Daily Documentation Essentials: A Tour of the Regulatory Binder

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Introduction

The road to market approval for orthopaedic devices can be long and arduous, but it is **impossible** without valid data. Regulations governing practices in clinical research demand the highest level of ethical and clinical standards, with patient protection as the highest priority. Historical precedents exist for each regulation, and each precedent comes with a story of violation or misuse of ethical obligation. While these regulations might seem overwhelming, it is important to understand that proper documentation of a clinical research trial is not just a means of organized filing for a multiplying mound of paperwork. It is a tangible trail that tells the story of the trial from conception to completion, reflecting adherence to applicable regulations and demonstrating trial integrity through transparency.

By perusing the Essential Documents, one can assess many elements of the administration of a clinical trial: the qualifications of the study staff, the accountability of the device under investigation and proper oversight controls, to name a few. The validity of data generated in a clinical trial is supported or defeated by these administrative elements. Consider this example: during a regulatory inspection, an auditor is unable to unearth any documentation indicating that the Investigator was ever trained on the deployment of an investigational artificial hip. What does that say about the data that the Investigator provided? Could the data be accepted as valid in the face of such an oversight?

The Code of Federal Regulations and International Conference on Harmonization's Good Clinical Practice (ICH GCP) can be frustratingly vague in defining the organization of Essential Documents needed to support the quality of a clinical investigation. This article will discuss the documents most essential in clinical research, and the regulatory basis for their maintenance.

A Tour of the Typical Regulatory Binder

There are many ways to organize the Essential Documents necessary for documentation of a clinical research trial. The most widely accepted path is through the use of a regulatory binder. This binder (also known as the investigator file, investigator binder or trial master file) is the place where all study-related regulatory documents are stored and maintained – and is not necessarily a binder at all! The purpose of a regulatory binder is to maintain consistent organization of documents required by regulations. When a complete and organized regulatory binder is kept current, it not only provides a tangible demonstration of documented regulatory compliance, it also facilitates the completion of other regulatory obligations, such as periodic monitoring visits and regulatory inspections.

While the Essential Documents maintained might vary from study to study depending on the documentation needed to demonstrate regulatory compliance, many documents are commonly present as required by the Code of Federal Regulations and ICH GCP. These documents are generated in one of three periods of the life cycle of a clinical trial: before the trial commences, during the active research phase of the trial and upon the trial's completion and close-out.

Documentation Before a Trial Commences

The Essential Documents generated during the planning phase of the trial should be finalized before any research takes place. These documents typically outline the procedures and expectations for conduct of the trial and are described in Table 1.

Essential Documents during Trial Conduct

The Essential Documents maintained during the active research phase of the clinical trial describe the day-to-day administration of protocol-defined activities, such as subject enrollment, device accountability and continuing IRB approval. These Essential Documents are comprised of many moving parts, and in order to properly understand the timeline of research activity, it is helpful to maintain these documents in real time. Table 2 summarizes these documents.

Essential Documents during Study Close-Out

The Essential Documents created at a study's termination summarize the study's efforts, outline study findings and describe the storage and archiving expectations of study-related documentation. In the U.S., the Code of Federal Regulations insists that all study documents be archived for a period of two years after study completion. Additional details regarding these documents can be found in Table 3.

