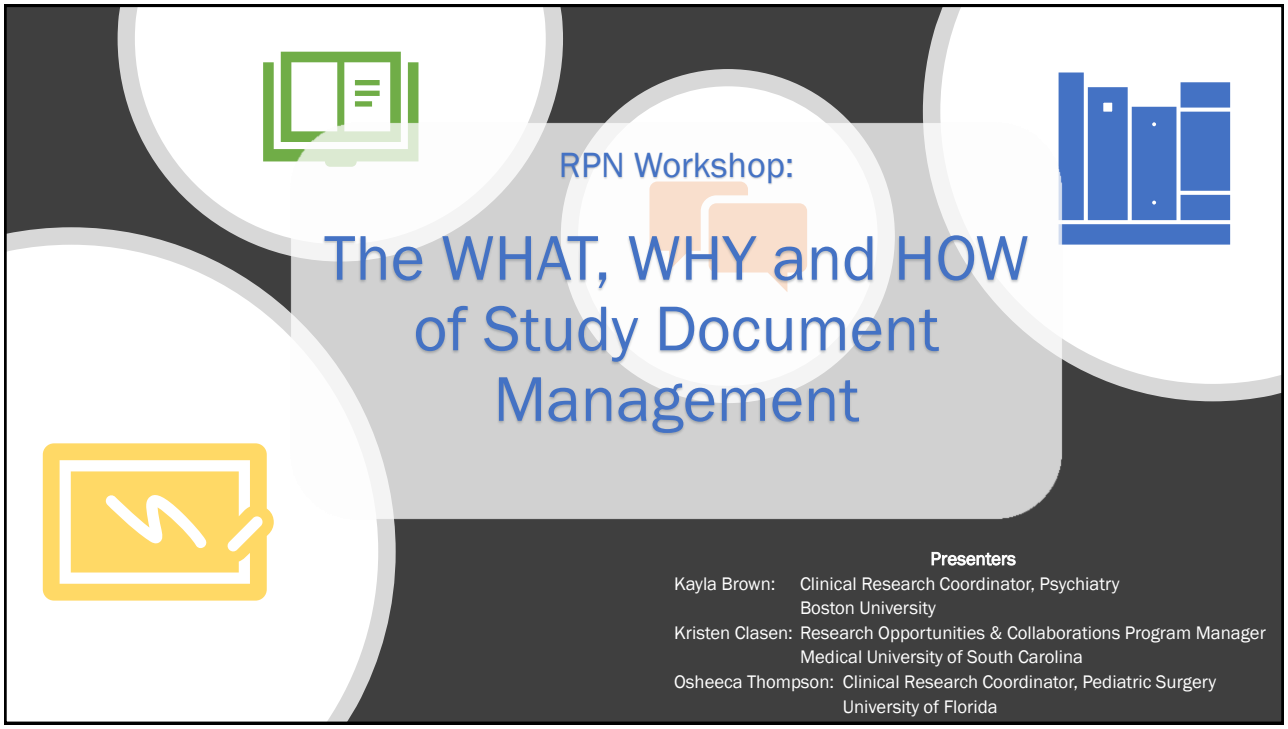


Learning Objectives

1. Understand what study document management encompasses and its importance; determine what documents are required and ways to keep them organized
2. Develop a framework for documentation strategies and create study-specific study documents
3. Collect and maintain study documentation to support data reliability and validity.

WHAT is Study Document Management?

Study Document Management may include:

- Document Creation, Collection, Completion
- Accessibility
- Maintenance
- Training
- Quality control
- Storage
- Archival & Retrieval

WHY is Study Document Management Important?

"If it is not documented, it did not happen"

'What is not documented is not done!'

- Evidence that the rights, safety and well-being of participants were protected
- Data integrity
- Compliance

"Quality documentation supports quality data and provides assurance that the data is reliable and valid to answer the study question."

"Document what is done as well as what is not done!"

Engagement Activity:
WHO is Involved in Study Document Management?

Join at

slido.com

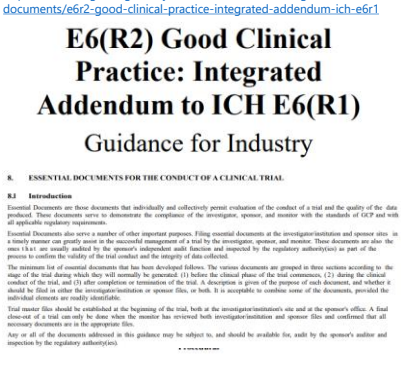
#3018 681

WHAT Documents are Important?

Essential Documents

- Demonstrate compliance with GCP and applicable regulatory requirements
- Support data reliability and validity

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1



E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

Guidance for Industry

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

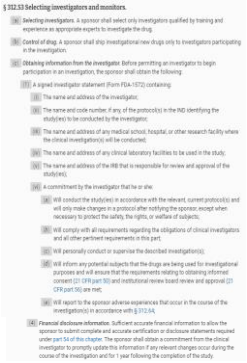
Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones ICH-GCP are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

PART 312 - INVESTIGATIONAL NEW DRUG APPLICATION
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312



§ 312.53 Selecting investigators and monitors.

(a) Selecting investigators. A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b) Control of drug. A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c) Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A signed investigator statement (Form FDA-1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:

(a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(b) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

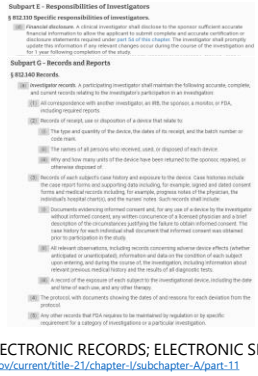
(c) Will personally conduct or supervise the described investigation(s);

(d) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(e) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64;

(2) Financial disclosure information. Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

PART 812 - INVESTIGATIONAL DEVICE EXEMPTIONS
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812



Subpart E - Responsibilities of Investigators

§ 812.110 Specific responsibilities of investigators.

(a) Financial disclosure. A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

Subpart G - Records and Reports

§ 812.140 Records.

(a) Investigator records. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

(1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports;

(2) Records of receipt, use or disposition of a device that relate to:

(i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark;

(ii) The names of all persons who received, used, or disposed of each device;

(iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of;

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

(i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study;

(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests;

(iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy;

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol;

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

PART 11 - ELECTRONIC RECORDS; ELECTRONIC SIGNATURES
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11

WHEN are Study Documents Collected?

