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University of Arkansas for Medical Sciences

Documentation Guidelines for ORRA-Sponsored Research

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INTRODUCTION TO GOOD DOCUMENTATION PRACTICE

Good Documentation Practice (GDocP) supports the systematic procedures necessary for collecting data that has quality, but more importantly integrity (i.e., reliable and accurate while also being complete, consistent, trustworthy and in context). GDocP is vital in the conduct of clinical research as this data is necessary for the evaluation, reconstruction, and validation of clinical findings, observations, and other study activities.

GDocP and recordkeeping support, demonstrate and facilitate multiple aspects of trial activities, including:

- Protecting the rights, safety and welfare of subjects
- Adherence to protocol requirements
- Good Clinical Practice (GCP) and compliance with applicable regulatory requirements
- Evaluation of data collected
- Evaluation of study conduct and practices
- Study management and oversight
- Monitoring and auditing visits

Documentation creates the story of subject activity over the duration of their time on study, beginning with the consent discussion through the end of the study period (e.g., last study visit or adverse event follow-up).

Remember the research mantras: 'Not documented, not done', 'If it's not documented, it didn't happen' and 'Document what is done, as well as what is NOT done'.

Recordkeeping requirements for investigators are outlined in both U.S. Food and Drug Administration (FDA) regulations and guidance documents, as well as Good Clinical Practice (GCP) guidelines.

21 CFR 312.62 (drugs) states that investigators are required to *'maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects'* and *'prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation'.*

21 CFR 812.140 (devices) states that investigators are required to maintain *'accurate, complete, and current records relating to the investigator's participation in an investigation'; 'Records of each subject's case history and exposure to the device; 'Documents evidencing informed consent'; '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';* and *'A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy'*.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) GCP Guidelines define the essential documents that must be maintained before, during and after the conduct of the study.

After review of FDA regulations, GCP guidelines, and other relevant guidances and practices, University of Arkansas for Medical Sciences (UAMS) Office of Research Regulatory Affairs (ORRA) has established the following 'Best Research Practices' for GDocP and recordkeeping when conducting FDA-regulated research

involving Investigational New Drug Applications (INDs) and Investigational Device Exemptions (IDEs) for which we act as sponsor on behalf of UAMS.

DOCUMENTATION STANDARDS AND CORRECTIONS

To achieve data integrity, the ALCOA+ principles should be applied to source documentation, which specifies the data should be:

Attributable	Is it obvious who wrote/did it and when?
Legible	Can it be read?
Contemporaneous	Was information recorded as it happened?
Original	Is it the first place data was recorded? A copy? Has it been altered?
Accurate	Are all details correct? Are conflicting data recorded elsewhere?
Complete	Has the information been recorded in its entirety?
Consistent	Is information organized in chronological order, logical?
Enduring	Is document long-lasting, permanent?
Available	Can data be maintained in a secure manner?
Accessible	Can data be accessed for the lifetime of the record?
Credible	Is data based on reliable source information?
Corroborated	Can data be confirmed and supported?

At a minimum, the following general standards must be followed for paper and/or electronic documents:

- Sign and date all entries in real-time (i.e., promptly, as soon as possible after the event).
- Make notes/signatures legible.
- Never destroy original documents, even if they require error correction.
- Never obliterate entries that require correction (i.e., maintain a clear audit trail).
- Do not alter past-dated notes.
- Do not back-date.
- Keep subject records secure yet accessible.
- Only use dark ink (blue/black).
- Never use pencil.
- Never use whiteout/correction tape.
- Use staples, not paper clips.

Error Correction (Paper)

- Person recording data should correct the error (if possible).
- Draw a single line through the incorrect information to permit reading of original information.
- Initial, date, and state a reason for the change (if necessary)*.
- Insert the correction near the error.

*If the change is obvious, (i.e., a transcription error that can be verified with the original source), then a rationale for the change is not required. If the change is not obvious, (i.e., a diagnosis or symptom that was deleted after initial entry), then there should be a rationale for change.

