticated tracking or come with additional packing materials.

Size and dispersion of the kit

Another crucial component of kit design is how many dosages, goods or collection items are included in each kit, as well as how frequently kits are given to patients. In this category, it is crucial to take into account both patient centricity and risk/cost reduction. For instance, an IND kit containing too many doses might overwhelm patients and result in medication waste, whereas one containing too few could raise distribution costs and/or necessitate too many journeys for patients to the trial site.

Rules governing international trials

Businesses are increasingly carrying out clinical studies in several nations at the same time. various nations have various labelling laws that specify what needs to be on the label.

Even when standards change, software may assist handle labelling for several nations and guarantee that laws are followed internationally.

Extensions of expiration

Kits must be relabelled with the updated date when expiration dates are extended. Relabelling may necessitate moving kits from depots back to a central production centre and kits that were initially scheduled to expire too soon to be used may become accessible as a result of these modifications. Trial managers can take expiration extensions into consideration both during the planning stage and throughout the actual research with the aid of the N-SIDE solutions. As expiration dates vary during the trial, trial managers may continue to improve their labelling approach by using N-SIDE to predict the impact of their stability plan using scenario planning.

Considerations for labelling

The process by which labels offer particular details about the IND or IMP is known as clinical trial labelling. These details might consist of, but are not restricted to: Directions, the way a medicine is administered, The batch or lot number Strength, concentration and dosage, date of expiration, needs for storage.

Product release records (batch release, qualified person release)

Three fundamental principles of pharmaceutical manufacture are efficacy, safety and quality. Batch release is a crucial step in this assurance procedure. A qualified person (QP) is in charge of this stringently regulated process. Our article seeks to clarify the subtleties of batch release and QP certification in the European Union (EU), emphasizing the strict rules and processes involved.

***The method of batch release*[21]**

Verification of production and testing

This first stage carefully examines the production, packing and testing documentation for every batch. To verify adherence to Good Manufacturing Practice (GMP) and the particular specifications listed in the product's Marketing Authorization (MA) or Clinical Trial Authorization (CTA), batch records, analytical test results, certificates of analysis (CoA) and other pertinent documentation are carefully examined.

Qualified person certification

By confirming production and testing records, the QP certifies the batch of final products. This certification serves as an official statement that the batch satisfies all GMP criteria as well as those of its MA or CTA. An approved QP connected to the EU manufacturer is capable of doing QP certification. An importer listed in the MA or CTA may also undertake it.

The qualified person's) function

The relevance of the QP in the pharmaceutical sector is highlighted by the fact that its role is legally recognized in the EU. QPs are highly skilled professionals who usually have graduate degrees in biology, chemistry or pharmacy in addition to a wealth of GMP expertise. The certification and release can be approved by the QP if completed and all documentation is in order. The EU's "control authority batch release of vaccines and blood

products" document and its updates serve as the foundation for the QP's certification procedure. This exacting procedure guarantees that each batch satisfies the exacting quality standards prior to being on sale.

Table 1: Clinical trials and quality issues.[27,28]

Inspection type	Category	%
FDA inspections	Voluntary action indicated (VAI)	59
	No action indicated (NAI)	40
	Official action indicated (OAI	1
For cause inspections	Official action indicated	23
India site inspections	No action indicated	52
	Voluntary action indicated	48

Patient safety and regulatory compliance

The EU's commitment to patient safety is demonstrated by the strict standards for batch release and QP certification. The EU makes sure that only goods that fulfil the highest quality requirements are put on the market by requiring that every batch go through a rigorous verification and certification process by a competent and approved QP.

Data management and stability testing[23]

Concern for the health of the patient with the illness for which the product is intended is the main justification for stability testing. In addition to the unstable substance breaking down into hazardous breakdown products, a loss of activity up to 85% of what is stated on the label might cause the therapy to fail and cause death, as in the case of nitro-glycerine tablets used to treat angina and cardiac arrest. Due to this worry, it is now legally required to give regulatory bodies data for certain stability testing before a new product is approved.

Assuring that the product will remain suitable for use in terms of all functionally essential features throughout the duration that it is on the market is the second crucial issue in order to safeguard the manufacturer's reputation. Additional advantages of stability studies include: establishing a database that could be useful in choosing suitable formulations, excipients and container closure systems for the creation of a new product; figuring out shelf life and storage conditions for the creation of a new product; preparing a registration dossier; verifying the claimed shelf life for the registration dossier; and confirming that no modifications have been made to the formulation or manufacturing process that could negatively impact the stability.

Titles and codes utilized in the ICH Guidelines[24]

Q1A. Testing for stability of novel drug ingredients and products (second revision). Q1B. Stability testing:new drug substances and products' photostability testing. Q1C Testing the stability of novel dosage forms. Q1D designs for bracketing and matrixing drug substance and product stability testing. Q1E. Analysis of stability data. Q1F. Package of stability data for applications for registration in climatic zones III and IV. Q5C. Testing the stability of biological and biotechnological products.

CAPA procedures and deviation reports[25]

The components of the PDHP can be included into a quality risk management strategy. Training on these strategies should be provided to all trial participants, including the sponsor, CRO and site level, with frequent supervision to guarantee compliance. Either the investigator meeting or the site initiation monitoring visit might be used for the training. Measures to guarantee uniformity among systems that can document possible protocol violations should also be part of the strategy (e.g., clinical data management/electronic data capture (CDM/EDC) systems, clinical trial management systems (CTMSs) and monitoring reports).

The procedures outlined in the strategy should specify the roles of those participating in the clinical research who have the ability to spot a deviation. study coordinators, site monitors, data reviewers, biostatisticians, medical monitors and other staff members who examine the data or analysis of trial participants, for instance. Preventive actions and a CAPA initiative, Identifying and promptly reporting, monitoring, grouping, participating in the CSR, historical.