ICH/GCP Guidance for Industry E6(R2)

Section 8: "Essential Documents for the Conduct of a Clinical Trial"

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.2.1	**INVESTIGATOR'S BROCHURE**			
8.2.2	**SIGNED PROTOCOL AND AMEND ANY, AND SAMPLE CASE REPORT (CRF)**			
8.2.3	**INFORMATION GIVEN TO TRIAL** – **INFORMED CONSENT FOR** all applicable translations)			
	– **ANY OTHER WRITTEN INF**			
	– **ADVERTISEMENT FOR SUE RECRUITMENT** (if used)			

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose
8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investig is informed in a timely ma of relevant information as becomes available
8.3.2	**ANY REVISION TO:** – Protocol/amendment(s) and CRF – Informed consent form – Any other written information provided to subjects – Advertisement for subject recruitment (if used)	To document revisions of t trial related documents tha take effect during trial
8.3.3	**DATED, DOCUMENTED APPROVAL/FAVORABLE OPINION OF INSTITUTIONAL REVIEW BOARD IRB)/INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** • Protocol amendment(s) • Revision(s) of: — Informed consent form — Any other written information to be provided to the subject — Advertisement for subject recruitment (if used) • Any other documents given approval/favorable opinion • Continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subje IRB/IEC review and were given approval/favorable opinion. To identify the version number and date o document(s).

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the follow

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X

HOW are Study Documents Organized?

Investigator Binder / Regulatory Binder / Study Binder / Investigator Site File (ISF) / Trial Master File (TMF)

- Study-specific, Site-specific, Participant, Financial
- Current vs Obsolete
- Paper, electronic, hybrid

Essential Document Categories

"Study-Specific" Documents

PROTOCOL AND AMENDMENT DOCUMENTS
- ☐ IRB-approved Protocol
  - ☐ Protocol Signature Page, signed by PI
- ☐ IRB-approved Protocol Amendments
- ☐ Protocol Changes Log
- ☐ IRB-approved Sample Case Report Forms (CRF)
- ☐ Protocol Deviation Forms or Memo
- ☐ Confidentiality Certificates

INFORMED CONSENT DOCUMENTS
- ☐ Log of Informed Consent versions
- ☐ IRB-approved Informed Consent Documents
- ☐ IRB-approved Informed Consent Documents
- ☐ Consent Process Summary Forms

ADVERTISEMENTS / RECRUITMENT MATERIALS
- ☐ IRB-approved Ads / Recruitment Materials

OTHER PATIENT-FACING DOCUMENTS
- ☐ IRB-approved Participant Information Sheets
- ☐ Other IRB-approved Documents

IRB APPROVAL, CORRESPONDENCE & DOCUMENTS
- ☐ IRB letters of approval / acknowledgements
- ☐ External IRB reliance
- ☐ IRB submission/application (original)
- ☐ IRB correspondence
- ☐ IRB annual renewal(s)
- ☐ IRB progress reports
- ☐ IRB final report/close-out
- ☐ IRB Federal Assurance Number
- ☐ IRB Roster, updated
- ☐ IRB Registration

FDA DOCUMENTS
- ☐ FDA Forms 1571 and 1572
- ☐ Regulatory Approval/Authorization
- ☐ FDA Correspondence

OPERATIONS / PROCEDURE DOCUMENTS
- ☐ Manual of Operations / Procedures
- ☐ Data Collection Guidelines
- ☐ Randomization Procedures
- ☐ Unblinding Procedures
- ☐ Departmental/Institutional SOPs
- ☐ Other guidelines/manuals

BIOSPECIMEN / IMAGING DOCUMENTS
- ☐ Collection, Process & Shipping Guidelines
- ☐ Specimen Tracking Log
- ☐ Specimen Collection Deviation Log
- ☐ Shipment Documentation

INVESTIGATIONAL PRODUCT / DEVICE DOCUMENTS
- ☐ Investigator brochure / Package Insert
- ☐ Approved labeling
- ☐ IP/Device Instructions Manual
- ☐ IP/Device Accountability Logs
- ☐ IP Destruction / Device Return Documentation

DATA & SAFETY MONITORING DOCUMENTS
- ☐ Adverse Event Report Forms
- ☐ Serious Adverse Event Report Forms
- ☐ Investigational New Drug Safety Reports
- ☐ Unanticipated Problems Forms
- ☐ Data and Safety Monitoring Plan
- ☐ Independent Safety Monitor Reports
- ☐ Independent Safety Monitor Meeting Minutes
- ☐ Independent Safety Monitor Correspondence

MONITORING / AUDIT DOCUMENTS
- ☐ Site Monitor Initiation Visit Report
- ☐ Site Monitor Correspondence
- ☐ Audit Notification
- ☐ Audit Reports
- ☐ Audit Correspondence

COMMUNICATION DOCUMENTS
- ☐ Sponsor
- ☐ Other

STUDY CLOSE-OUT DOCUMENTS
- ☐ Sponsor Notification
- ☐ Clinical Study Report
- ☐ Final (completed) documents:
  - ☐ IP/Device Accountability Logs
  - ☐ IP Destruction / Device Return Documentation
  - ☐ Subject Identification Code List

Essential Document Categories

"Site-Specific" Documents

DELEGATION OF AUTHORITY / SIGNATURE LOGS
- ☐ Delegation of Authority & Site Signature Log

PROTOCOL & STUDY RELATED TRAINING DOCUMENTS
- ☐ Protocol Training Logs
- ☐ Protocol Training Materials
- ☐ Biospecimen / Imaging Training Logs
- ☐ Biospecimen / Imaging Training Materials
- ☐ IP / Device Training Logs
- ☐ IP / Device Training Materials
- ☐ EDC / Randomization Training Logs
- ☐ EDC / Randomization Training Materials

CONFLICT OF INTEREST/FINANCIAL DISCLOURE FORMS
- ☐ Financial Disclosure Forms, signed
- ☐ Conflict of Interest Reporting Documentation

INVESTIGATOR/PERSONNEL QUALIFICATIONS DOCUMENTS
- ☐ Investigators
  - ☐ Medical/Dental/Professional Licenses
  - ☐ GCP Training Certificates
  - ☐ HSP Training Certificates
- ☐ Staff
  - ☐ Professional Licenses
  - ☐ GCP Training Certificates
  - ☐ HSP Training Certificates
  - ☐ IATA Training Certificates

LABORATORY CERTIFICATION
- ☐ Normal-range Values for each Reference Lab
- ☐ Certification or Accreditation documentation

CONTRACTS & FINANCIAL DOCUMENTS*
- ☐ Contract Agreement, fully executed
- ☐ Budget Negotiations/Agreements
- ☐ Letter of Understanding/ Confidentiality Agreement
- ☐ Insurance/Indemnification Statement
- ☐ Data Sharing Agreement(s) (DSAs)
- ☐ Material Transfer Agreement
- ☐ Notes relevant to study
- ☐ Any other signed agreements