Error Correction (Electronic) - If system allows:

- Strike through/Delete information from all incorrect entries/fields.
- Type in initials, date, and reason for change.
- On the next available line, type all information including the corrected information.

Electronic systems should not allow for any changes to occur without an audit trail.

INFORMED CONSENT AND HIPAA

Informed consent is the primary ethical requirement underpinning research involving humans and inarguably one of the most important documents completed during a trial.

Informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for determining eligibility for research. Unless consent has been signed, testing done for screening cannot include any procedures that are being done for research purposes only.

Informed consent is not a singular event and is not simply a signature on a document, rather, it is an ongoing process that continues throughout a subject's participation.

Anyone trained and delegated by the Principal Investigator (PI) (as documented on Delegation of Authority [DOA] log) may obtain consent for studies.

Each person completing the form (subject/legally authorized representative [LAR] and person obtaining consent) must personally sign and date (in real-time) the informed consent form (ICF). If the potential subject has taken the form home and signed it, a blank copy should be printed and signed/dated in the presence of the person obtaining consent.

In addition to obtaining a signed ICF, the process for obtaining informed consent must be documented in the research record with an Informed Consent Process Note (ICPN). The note should document that written informed consent was obtained prior to participation in the study*, unless the IRB granted an exception for the evaluation of an emergency procedure. Best Research Practice is for the person obtaining consent to complete the ICPN and file with research records at the time of consent.

The ICPN should include the following additional information, per UAMS IRB Policy 15.5:

- Title of the study
- Name of the PI
- Date the subject signed consent
- *Time the subject signed consent (per 21 CFR 312.62(b), to confirm consent prior to participation)
- Name of the person or people obtaining the informed consent
- Statement that the subject or LAR was given a copy of the signed form.

While not required, the following additional elements are strongly encouraged to fully document the process:

- A description of anyone else present during the process (e.g., subject's spouse or other family; study coordinator; PI).
- The types of questions the subject had during the process or that the subject had no questions.

- Any other details specific to that particular consent process (e.g., reason for any date discrepancies on consent form signatures) that help complete the description of the process.

If re-consenting is required, follow the same process as performed with initial consent, including documentation with note added to research records at the time of re-consent.

If consenting non-English speaking subjects, see IRB Policy 15.4 regarding use of Short Form Consent.

All pages of the original signed consent form (and HIPAA form, if separate) with original signatures, along with documentation of the consent process, must be maintained. We often see the ICF stored in hard copy form in subject files with the ICPN stored in the electronic medical record (eMR).

Signed consent forms can be kept in a file separate from or with the subject research records, provided this process is consistently implemented for all subjects and any original revised or addendum consent forms are maintained in the same manner.

Each ICF should be uploaded into the eMR system in a timely manner. If desired, a copy can be made of the original form with medical record labels attached to each page of the copy, leaving the original unmarked.

CASE REPORT FORMS

GCP 1.11 defines a Case Report Form (CRF) as, *"A printed, optical, or electronic document designed to record all of the protocol required information [e.g., study data] to be reported to the sponsor on each trial subject."*

CRFs are the most important document (outside the ICF) in a clinical trial since they are the last point of data entry, which ultimately influences the outcome of a study. While the protocol outlines hypothesis and objectives, CRFs support the final steps of data gathering and analysis that are used when reporting conclusions.

CRFs should be well-thought out in terms of form and content. They should be clear and concise, collecting the critical data needed in order to answer the research questions while eliminating any unnecessary information. Format should be 'user friendly' for downstream users (i.e., coordinators, monitors/auditors, data analysts).

When completing CRFs, following all ALCOA+ principles, including:

- Ensure data entries are consistent with source data.
- Complete in a timely (i.e., prompt) manner.
- Write legibly.
- Avoid abbreviations and acronyms.
- Complete all fields, unless otherwise indicated; strike through empty fields.
- Enter reason for missed data (ND/UK/NA).
- Do not write outside designated boxes; if necessary, write comments separately.
- Record dates in the requested format (e.g., 01JAN2023).
- Use correct and consistent units for weight, height, lab results.
- Use GDocP to correct errors.