Table 1: Essential Documents Before Trial Commences

Essential Document	Purpose	Who is responsible for maintenance?
Investigator's Brochure	Provides Investigator with scientific background regarding investigational product	Sponsor and Investigator
Signed Protocol and Amendments	Documents Sponsor and Investigator agreement to conduct study according to approved protocol	Sponsor and Investigator
Sample Case Report Forms	Documents expectation of data collection	Sponsor and Investigator
Informed Consent Form	Documents patient protection by means of proper informed consent	Sponsor and Investigator
Advertisements for Subject Recruitment (if used)	Documents ethical recruitment of subjects	Investigator
Financial Aspects of the Trial	Documents financial agreement between Sponsor and Investigator	Sponsor and Investigator
Insurance Certificate (if needed)	Documents that financial recompense will be available for subjects in event of study-related injury	Sponsor and Investigator
Signed Agreements	Documents agreements regarding expectation of study conduct	Sponsor and Investigator
Financial Disclosures	Documents Investigator bias caused by financial interests relating to trial	Sponsor and Investigator
IRB Approvals	Documents that trial has been assessed by an IRB and found to be in compliance with Federal and local regulations	Sponsor and Investigator
IRB Roster	Documents that IRB membership is balanced according to good clinical practice	Sponsor and Investigator
Regulatory Approval	Indicates that regulatory authorities provided approval for study prior to study commencement	Sponsor and Investigator
Evidence of Investigator Qualification (CVs, medical license, etc.)	Provides evidence that Investigator is adequately qualified by education and training	Sponsor and Investigator
Normal laboratory values	Documents what institution considers a normal laboratory value	Sponsor and Investigator
Laboratory certification	Indicates lab's qualifications to perform protocol-required tests	Sponsor and Investigator
Sample of label affixed to investigational product	Documents clarity of device labeling for subject use	Sponsor and Investigator
Instructions for use	Documents instructions for proper device storage, handling, packaging, deployment and disposition	Sponsor and Investigator
Decoding procedures (for blinded studies)	Documents process for unblinding a subject in case of emergent need	Sponsor and Investigator
Randomization list	Documents method of subject randomization	Sponsor and Investigator
Shipping records	Documents device accountability	Sponsor and Investigator
Certificate of analysis	Documents identity, purity, strength and soundness of an investigational device	Sponsor and Investigator
Site assessment documentation	Documents that site has been assessed and found to be qualified to conduct a clinical trial	Sponsor and Investigator
Site initiation documentation	Documents that a site study team has received proper training on trial protocol and device details	Sponsor and Investigator

Table 2: Essential Documents During Trial Conduct

Essential Document	Purpose	Who is responsible for maintenance?
Investigator's Brochure updates	Documents that Investigator was provided with current information regarding investigational device	Sponsor and Investigator
Revisions to: • Protocol • Informed Consent Form • Subject Recruitment advertisements	Documents Sponsor and Investigator agreement to conduct study according to currently approved protocol, patient protection by means of informed consent and ethical recruitment of subjects	Sponsor and Investigator
Continuing IRB Approvals	Documents that all changes and amendments to study have been assessed and approved by IRB	Sponsor and Investigator
Regulatory Approval of protocol amendments	Documents that all changes and amendments to study have received approval from appropriate regulatory authorities	Sponsor and Investigator
Documentation of qualifications of new Investigators	Provides evidence that investigators added after start of study are adequately qualified by education and training	Sponsor and Investigator
Updates to Normal Lab Values	Provides documentation for any lab values that have changed over the course of study	Sponsor and Investigator
Updates to Lab Certification	Provides documentation that a lab remained qualified to perform protocol-required testing through life cycle of study	Sponsor and Investigator
Device Log	Documents device accountability through life cycle of study	Sponsor and Investigator
Monitoring reports	Documents periodic site visits conducted and any identified findings and recommended corrective action	Sponsor
Relevant Sponsor communication: • Letters • Meeting notes • Notes of telephone calls	Documents any important study-related communications between site and Sponsor	Investigator
Signed Informed Consent Forms	Documents that consent has been obtained in compliance with regulations and good clinical practice	Investigator
Source Documents	Provides clinical evidence of existence of subject and validates data reported on case report forms	Investigator
Signed, dated and completed Case Report Forms (including corrections)	Provides confirmation of observations substantiated by source documents	Sponsor (original) and Investigator (copy)
Serious Adverse Events	Provides notification to Sponsor of Serious Adverse Events identified by Investigator; provides notification to regulatory authorities of Serious Adverse Events identified by Sponsor	Sponsor and Investigator
Interim Reports to IRB (per IRB SOPs)	Provides evidence of regular interim reporting from site to IRB	Sponsor and Investigator
Subject Identification Code List	Provides a means to identify a subject in case of emergent need	Investigator
Subject Screening Log	Documents all subjects screened for clinical trial	Investigator and Sponsor
Subject Enrollment Log	Documents chronological enrollment of subjects at site by study identification number	Investigator
Product Accountability Log	Documents usage of investigational product at research site	Investigator and Sponsor
Signature Log	Documents signatures and initials for study staff authorized to make entries and/or corrections to CRFs	Investigator and Sponsor
Record of Retained Body Fluids/Tissue Samples	Documents location and identification of fluids or tissue samples retained in the event assays need to be repeated	Investigator and Sponsor