*Stored in a separate location away from other essential documents

Essential Document Categories

"Participant" Documents

CONSENT DOCUMENTS

- ☐ Informed Consent Documents, signed
- ☐ HIPAA Authorization Forms, signed
- ☐ Consent Process Summary Documents

SOURCE DOCUMENTS

- ☐ Eligibility Checklist / Supporting Source Documents
- ☐ Case Report Forms / Supporting Source Documents
- ☐ Other Source Documents

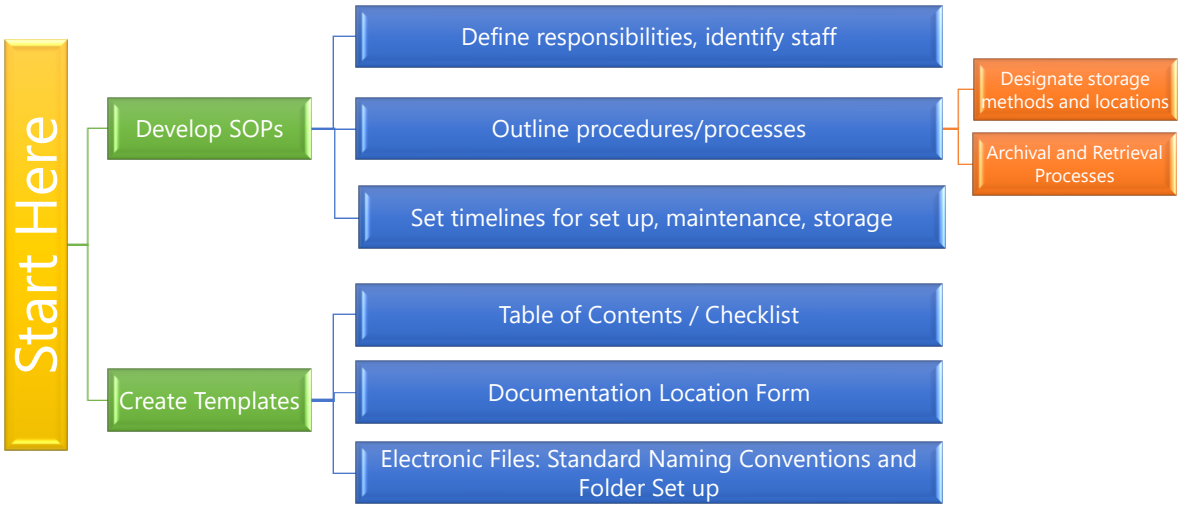
SCREENING AND ENROLLMENT DOCUMENTS

- ☐ Screening Logs
- ☐ Enrollment Logs

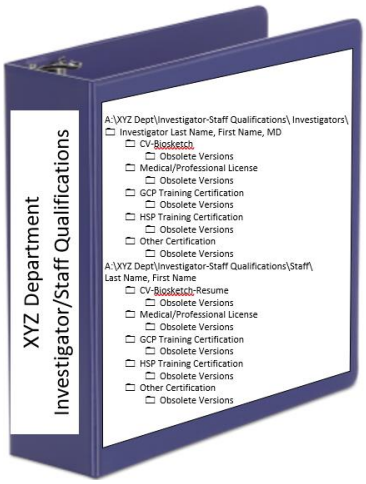
SUBJECT IDENTIFICATION CODE LISTS*

*Stored in a separate, secure location away from other essential documents

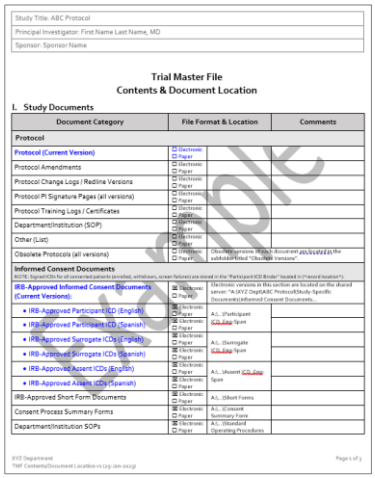
Organization Strategies: First Things First



Organization Tips



- Be AUDIT Ready!
- Store documents in a secure location
- Make appropriate documents accessible to appropriate study personnel
- File in reverse chronological order
- Review documentation routinely
- Resolve discrepancies upon discovery
- Avoid duplication
- Update in real-time


Study Title: ABC Protocol
Principal Investigator: First Name Last Name, MD
Sponsor: Sponsor Name

Trial Master File
Contents & Document Location

I. Study Documents

Document Category	File Format & Location	Comments
Protocol		
Protocol (Current Version)	☐ Electronic ☐ Paper	
Protocol Amendments	☐ Electronic ☐ Paper	
Protocol Change Logs / Redline Versions	☐ Electronic ☐ Paper	
Protocol PI Signature Pages (all versions)	☐ Electronic ☐ Paper	
Protocol Training Logs / Certificates	☐ Electronic ☐ Paper	
Department/Institution (SOP)	☐ Electronic ☐ Paper	
Other (List)	☐ Electronic ☐ Paper	
Obsolete Protocols (all versions)	☐ Electronic ☐ Paper	Obsolete versions of each document are located in the subfolder titled "Obsolete Versions".
Informed Consent Documents		
IRB-Approved Informed Consent Documents (Current Versions):	☒ Electronic ☐ Paper	Electronic versions in this section are located on the shared server: "A:\XYZ Dept\ABC Protocol\Study-Specific Documents\Informed Consent Documents...
• IRB-Approved Participant ICD (English)	☒ Electronic ☐ Paper	A:\...\Participant ICD.docx Spain
• IRB-Approved Participant ICD (Spanish)	☒ Electronic ☐ Paper	
• IRB-Approved Surrogate ICDs (English)	☒ Electronic ☐ Paper	A:\...\Surrogate ICD.docx Spain
• IRB-Approved Surrogate ICDs (Spanish)	☒ Electronic ☐ Paper	
• IRB-Approved Assent ICDs (English)	☒ Electronic ☐ Paper	A:\...\Assent ICD.docx Spain
• IRB-Approved Assent ICDs (Spanish)	☒ Electronic ☐ Paper	
IRB-Approved Short Form Documents	☒ Electronic ☐ Paper	A:\...\Short Forms
Consent Process Summary Forms	☒ Electronic ☐ Paper	A:\...\Consent Summary Form
Department/Institution SOPs	☒ Electronic ☐ Paper	A:\...\Standard Operating Procedures

Sample

XYZ Department
TMF Contents/Document Location vs (yy-mm-xxx)

Page x of y

Engagement Activity

There's no single "right" way to organize study documents.