CRFs should not be labeled with subject name or Medical Record Number (MRN) (either by writing information on form or using a sticker) in order to maintain Protected Health Information (PHI). Instead, they should be labeled with unique subject ID.

Your regulatory binder should include a copy of all approved CRFs (both clean and tracked). If CRFs are modified during the course of the study, a copy of each approved CRF must be stored in this section. Each CRF should be dated and versioned for tracking purposes and to ensure the correct version is utilized.

ORRA will work with you to create and modify your CRFs, if necessary.

NOTE-TO-FILE

Note-To-Files (NTF), while not CRFs, are a useful tool in terms of documentation. NTFs can and should be used in the context of explaining errors, however, overuse of NTFs is a red flag to any monitor or auditor, possibly leading them to dig deeper into your files, so use sparingly.

Best Research Practice guidelines to follow:

- Use letterhead
- NTF should be initiated/authored by the person responsible for its content.
- NTFs should be generated only when needed. While a template can provide a useful starting point, no template is a one-size-fits-all solution and they should be customized UNLESS discrepancy is a recurring event.
- Include (if applicable) the subject and protocol ID and clearly explain the issue and what is being done to correct and prevent the issue in the future.
- As with all source, person completing the note should add their signature and the date and file the document in the most appropriate location (e.g., subject or regulatory binder).

SOURCE DOCUMENTATION

Source data is defined in research, per GCP 1.51 as: '*All information in original records and certified copies of original records of clinical findings, observations, or other activities (in a clinical investigation) used for the reconstruction and evaluation of the trial.'*
Source documents contain source data and are defined in research, per FDA and GCP 1.52 as: '*Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).'*

The most common definition of 'source' is: 'the first place you wrote it down'.

These documents serve to substantiate the integrity of the study data, confirm the recorded observations, and validate information recorded on CRFs. There must be source documentation to substantiate all data recorded on CRFs.

Do not destroy original source or attempt to obscure it – instead, add to it or revise current documentation to maintain a clear audit trail.

Signing/Initialing and Dating Source

Each source document should be signed and dated by the person completing it. If more than one person makes an entry on the same source document, each entry must be signed and dated. However, multiple entries to a source document made by the same person on the same day require only one signature and date on the page if there have been no interim entries made by other individuals.

Initials may be used in place of signatures on source documents if a signature key (e.g., DOA log) is maintained by the research staff. The signature key should include initials, signatures and credentials (if applicable).

Subject Identifiers

All source documents must be consistently labeled with unique subject ID to enable verification that the documents correspond to a particular subject.

Case Report Forms Used as Source Documentation

CRFs may be used as source documents if they represent a tool used for initial data collection. As a source document, the original CRF must be signed/initialed and dated at the time of entry by the person collecting the information (e.g., the coordinator).

A list of the CRFs that are considered source documents should be listed in the 'Source Data Agreement' to clearly indicate for potential reviewers (e.g., monitors, auditors and regulatory authorities) where original documentation can be found. ORRA will provide this document for completion prior to study initiation.

An example of data initially recorded on CRFs may include responses from the subject (e.g., questionnaires, diaries).

Questionnaires/Diaries

The actual data on a subject-completed form does not need supporting source documentation because the form IS the source document. However, documentation is required to demonstrate that the questionnaire was given to the subject in accordance with protocol requirements. This can be accomplished by a signature/date on a checklist or with documentation in the research record indicating the form was given to the subject to complete on a specified date. This is important in cases where the subject refuses or fails to complete the questionnaire.

CRFs completed by subjects must be initialed (full signatures could allow for subject identification and should be avoided) and dated by the individual recording the data.