Table 3: Essential Documents During Study Close-Out

Essential Document	Purpose	Who is responsible for maintenance?
Final Product Accountability	Documents final accounting of investigational product used at site	Investigator and Sponsor
Completed Subject Identification Code List	Documents identification of all enrolled subjects in case post-trial follow-up is needed	Investigator
Final Trial Close-out Monitoring Report	Documents all activities required for trial close-out have been completed	Sponsor
Final Report to IRB	Documents completion of trial to site's IRB	Investigator
Clinical Study Report	Documents results and analysis of trial	Investigator and Sponsor

Dos and Don'ts of Documentation

The regulations are deliberately vague in describing the process of documentation in clinical trials. Each study has unique moving parts, and a process that works well for one study might hinder progress of another. However, some common techniques can help Sponsors fulfill their regulatory documentation obligations.

- ***Know the regulations that affect your trial.*** Whether a piece of documentation is required by 21 CFR 812, 50, 54 or 56; ICH GCP; a state or local law or an institution's IRB – it is important to know and understand what the regulations say about the conduct of your clinical trial, and the obligations of key study personnel administering the study.
- ***Establish a system of document control and organization prior to study initiation.*** The regulations might not say that your Essential Documents need to be organized – but they do say they need to be complete and accurate. It is helpful to have a clear method of organization and control established with key study personnel from the very start: issues such as documentation storage and maintenance

responsibility throughout the study's life cycle should be defined before the first protocol is submitted for IND consideration. It's a good idea to update the regulatory documents continuously and file documents in chronological order.

- ***The Essential Documents should leave an audit trail that tells the story of the trial from conception to completion – the good, the bad and the ugly.*** It's better to have too much documentation than too little. Be sure to keep any IRB correspondence, Sponsor correspondence, training documents, meeting minutes, Notes-to-file offering clarification of practices, etc. If any protocol deviations occurred, document them by thoroughly describing the situation and any corrective action taken. Don't try to hide your mistakes!
- ***If it wasn't documented, it wasn't done!*** Can you imagine spending thousands of dollars on an elaborate wedding, and then forgetting to sign the marriage certificate? Don't do it in research, either! Take credit for work done, by means of properly maintained Essential Documents.
- ***Conservatively control access to study-related documentation.*** All Essential Documents should be stored in a locked cabinet or office. Only the study team, monitor and regulatory authorities should have access to study-related documentation.

Conclusion

The regulations governing the maintenance of Essential Documents hold all study administrators to the highest ethical standards in order to ensure that subject rights and protections are not violated. Essential Documents provide study Sponsors with an opportunity to tell the story of a trial from conception to completion, and to offer regulatory authorities a tangible trail to support the validity of the data generated by the study. However, incomplete or inaccurate Essential Documents can leave a smudge of doubt upon the study's integrity.

While the Essential Documents maintained might vary from study to study depending on the documentation needed to demonstrate regulatory compliance, many documents are commonly present as required by the Code of Federal Regulations and ICH GCP. It is important to know the types of documents typically maintained during the various phases of a trial's life cycle, and the regulatory purpose that these documents fulfill. Additionally, it is helpful to identify study-specific strategies that ensure compliance with regulatory documentation obligations.

Essential Documents are named such because that is exactly what they are: absolutely necessary to the conduct of a trial. But perhaps the most essential concept in understanding the regulatory obligation of Essential Documents is not a document at all, but a phrase that merits repeating: ***if it wasn't documented, it wasn't done!*** As clinical research professionals, proper documentation to support adherence to regulations serves to tell the story of that trial. Is the data accurate? Was there integrity to trial conduct? And ultimately, were patients protected? The road to market approval is long and difficult, but impossible without the validity provided by a well-maintained regulatory binder.

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Running a Clinical Trial: How to Navigate Through the Regulatory Maze
Wednesday, June 13, 1:30 pm - 3:00 pm

Whether you are a company owner, project manager, engineer or assistant, you may be called upon to run a clinical trial or be involved, in some way. Attendees will learn about the FAIR Shake™ concept which takes a complicated set of regulations and breaks it into four very simple questions to enable you to make educated decisions as you move through a trial.

The session begins with a "current climate" look at FDA, then moves to the "how to" of navigating through regulations, specifically targeting what that will mean to attendees who will return to research settings. This presentation will be highly interactive, using case studies with an orthopaedic focus.

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