What has worked for you and why?

What has not worked and why?

Study Guidelines and Documentation Creation

Guidelines

Why are guidelines important?

They provide a framework for how things are expected to be completed. They also establish structure and uniformity when completing study procedures

Types of Guidelines

- Manual of Procedures, Manual of Operations (MOPs)
- Standard Operating Procedures (SOPs)
- Checklists
- Workflows

Manual of Procedures, Manual of Operations (MOPs)

Standard Operating Procedure (SOPs)

Details study procedures and operations, facilitate consistency in protocol implementation and data collection across study participants and sites

Includes

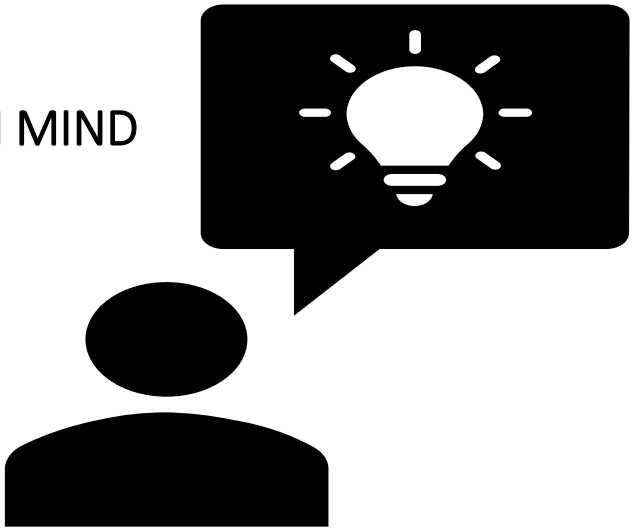
- Purpose
- Scope
- Step by step procedure
- Tasks and goals
- Roles and Responsibilities

U.S. Dept. of Health & Human Services Clinical Research Study Investigator's Toolbox
Guidance Portal

Let's Talk About It

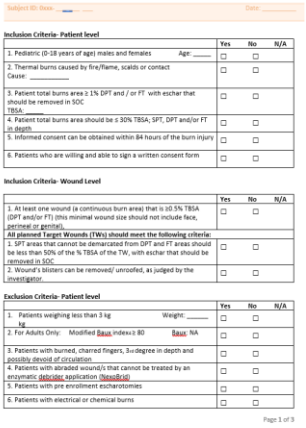
❑What kind of guidelines do you utilize?

KEEP IN MIND



Your checklist can be considered source documentation

Source Documentation



Subject ID: Dxxx-___-____ Date: _____

Inclusion Criteria- Patient level

	Yes	No	N/A
1. Pediatric (0-18 years of age) males and females Age: _____	☐	☐	
2. Thermal burns caused by fire/flame, scalds or contact Cause: _____	☐	☐	
3. Patient total burns area ≥ 1% DPT and / or FT with eschar that should be removed in SOC TBSA: _____	☐	☐	
4. Patient total burns area should be ≤ 30% TBSA; SPT, DPT and/or FT in depth	☐	☐	
5. Informed consent can be obtained within 84 hours of the burn injury	☐	☐	
6. Patients who are willing and able to sign a written consent form	☐	☐	

Inclusion Criteria- Wound Level

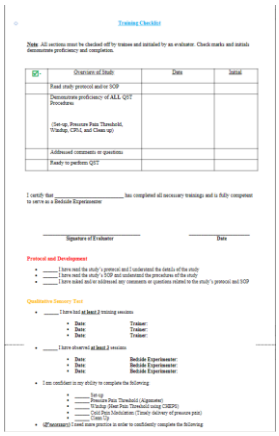
	Yes	No	N/A
1. At least one wound (a continuous burn area) that is ≥0.5% TBSA (DPT and/or FT) (this minimal wound size should not include face, perineal or genital).	☐	☐	
All planned Target Wounds (TWs) should meet the following criteria:			
1. SPT areas that cannot be demarcated from DPT and FT areas should be less than 50% of the % TBSA of the TW, with eschar that should be removed in SOC	☐	☐	
2. Wound's blisters can be removed/ unroofed, as judged by the investigator	☐	☐	

Exclusion Criteria- Patient level

	Yes	No	N/A
1. Patients weighing less than 3 kg Weight: _____ kg	☐	☐	
2. For Adults Only: Modified Baux index ≥ 80 Baux: NA	☐	☐	
3. Patients with burned, charred fingers, 3rd-degree in depth and possibly devoid of circulation	☐	☐	
4. Patients with abraded wound/s that cannot be treated by an enzymatic debridet application (NexoBrid)	☐	☐	
5. Patients with pre enrollment escharotomies	☐	☐	
6. Patients with electrical or chemical burns	☐	☐	

Page 1 of 3

Not Source Documentation



Training Checklist

Note: All sections must be checked off by trainee and initialed by an evaluator. Check marks and initials demonstrate proficiency and completion.

☑	Overview of Study	Date	Initial
	Read study protocol and/or SOP		
	Demonstrate proficiency of ALL QST Procedures: (Set-up, Pressure Pain Threshold, Wind-up, CPM, and Clean-up)		
	Addressed comments or questions		
	Ready to perform QST		

I certify that _____ has completed all necessary trainings and is fully competent to serve as a Bedside Experimenter

_____ _____
Signature of Evaluator Date

Protocol and Development

- _____ I have read the study's protocol and I understand the details of the study
- _____ I have read the study's SOP and understand the procedures of the study
- _____ I have asked and/or addressed any comments or questions related to the study's protocol and SOP

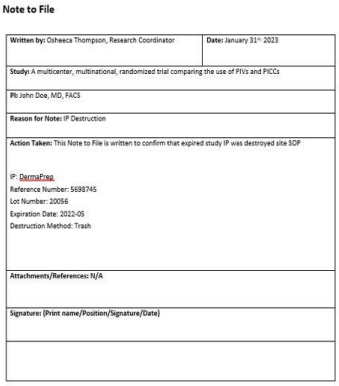
Qualitative Sensory Test

- _____ I have led at least 2 training sessions
  - Date: Trainee:
  - Date: Trainee:
  - Date: Trainee:
- _____ I have observed at least 2 sessions
  - Date: Bedside Experimenter:
  - Date: Bedside Experimenter:
  - Date: Bedside Experimenter:
- I am confident in my ability to complete the following:
  - _____ Set-up
  - _____ Pressure Pain Threshold (Algometer)
  - _____ Windup (Wind Pain Threshold using CHEPS)
  - _____ Cool Pain Modulation (Timely delivery of pressure pain)
  - _____ Clean-up
- (If necessary) I need more practice in order to confidently complete the following:

Note to File (as known as Memo to File)

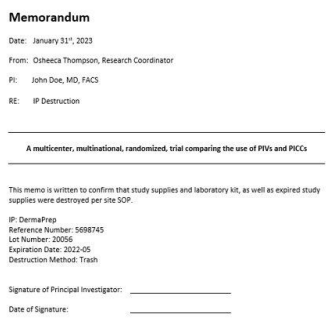
- An NTF is used to document discrepancies, errors, clarify, etc. NTFs can also be used to clarify or formally address documents

- ❑IRB Number, Protocol Title, Study Name
- ❑Person completing NTF
- ❑Date
- ❑Principal Investigator
- ❑Logo and Watermark
- ❑Subject
- ❑NTF narrative
- ❑ Signature & date



Note to File

Written by: Osheeca Thompson, Research Coordinator	**Date:** January 31th 2023
Study: A multicenter, multinational, randomized trial comparing the use of PIVs and PICCs	
PI: John Doe, MD, FACS	
Reason for Note: IP Destruction	
Action Taken: This Note to File is written to confirm that expired study IP was destroyed site SOP IP: DermaPrep Reference Number: 5698745 Lot Number: 20056 Expiration Date: 2022-05 Destruction Method: Trash	
Attachments/References: N/A	
Signature: (Print name/Position/Signature/Date)	



Memorandum

Date: January 31st, 2023

From: Osheeca Thompson, Research Coordinator

PI: John Doe, MD, FACS

RE: IP Destruction

A multicenter, multinational, randomized, trial comparing the use of PIVs and PICCs

This memo is written to confirm that study supplies and laboratory kit, as well as expired study supplies were destroyed per site SOP.

IP: DermaPrep
Reference Number: 5698745
Lot Number: 20056
Expiration Date: 2022-05
Destruction Method: Trash

Signature of Principal Investigator: _____

Date of Signature: _____

Note to File (as known as Memo to File)

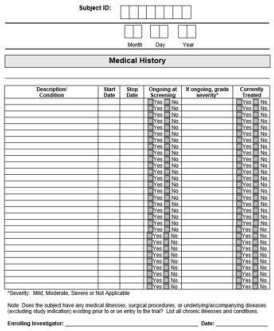
- **<u>Narrative Content</u>**
- In the narrative section, describe the specific event or information that necessitated the NTF. Include a clear chronology of:
  - what happened
  - when it happened
  - who was involved
- When describing an event occurring in the past (which is often the case in Notes-to-File) include:
  - when the issue/event was discovered and
  - what is triggering the completion of the note-to-file at this time.
- If applicable, include:
  - actions taken in response to the issue or event (either at the time and/or now)
  - how the event happened
  - what action is being taken to prevent re-occurrence of the same type of event in the future.

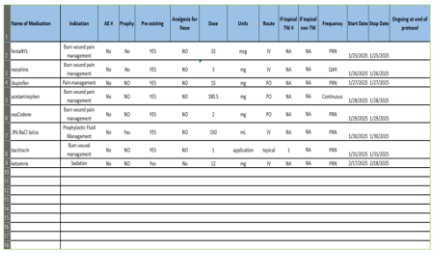
Training

- Training documentation provides proof of proficiency and understanding of research related procedures.
- Training can either be general research training such as:
  - GCP
  - HSP
  - IATA
  - BBP
- Or Protocol Specific training
  - Sponsors and Coordinating sites usually specify how they want training documented (i.e. Training log)
- Training documentation should be filed in the Regulatory Binder and/ or electronically
- Study specific training should be updated with each protocol amendment

Case Report Forms (CRFs)

- CRFs:
  - Based on protocol; tool to collect and record the data generated by study procedures in a consistent way to be analyzed
  - Is most cases provided by the sponsor or coordinating site
  - Can be paper documents or electronic files
  - Drafted after the protocol has been finalized
  - liable to change, as the protocol changes
    - Make sure you have a system for version control
- Types of CRFs include
  - Demographics
  - Medical History
  - Screening Form
  - Weekly Follow Up
  - Concomitant Medication

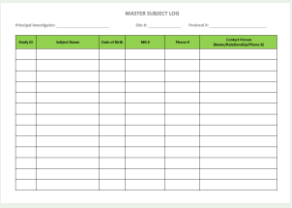




Case Report Forms

- Consistent Format
- Data Elements/ Question are simplified, precise
- Defined terms and units
- Datas points are related
- User friendly
- Avoid redundant data points

PRE 1ST APPLICATION – VITAL SIGNS Within 24h prior to 1st application	
Were vital signs taken?	☐ YES* ☐ NO **If YES, please fill the date and time:* _____/_____/_____ ____:____ *(DD/MMM/YYYY)* *(hh : mm) (24 hr clock)* *If Not Done, please specify:*_____ **If vital signs results are not recorded here, indicate location of source document:** _____
Blood Pressure: ___ __/ __ _ __ *Systolic/ Diastolic (mmHg)* ☐ Not Obtained **Systolic BP Results Assessment:** ☐ All Normal ☐ Abnormal NCS ☐ Abnormal CS **Diastolic BP Results Assessment:** ☐ All Normal ☐ Abnormal NCS ☐ Abnormal CS	**Temperature:** ___ ___. ___ ___ ☐°C ☐°F ☐ Not Obtained *Please check the appropriate box below:* ☐ Oral ☐ Rectal ☐Tympanic ☐ Bladder ☐Other: _____ **Temperature Results Assessment:** ☐ All Normal ☐ Abnormal NCS ☐ Abnormal CS
Heart Rate: ___ ___ __ *(beats/ min)* ☐ Not Obtained	**Heart Rate Results Assessment:** ☐ All Normal ☐ Abnormal NCS ☐ Abnormal CS
Investigator Signature: _____ Date: _____/_____/_____ Please ensure that any clinically significant vital signs are reported as an Adverse Event	

(Pre)Screening Log	Enrollment Log	Master List
• A list of individuals who have been pre-screened that includes eligibility status based on the inclusion/exclusion criteria. • Screening cannot happen until participant has signed the informed consent. It is a more in depth look at the patient's medical history.	A list of participants who meet eligibility criteria based on pre-screening, have signed the informed consent and attended a screening visit. This log should not contain PHI.	A list that links the names of the participants on the enrollment log to their subject ID. This is not shared nor transmitted outside of your institution; it contains PHI. This document should be kept in a secure location (locked filing cabinet), encrypted, or password protected
		

Engagement Activity

- Identify what is what wrong with the CRF. How would you improve it?