If a form is not personally completed by the subject (e.g., data are obtained after the study visit via phone call), documentation should be present to indicate who completed the form and the reason this individual completed it. If fields are completed by research staff, the staff member should sign/initial and date those questions/sections and document in the research record the method for obtaining the information and verification that responses are accurately documented (e.g., coordinator personally interviewed subject via phone and copied answers exactly onto the CRF as verbally given).

Electronic Records Used as Source Documentation

Transcription

If data are transcribed from another source onto the CRF, the CRF is not considered to be the original source document and it cannot be used as source documentation. Examples of data that are routinely transcribed from other sources include information from medical records (e.g., vitals, laboratory results, radiology reports, medical history, and demographics).

An example of transcription is the collection of vital signs during a study visit with initial documentation on paper, then entered into the eMR. The data recorded on paper would be considered the original source and not the data in the computer system.

Direct Data Entry

When data is entered directly into a computer system that is 21 CFR Part 11 compliant, the electronic data in the computer system is the original source document (eSource). A paper record (e.g., a printout or print screen of the electronic data) is considered to be a copy.

An example of direct data entry is the collection of vital signs during a study visit with immediate documentation in eMR without first recording the vital signs on paper. The computer system would be considered the original source.

eSource should be discussed prior to study implementation with a clear plan for how data will be collected and by whom, where it will be stored and how and by whom it will be accessible.

For studies using electronic programs that lack an audit trail to capture changes (e.g., Microsoft Excel), ORRA requires that one of two methods be used to present data for verification during monitoring visits:

- Print/Sign/Date Excel document. That paper copy then becomes 'source'.
- Add documents to dated Box files to allow for 'version' comparison between visits.

For systems like electronic data capture (EDC) systems (e.g., OpenClinica, REDCap) that do have audit trails and controls, we recommend read-only access for anyone not 'handling' the data. If there is not a way to allow monitors to see de-identified, study-specific data, the staff member can log-in and offer monitors an 'over-the-shoulder' view.

Most studies use a hybrid model of source documentation with some direct data entry into eMR (e.g., vitals, demographics, laboratory results, physician notes) with select data transferred to a CRF/entered into the EDC, and other data captured on hard copy CRFs (like subject-facing questionnaires), which may then be transferred into the EDC.

We are seeing an increasing number of studies that use EDC as direct source, although specific criteria must be met in order to ensure 21 CFR Part 11 compliance.

ELIGIBILITY CHECKLIST

Eligibility requirements help to ensure that subjects in a trial are like each other in terms of specific factors (i.e., age, disease type, health status), so that the desired hypotheses can be tested. Adhering to these criteria could significantly impact the safety of the subjects and the trial results, as a non-uniform population could lead to inconclusive study results or safety issues.

Eligibility checklists should be developed to capture each inclusion/exclusion criterion outlined in the protocol. To confirm and allow verification of eligibility, it is not enough to simply rely on 'yes' and 'no' check boxes with a general statement like 'The participant does/does not meet the inclusion or exclusion criteria outlined in the protocol.' Instead, develop and use a study-specific eligibility checklist that matches the current version of the protocol.

Verification of this checklist should precede any study-specific activities, including randomization.
There must be source documentation in the form of test results, physical exams, and laboratory results, to support the fulfillment of each criterion.

The staff member completing this checklist should be qualified, delegated and trained.

ORRA can assist you with creation of an Eligibility Checklist. A template can be found on our website.

SCREENING-ENROLLMENT LOG

GCP 8.3.20 recommends a Screening Log *'To document identification of subjects who entered pre-trial screening.'*

GCP 8.3.22 recommends an Enrollment Log *'To document chronological enrolment of subjects by trial number.'*
Screening-Enrollment Logs follow the progress of each potential and actual subject through the study process. This documentation is recommended as Best Research Practice for all studies. These logs not only offer a snapshot of current subjects, but also track information like reasons for screen failures, withdrawals or terminations, which can help with future study design and completion of continuing review.