Regulatory compliance and quality control[26]

The Value of Quality Assurance at Different Phases of Pharmaceutical Research and Development From the first stages of research to commercialization, quality assurance (QA) is essential to guaranteeing the safety, effectiveness and consistency of pharmaceutical goods. Quality assurance (QA) is used in pharmaceutical research and development (R&D) to ensure adherence to regulatory requirements, reduce possible hazards, improve repeatability and preserve product integrity. This section examines the crucial role that quality assurance plays in the preclinical research, clinical trials, manufacturing and quality control phases of pharmaceutical R&D.

THE QUALITY CONCEPT IN CLINICAL TRIAL

The global ethical and scientific quality standard for carrying out clinical studies is called Good Clinical Practice (GCP). All facets of the clinical trial procedure are covered by the GCP standard. According to the GCP standards, quality is a continuum that starts with trial design, continues through trial conduct and documentation and is crucial throughout trial reporting. Therefore, more monitoring results and data inquiries would result from a protocol or case record form (CRF)

quality issue. Following the GCP quality standard throughout the clinical trial process ensures that the trial subjects' rights, integrity and confidentiality are upheld as well as that the data and findings provided are reliable and correct. The concepts of benefit and risk of a novel medical entity (NME) have been added to the GCP concept of quality. "The ability to effectively answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure, while assuring protection of human subjects" is how the Clinical Trials Transformation Initiative (CTTI) defines quality.[1,2] Despite the fact that clinical trial quality criteria have remained constant throughout time, the evolving nature of clinical trial conduct has made it harder to meet these standards.

During site inspections, some frequent flaws found include[29]

Study integrity may be jeopardized by protocol variations, inadequate documentation, inadequate subject protection, inappropriate adverse event reporting, lack of research product responsibility and noncompliance with the investigator agreement.

The sponsor and its team monitors play a significant role in the site performance. In FDA inspections, some of the common sponsor deficiencies

Research integrity and compliance may be compromised by inadequate monitoring, non-compliance by investigators, incomplete progress reports, failure to notify the FDA or IRB, insufficient responsibility for experimental products, missing investigator agreements, unapproved trials and unqualified monitors.[27]

Inadequate monitoring is another issue mentioned in the FDA warning letters. Among the conclusions

The regulatory bodies are being forced to think of new methods for evaluating the conduct of clinical trials due to their worries about quality problems in studies. The FDA is creating new methods for arranging risk-based inspection.[29]

The risk-based site selection tool from the centre for drug evaluation and research (CDER) IRB inspection mode for bioequivalence inspection CRO/sponsor monitoring Model of inspection The FDA intends to change the focus of its inspections from post-New Drug Approval (NDA) application to real-time clinical trial inspection and monitoring.

During the trial's duration, this would entail monitoring inspections of sponsors and clinical investigators. At the conclusion of phase 2, the FDA will also suggest evaluating the sponsor quality management strategy and sponsor quality systems. The FDA and EMA would share information on best practices and work together in simultaneous, sequential and collaborative inspections. The government also uses data as information to guide the planning, scope and prioritizing of inspections.[30]

Several significant clinical trials transformation initiatives[31]

Effective monitoring ensures quality, improves serious adverse event reporting, enhances ClinicalTrials.gov for data use, optimizes study start-up metrics and promotes central IRB use for multicentre trials. The CTTI has offered suggestions for incorporating quality into clinical trial conduct as well as scientific and operational design.[32]

Pay attention to important mistakes that impact data interpretation or patient safety. Create a quality management plan that focuses on high-risk regions and evaluates mistake rates in advance. To maintain trial integrity, use customized monitoring techniques, improve procedures and training and record quality problems, remedial measures and their effects on research analysis and interpretation.

Future directions for clinical trial manufacturing and TMF

As demonstrated in Figure 1, from 2024 to 2030, the global market for eTMF systems is projected to expand at a compound annual growth rate (CAGR) of 14.7%, from its estimated USD 728.9 million in 2023. The growing number of clinical studies and the expanding use of eTMF devices are responsible for the market's expansion. As of January 2024, there were 477,237 registered clinical studies worldwide, according to ClinicalTrials.gov. Additionally, expanding collaborations between biopharma firms and contract research organizations (CROs) support market expansion.[33]

CONCLUSION

To ensure regulatory compliance and uphold quality in clinical trial manufacturing, the TMF must be successfully moved to a centralized repository. An integrated and efficient documentation process begins with acknowledging the necessity of TMF migration in accordance with regulatory criteria. Thorough project planning is essential because it lays the groundwork for in-stream monitoring, which aids in the real-time identification and mitigation of possible problems.

To guarantee that the centralized TMF continuously satisfies strict regulatory requirements while facilitating effective clinical trial manufacturing operations, regular quality evaluations are crucial during the transfer process the integrity of clinical trials depends on this all-encompassing strategy's reduction of risks and encouragement of openness. Organizations can increase accountability and accuracy in recording trial activities by coordinating TMF migration with careful project

management and ongoing supervision. Additionally, this kind of integration strengthens manufacturing procedures, guaranteeing that all phases from paperwork to production follow strict quality requirements. In the end, this combination of meticulous quality control, real-time monitoring and strategic planning not only supports the close to successful TMF migration but also the general dependability and effectiveness of clinical trial manufacturing, establishing a new standard for upcoming research projects and regulatory filings.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sanap SL, Kale VV, Harane SA, Umekar MJ. Steps and requirements of preparing trial master file and clinical trial manufacturing documentation. Int J Clin Trials 2025;12(3):252-61.