Subject ID **Date:** ____/____/_____

Demographics

Birthdate: ☐☐/☐☐/☐☐☐☐

Age:

Gender: (circle one)
1. Male
2. Female
3. Unknown or Not Reported

Ethnicity: (check one)
☐ Hispanic
☐ Non-Hispanic
☐ Unknown or Not Reported

Race: (check all that apply)
☐ American Indian or Alaska Native
☐ Asian
☐ Black or African American
☐ Native Hawaiian or Other Pacific Islander
☐ White or Caucasian
☐ Unknown or Not Reported

Height: _____cm **Weight**_____lb **BMI:** ___ ___

Temperature: ___ ___ ___ **Blood Pressure:** ___ ___ ___/___ ___ ___

HR: ___ ___ ___beats/min

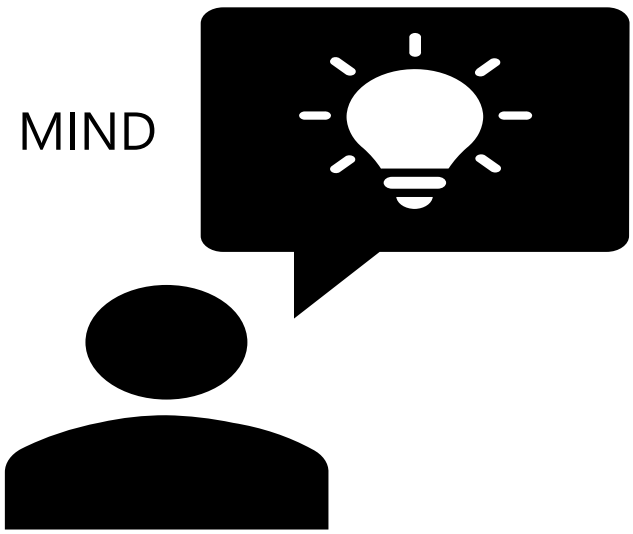
For Females of child bearing potential
Urine Pregnancy Test

Date of Test: ____/____/_____

☐ Positive
☐ Negative
☐ Not done

Form Completed By: _____**Date:** _____

KEEP IN MIND



- If it was not documented, IT WAS NOT DONE!!!!!

Collecting and Maintaining Study Documentation to Support Data Reliability and Validity

Data Integrity

Refers to the completeness, consistency and accuracy of data

Can we rely on the data to answer the research question?

Essential Documents: "Individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced." (ICH GCP 8.1)

Two Types of Essential Documents

1. **Participant Files**: data collected from individual subjects
   - Informed Consent Forms (ICFs)
   - Case Report Forms (CRFs)
   - Surveys
   - Lab reports
   - Medical records
   - Subject Eligibility Checklist

2. **Regulatory Files**: other documents that substantiate conduct of study
   - CVs
   - Licenses
   - Delegation of Authority Log
   - Training Log
   - Pre-screening Log
   - Enrollment Log
   - Subject Withdrawal Log
   - Data Change Log

Source Data

Information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for reconstruction and evaluation of the study conduct (ICH GCP 1.51)

- Contained in source documents (paper or electronic)
- May exist independent of research
- Generated specifically for research purposes

Source Documents

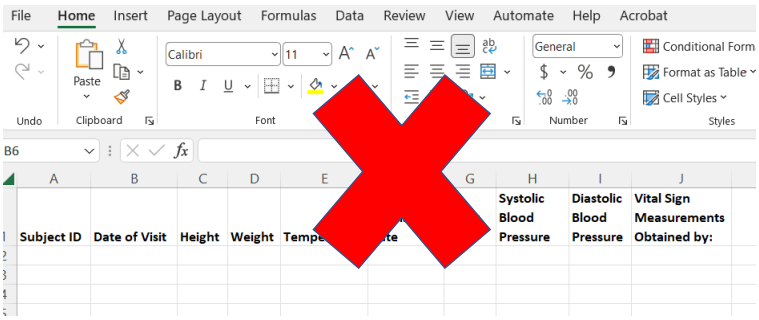
Original record where the source data is first documented

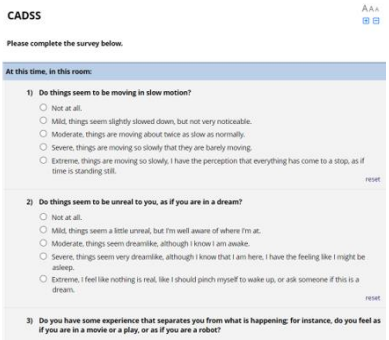
- ICFs
- CRFs
- Medical records
- Lab reports
- Data provided by subjects via questionnaires or surveys
- Study progress notes
- Assessments of AEs
- Checklists that are the first record of data or for eligibility assessment
- Note to file

Audit Trail

Allows for reconstruction of course of events relating to the creation, modification or deletion of original records

- Hardcopy OK if there is appropriate documentation
- If electronic, system must have capability for audit trail



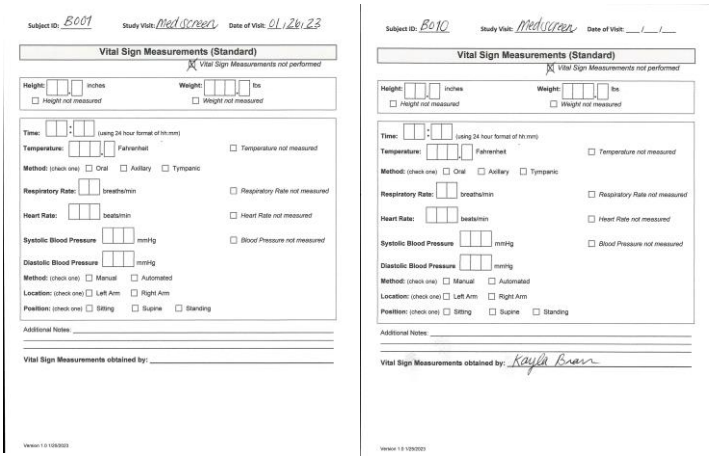


ALCOA-C Documentation Standards

- Attributable
- Legible
- Contemporaneously recorded
- Original copy
- Accurate
- Complete

Attributable

- Linked to person who observed and recorded data or made determination and when
  - Signed or initialed
  - Dated on date of entry
  - Time (if relevant)
- Data Changes
  - Who?
  - When?
  - Why?