Logs should be created prior to study start and completed in a timely manner.

Note, per ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies, enrolled means *'a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process.'* Therefore, ORRA has established the guideline, Consent = Enrolled.

ORRA can assist you with creation of a Screening-Enrollment Log. A template can be found on our website.

DELEGATION OF AUTHORITY LOG

There is no FDA or GCP Requirement that sites must have a DOA Log, per se.

Per FDA Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects: '*The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.*'

Per GCP:

- '4.1.5 Investigator's Qualifications and Agreements: *The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.*'
- '8.3.24 Essential Documents for the Conduct of a Clinical Trial – Signature Sheet: *To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.*'

In theory, all key staff members making a direct and significant contribution to the clinical data and/or performing any duty/ task that could impact significantly on subject safety, protocol compliance or data quality and integrity should be included.

DOA Log is the best way to document the roles and responsibilities that have been delegated to various staff members. PI may delegate tasks, however, he/she is ultimately responsible for oversight of all trial-related activities. This oversight extends to supervising all aspects of the study, including all parties that are delegated, ensuring proper training of staff and ensuring that data meet ALCOA+ standards. In addition to PI, Sub-Is, Clinical Research Nurses and Coordinators, ORRA recommends that the primary clinical research pharmacist and Medical Monitor be added to the log.

Pharmacy staff working under the primary pharmacist should have their signatures captured on a pharmacy-specific DOA log. Site may find it beneficial to create a NTF (filed with pharmacy DOA log) to document that the primary clinical research pharmacist has delegated a portion of his/her study-related duties to other individuals employed by the pharmacy and selected by the pharmacist.

While there are no regulations to address inclusion of Medical Monitor, if he/ she ever had to weigh in regarding a consent waiver, AE/ SAE evaluation or any other important trial-related decision, it would be important to match a signature to the written report.

Staff functioning in the scope of routine practice should not be added; however, use caution when allowing these staff members to complete study forms, as this may be considered a significant trial-related duty. It is important to ensure that it is clear what activities an individual has been delegated to perform. Prior to delegation of the task, all study training appropriate to the role should be completed. IRB acknowledgement should also be received prior to staff's participation in study activities.

It is important to ensure that the DOA accurately documents activities an individual has been delegated to perform. Delegate the appropriate staff to the appropriate role, those that are qualified by training (e.g., physical exams should be performed by nurse, MD, DO).

The start date refers to the date that the individual has been delegated tasks by the PI. As this date marks the beginning of the period during which the staff member is directly involved with conduct of the study, it must precede the performance of any study-specific procedures.

The stop date is the date staff is no longer delegated by PI to perform the assigned tasks (whether that be because they have taken on a new role or responsibilities or are leaving the institution).

According to the log being used, PI may initial/date each entry at only at the beginning of staff participation or initial/date entries at both start and stop.

Regarding PI Authorization found at the bottom of each log, there are two acceptable options:

- Option 1: Sign prior to consenting first subject.
- Option 2: Sign at the conclusion of study.

If PI changes during the course of the study there are two options to revising fields on the log:

- Option 1 – Decommission Old Log and Create a New Log:
  - Add stop date for all staff listed.
  - Obtain PI initial/date for all entries.
  - PI should complete 'authorization' field, if not already done.
  - Stop date on previous log & start date on new log should coincide with IRB confirmation of PI change.

- Option 2 – Keep current log:
  - Strike through PI name at the top of each page of the log.
  - New PI should review log and initial/date beside previous PI initials to confirm acknowledgement.
  - Create NTF documenting details of change, including IRB approval date.

PI must confirm his/her approval and oversight by initialing and dating each entry. Best Research Practice would be obtaining this approval prior to staff performing their delegated task.

GDocP dictates that study staff sign a hard copy form that allows for comparison between original wet-ink signatures or initials on documents like consent, source and CRFs. Handwritten capture of signatures and initials of delegated staff allows study documentation attributed to these staff members to be verified.

If site or sponsor choose not to use a traditional DOA Log, ORRA approves of the use of Individual Signature Pages to be completed one time by each study member and kept in a central location.
Remember the GCP purpose of the signature sheet, to document the writing of those who will edit CRFs.

Updates to DOA

Any changes in research staff or staff responsibilities during the course of the study require an update to the log.

If staff's role changes or responsibilities are added or removed, Best Research Practice would be to add an end date to the current entry corresponding to the date the roles or responsibilities are no longer being completed by the individual. A new entry would then be created corresponding to the new role or responsibilities.

ORRA can assist you with creation of DOA Log. A template can be found on our website.

ACCOUNTABILITY LOGS

Investigational Drug Accountability Log

Per 21 CFR 312.62, '*An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects'*.

If the services of the UAMS or Arkansas Children's (AC) Research Pharmacies are utilized, the pharmacy and their Investigational Drug Services (IDS) systems will ensure that procurement, receipt, storage, accountability, preparation, dispensing and labeling of investigational agents comply with state, federal and institutional Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for handling Investigational Drug Product.

Investigational Device Accountability Log

Per 21 CFR 812.140(a), '*A participating investigator shall maintain the following accurate, complete, and current records …* :

(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) Case histories…

(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.'

ORRA can assist you with creation of Device Accountability Logs to document Use, Receipt, Return, Repair and Destruction. Templates can be found on our website.

Both Drug and Device Studies

All logs should be completed in real-time by a qualified, trained and delegated staff member, to ensure completeness and accuracy of the data.

A new line should be completed each time study product is dispensed, used, received, returned, repaired and/or destroyed.

For studies that are not blinded, it is recommended that accountability logs be filed in the regulatory binder. For blinded studies, it is recommended that accountability logs be filed in a separate location (e.g., research pharmacy, laboratory) to maintain the blind.

If the task of accountability has been delegated to another entity, the records may be stored with that entity. A memo should be filed in the site regulatory binder documenting who is maintaining accountability and where the records are located. At the conclusion of the study, the accountability records should be retrieved from the entity for storage in the site and sponsor regulatory binders.

DEVIATION LOG

A written protocol is at the heart of every scientific investigation, including in the context of clinical trials. Deviations from the directions given in the protocol, whether intentional or unintentional, isolated or systematic, big or small, affect the strength of the results and possibly the safety of participants. It is therefore natural that tracking, recording and reporting deviations is a major concern in product development.

Because the protocol is written to be conducted in a specific manner, deviations can impact the:

- Strength of the results
- Data integrity
- Completeness and accuracy of the data
- (Most seriously) Safety of participants

There is no definition of 'Deviation' or 'Violation' in the regulations. From FDA Guidance for Industry, E3 Structure and Content of Clinical Study Reports:

- Deviation: *'Any change, divergence, or departure from the study design or procedures defined in the approved protocol.'*
- Violation (aka 'Important Protocol Deviation'): *'Subset of protocol deviations that might significantly affect the completeness, accuracy, and/ or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.'*

All protocol deviations must be recorded on a Deviation Log and if pertinent, the reasons for the deviations and/or attempts to prevent or correct the deviations are to be included in the documentation using a NTF. For example, a missed visit needs a note stating why visit was missed and what attempts were made by research staff to locate the subject to request that he/she come in to make up that visit.

Documenting deviations allows for a determination to be made as to the root cause, and whether or not such a deviation(s) constitutes an unanticipated problem involving risks to subjects or others (UPIRTSO) and/or constitutes serious or continuing non-compliance. Deviations should be periodically trended over time to look for systemic problems with the study. Ongoing and repeated deviations could signify changes needed to protocol, logistical or workflow issues in the clinic/laboratory, or deficiencies with current research staff that require training.

It is crucial to document PI oversight of deviations. Logs, whether hard copy or electronic, should have a method for signing or initialing and dating each event (or at the very least, a field for signature/date at the bottom of the page) as evidence that the Investigator has reviewed and agrees with the assessment recorded.