Subject ID: B001 Study Visit: Med Screen Date of Visit: 01/26/23

Vital Sign Measurements (Standard)

☒ Vital Sign Measurements not performed

Height: ☐☐.☐ inches ☐ Height not measured

Weight: ☐☐☐.☐ lbs ☐ Weight not measured

Time: ☐☐:☐☐ (using 24 hour format of hh:mm)

Temperature: ☐☐☐.☐ Fahrenheit ☐ Temperature not measured

Method: (check one) ☐ Oral ☐ Axillary ☐ Tympanic

Respiratory Rate: ☐☐ breaths/min ☐ Respiratory Rate not measured

Heart Rate: ☐☐☐ beats/min ☐ Heart Rate not measured

Systolic Blood Pressure ☐☐☐ mmHg ☐ Blood Pressure not measured

Diastolic Blood Pressure ☐☐☐ mmHg

Method: (check one) ☐ Manual ☐ Automated

Location: (check one) ☐ Left Arm ☐ Right Arm

Position: (check one) ☐ Sitting ☐ Supine ☐ Standing

Additional Notes: _____

Vital Sign Measurements obtained by: _____

Version 1.0 1/25/2023

Subject ID: B010 Study Visit: Med Screen Date of Visit: ___/___/___

Vital Sign Measurements (Standard)

☒ Vital Sign Measurements not performed

Height: ☐☐.☐ inches ☐ Height not measured

Weight: ☐☐☐.☐ lbs ☐ Weight not measured

Time: ☐☐:☐☐ (using 24 hour format of hh:mm)

Temperature: ☐☐☐.☐ Fahrenheit ☐ Temperature not measured

Method: (check one) ☐ Oral ☐ Axillary ☐ Tympanic

Respiratory Rate: ☐☐ breaths/min ☐ Respiratory Rate not measured

Heart Rate: ☐☐☐ beats/min ☐ Heart Rate not measured

Systolic Blood Pressure ☐☐☐ mmHg ☐ Blood Pressure not measured

Diastolic Blood Pressure ☐☐☐ mmHg

Method: (check one) ☐ Manual ☐ Automated

Location: (check one) ☐ Left Arm ☐ Right Arm

Position: (check one) ☐ Sitting ☐ Supine ☐ Standing

Additional Notes: _____

Vital Sign Measurements obtained by: Kayla Brown

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FDA Part 11 Electronic Signatures

Must include:

- Printed name of signer
- Date and time when signature executed
- Meaning (review, approval, responsibility, authorship) associated with signature
- Linked to respective source document
- Safeguards to confirm identity of signer
- Safeguards to prevent alteration of electronic signature

Kayla Brown

Digitally signed by Kayla Brown
Date: 2022.07.29 11:00:22 -04'00'

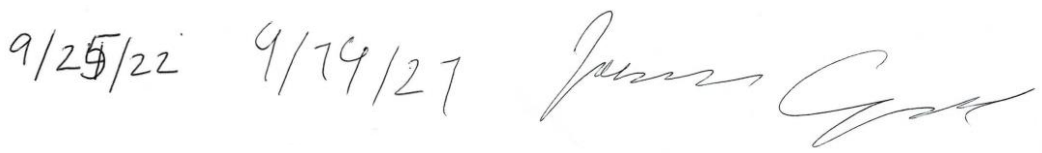
DocuSigned by:
KB
Signer Name: Kayla Brown
Signing Reason: I approve this document
Signing Time: 1/25/2023 | 7:36:48 PM EST
0DF6BEFBA4F0451A895BE2E438AE9AEF

DocuSigned by:
Kayla Brown
Signature of subject
Signer Name: Kayla Brown
Signing Reason: I approve this document
Signing Time: 1/25/2023 | 7:53:57 PM EST
0DF6BEFBA4F0451A895BE2E438AE9AEF

Use-of-Electronic-Records-and-Electronic-Signatures-in-Clinical-Investigations-Under-21-CFR-Part-11.pdf

Legible

- Capable of being easily read
- Recorded in a permanent medium→ not pencil
- Changes do not obscure original entry

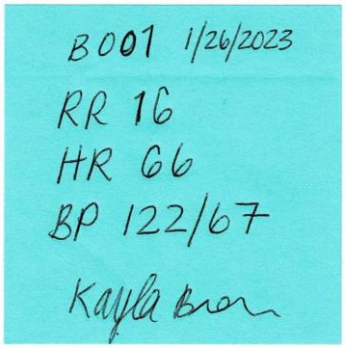


Contemporaneous

- Data, signature and date should be recorded at time of observation or measurement or as close as possible
- Data should not be back dated
- Delayed data documentation with respect to time of observation → risk individual recalls information wrong→ poor data quality

Original

- First and most accurate recording of the data
- Data should be recorded directly onto paper or into electronic medium

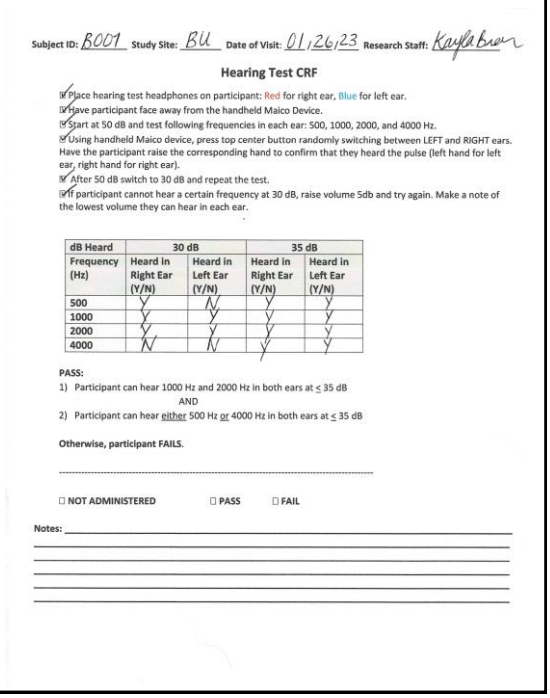


Accurate

- Free from errors, consistent, truthful, and reflective of the observation
- Give full account of the research process
- Conform to a standard (i.e. protocol)
- Errors have been identified and corrected with explanations (if necessary)

Complete

- Study documentation must be complete
- Properly recorded



Subject ID: B001 Study Site: BU Date of Visit: 01/26/23 Research Staff: Kayla Brown

Hearing Test CRF

- ☑ Place hearing test headphones on participant: Red for right ear, Blue for left ear.
- ☑ Have participant face away from the handheld Maico Device.
- ☑ Start at 50 dB and test following frequencies in each ear: 500, 1000, 2000, and 4000 Hz.
- ☑ Using handheld Maico device, press top center button randomly switching between LEFT and RIGHT ears. Have the participant raise the corresponding hand to confirm that they heard the pulse (left hand for left ear, right hand for right ear).
- ☑ After 50 dB switch to 30 dB and repeat the test.
- ☑ If participant cannot hear a certain frequency at 30 dB, raise volume 5db and try again. Make a note of the lowest volume they can hear in each ear.

dB Heard	30 dB		35 dB	
Frequency (Hz)	Heard in Right Ear (Y/N)	Heard in Left Ear (Y/N)	Heard in Right Ear (Y/N)	Heard in Left Ear (Y/N)
500	Y	N	Y	Y
1000	Y	Y	Y	Y
2000	Y	Y	Y	Y
4000	N	N	Y	Y

PASS:

1) Participant can hear 1000 Hz and 2000 Hz in both ears at ≤ 35 dB

AND

2) Participant can hear either 500 Hz or 4000 Hz in both ears at ≤ 35 dB

Otherwise, participant FAILS.