See 'Direct Data Entry' section regarding use of Excel to capture deviations.

Note, deviations can and will involve events that fall outside the confines of the protocol (e.g., consent process not completed per GCP or GDocP, non-delegated staff performing study-related tasks, non-timely completion of documentation).

ORRA can assist you with creation of a Deviation Log. A template can be found on our website.

ADVERSE EVENT LOG

While the term 'Adverse Event' (AE) is found in the drug regulations, the device regulations have no such definition, rather you will find 'Unanticipated Adverse Device Effect'. In addition to multiple definitions of adverse event, there are also multiple names and variations like adverse effect, adverse reaction, suspected adverse reaction, serious adverse event

21 CFR 312.32 (a)) Adverse Event: '*Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related*.'

21 CFR 812.3(s) Unanticipated Adverse Device Effect: '*Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to tights, safety, or welfare of subjects*.'

Documentation of AEs is essential for two reasons:

- To keep subjects safe (most importantly).
- To meet reporting regulations and requirements.

GDocP when recording AEs:

- AE Logs are the dedicated space for recording AEs that may be documented in multiple places throughout the subjects' records. Through careful documentation, it can be determined whether conditions, including those present at baseline are worsening and whether events across the subject AND the study are becoming more frequent, severe or prolonged.

- Your protocol will determine when official AE collection begins. Some will indicate that collection begins at consent and continues throughout study participation. Others will call events that occur between consent and administration of treatment 'Pre-Treatment events', with true AEs starting with investigational product (IP) administration. If not otherwise specified in the consent, you should consider that the subject is still 'on study' during their final study visit and events noted at this time point should be sent for review and assessment. Further follow-up would depend on the seriousness and relatedness of the event.

- Report a diagnosis rather than a list of symptoms (e.g., Upper respiratory infection instead of runny nose, coughing, shortness of breath). If you can only report individual symptoms, that is fine. Report what you can, when you can, reporting/recording final diagnosis when received.

- Regarding abnormal labs, it is recommended that out-of-range values be designated as 'clinically significant' (CS) or 'not clinically significant' (NCS). It may be the case that you are not required to report values deemed NCS. For those studies, a qualified Investigator should review laboratory reports and as documentation of this review, sign/initial and date the laboratory report or note the completion of this review in the research record. It may also be necessary to document any action taken with respect to the assessment.

- Traditionally, baseline conditions are recorded at screening and added to the medical history. You may also put these on AE logs so that they can be graded and assessed for future comparisons. If baseline events worsen during the study, Best Research Practice would be to add the increased grade as an Adverse Event with start date as the date it increased in severity. It is important to refer to 'study period' mentioned in your protocol in order to differentiate between pre-existing/ baseline conditions and AEs.

- Much the same as with baseline events that worsen and become AEs, the same applies to AEs that worsen during the study. Add end date for previous grade and create new event with start date as the date the condition worsened.

- Enter dates to the highest level of detail/granularity possible.

- 'Severity' should not be confused with 'seriousness'. Severity refers to grade, while seriousness is based on outcome of the event or action taken, usually associated with events that threaten life or functioning. Severity is intensity (e.g., you can have a severe headache but it isn't serious) while seriousness is the driver behind reporting to sponsor and FDA.

- All AEs must be assessed for their relationship to IP. Because the assessment of relatedness is similar to diagnosis, someone with medical knowledge (an Investigator is recommended) should make these decisions.

- Relatedness (aka Causality) is an assessment regarding the causal (not casual) relationship between IP and an adverse event. When determining relatedness, the clinician should ask:
    - Was the condition present at baseline and can underlying disease explain it?
    - Is the event a known reaction that has been documented in the Investigator Brochure (IB), Product Package Insert (PPI), protocol or consent?
    - Has the event occurred before in the study?
    - Did the event happen contemporaneously with the intervention and does it go away when the intervention is stopped?
    - Finally, can any other potential causes explain the condition?