☐ NOT ADMINISTERED ☐ PASS ☐ FAIL

Notes: _____

Data Corrections to Study Documents

Proper Corrections:

- One line through error
- Write new data, initial, date and explain (if necessary)
- Changes to data entries are made by study team members delegated by PI

Unacceptable Corrections:

- New information obscures previous information
- Scribble cross-out, white out, writing over
- Changing participant's personal writings or survey responses

Data Quality Assurance

Implementation of procedures to ensure quality of data

- Source data verification
  - Ensure accuracy of data entry into electronic data capture (EDC) system
- Data quality rules in EDC system
  - Identify data entry mistakes, outliers
- Quality Assurance Visits
  - Ensure source documents adhere to ALCOA-C standards

Data Integrity Issues

- FDA Drug Approval Delays
- Death
- Chronic Illness
- Injury/Disability

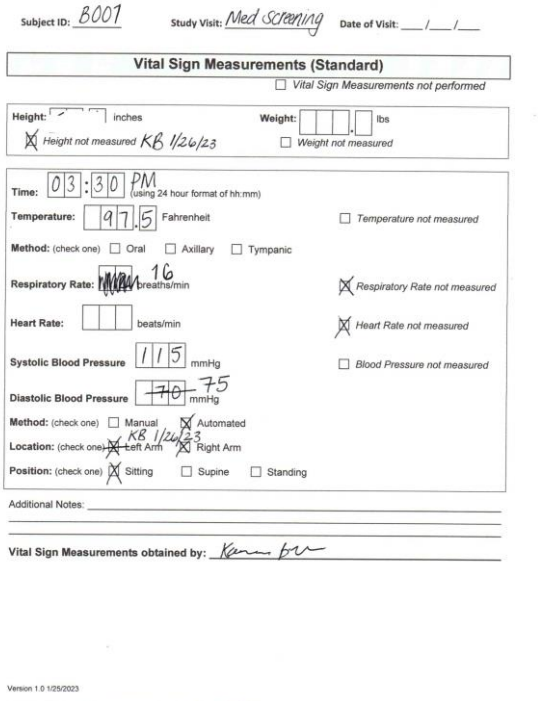
New England Compounding Pharmacy incident: 753 were sickened from fungal meningitis as a result of sterility negligence and data integrity issues and > 100 patients died

- Pharmacy technicians were instructed to lie on cleaning logs, showing rooms as being properly cleaned when they had not been

December 13, 2018: Owner and Four Former Employees of New England Compounding Center Convicted Following Trial | FDA
https://www.eagletribune.com/news/update-14-charged-for-roles-in-meningitis-outbreak-that-killed-64/article_ad39a0d5-a403-5959-b5e3-5dd502fee454.html

Breakout Activity

1. Discuss the errors in data documentation, how they pertain to ALCOA-C standards, and how the data should have been documented



Subject ID: B001 Study Visit: Med Screening Date of Visit: ___/___/___

Vital Sign Measurements (Standard)

☐ Vital Sign Measurements not performed

Height: ___ inches ☒ Height not measured KB 1/26/23

Weight: ___.___ lbs ☐ Weight not measured

Time: 03:30 PM (using 24 hour format of hh:mm)

Temperature: 97.5 Fahrenheit ☐ Temperature not measured

Method: (check one) ☐ Oral ☐ Axillary ☐ Tympanic

Respiratory Rate: ~~WNL~~ 16 breaths/min ☒ Respiratory Rate not measured

Heart Rate: ___ beats/min ☒ Heart Rate not measured

Systolic Blood Pressure 115 mmHg ☐ Blood Pressure not measured

Diastolic Blood Pressure ~~70~~ 75 mmHg

Method: (check one) ☐ Manual ☒ Automated

Location: (check one) ~~☒ Left Arm~~ KB 1/26/23 ☒ Right Arm

Position: (check one) ☒ Sitting ☐ Supine ☐ Standing

Additional Notes: _____

Vital Sign Measurements obtained by: _____

Version 1.0 1/25/2023

Conclusion / Summary

- Study document management encompasses document creation, collection, completion, maintenance, quality control, storage, accessibility and training.
- The purpose of study documentation is to serve as evidence that the rights, safety and well-being of participants were protected, support data reliability and validity, and demonstrate compliance with GCP and applicable regulations.
- Quality study document management systems can be achieved in many different ways.
- Create guidelines to ensure consistency across all areas of research
- CRFs and their importance to study management, protocol implementation, and data collection
- Essential documents help evaluate whether data can be relied on to answer the research question.
- Source data documentation should follow ALCOA-C standards.

References & Resources

ACRP Blog: Beginner's Guide to eTMF, eISF, and Regulatory Research Documents
https://acrpnet.org/2022/12/21/beginners-guide-to-etmf-eisf-and-regulatory-research-documents/

Bargaje C. Good documentation practice in clinical research. Perspect Clin Res. 2011 Apr;2(2):59-63. doi: 10.4103/2229-3485.80368. PMID: 21731856; PMCID: PMC3121265.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121265/#:~:text=The%20most%20important%20purpose%20of,investigation%20if%20and%20when%20required

BU/BMC Clinical Research Resources Office: FAQs on Regulatory Documentation for Clinical Research (6/15/2019)
https://www.bumc.bu.edu/crro/files/2019/06/Regulatory-binder-FAQs-6-26-2019.pdf

FDA Regulations Relating to Good Clinical Practice and Clinical Trials
https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

Federal Code of Regulations
https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/ich-guidance-documents

Harvard University, Regulatory Binder: Instructions and Guidance
https://cdn1.sph.harvard.edu/wp-content/uploads/sites/2352/2022/11/HRP-603-QAQI-TOOL-Regulatory-Binder-Tabs-ORARC-ALL.pdf

HIPAA: Research 45 CFR 164.501, 164.508, 164.512(i) (See also 45 CFR 164.514(e), 164.528, 164.532)
https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html

ICH Guidelines \ Efficacy Guidelines
https://www.ich.org/page/efficacy-guidelines

Thank you!