  See Bradford Hill criteria.

- There are two type of Expectedness – Regulatory and Clinical. Regulatory expectedness refers to those events that may be anticipated as possibly/probably/definitely related to IP and documented in study documents and safety information like the protocol, consent, IB, PPI, or device manual. Expectedness in the regulatory sense is not determined by what could happen in the course of the treated disease. Unexpected events would not have been documented in study documents and/or safety information or their nature, specifics, severity or outcome is not consistent with these materials. Unless the event is mentioned in these documents, it is most likely to be determined to be unexpected.

- It is crucial to document PI or Investigator oversight of AEs. Logs, whether hard copy or electronic, should have a method for signing or initialing and dating each event as evidence that the Investigator has reviewed and agrees with the assessment recorded.

- If the PI is a PhD, an MD or DO participating in the study should be involved in review and assessment of AEs.

PI should be periodically reviewing logs to track and trend events over time to look for systemic problems that may be related to the treatment.

ORRA can assist you with creation of an Adverse Event Log. A template can be found on our website.

CONCOMITANT MEDICATION LOG

21 CFR 312 and 812 contain no regulations governing the filing and/or maintenance of Concomitant Medication (Con Med) Logs.

However, there is mention of keeping track of medications taken during a study in GCP 5.18.4(m)(iii): '*Monitor's Responsibilities - Monitor should specifically verify that adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs'* and FDA guidances (Concomitant Medication, Concomitant Therapy, Concomitant Treatment).

There are multiple reasons for the thorough documentation of con meds:

- Con meds may interact with the study treatment, leading to faulty conclusions regarding safety and efficacy and impacting subject's ability to complete the trial or meet trial obligations.
- Con meds may also indicate a medical condition which potentially affects the pharmacokinetics of the study drug.
- Beyond that, the earliest indication of a serious adverse event may have been self-treatment with an over-the-counter con med.

When writing your protocol, specify allowable and not allowable con meds and their doses.

GDocP when recording Con Meds:

- Beginning at screening/baseline, record all medications being currently taken by the subject, using the generic name, if known. This will reduce confusion due to use of different names for the same product (e.g., Motrin, Advil and Midol vs. ibuprofen).
- At subsequent visits, record new meds, and document changes in or discontinuation of previously listed meds, adding a new entry if needed to captures changes.
- Record only one medication per line.
- For multiple ingredient (i.e., combination) medications, include the strength if known.
- If a medication is used for multiple indications, list the medication again with each indication as a new line or entry.
- It is important to record an accurate indication (reason for use), as this could be tied to Adverse Events. If the reason for use is truly unknown, enter 'Unk' to avoid a blank field.
    - Do not confuse 'Indication' with 'Intended Use', as the latter term is synonymous with labeling.
- For each medication and administration, record:
    - Dose - amount that someone takes or should take, and how often they should take it.
    - Route - the way by which a substance is taken into the body (e.g., oral, IV, g-tube).
    - Frequency - number of times something should be administered/given (e.g., once per day).
- While collecting Con Med information considered unrelated to the study treatment or an AE is a gray area in the regulations, the industry standard is to record all medications that a subject takes in the interest of safety evaluations, potential drug interactions, etc.
- Investigators should definitely focus on collection of Con Meds related to AEs, both treatment and non-treatment related.
- If a medication is taken while subject is on study, complete information should be available.
- If a medication has been taken for a considerable amount of time prior to subject starting study, it is acceptable for an exact start date to be unknown.
- For prior medications, it is important to know stop dates, especially for exclusionary medications (i.e., wash-out periods).

- If date cannot be determined, enter date as closely as possible, narrowing down to day or month or at least year.
- Always indicate whether drug remained ongoing at the time subject was off-study.

COMPENSATION LOG

Although a Compensation Log is not mentioned in regulations, this documentation represents Best Research Practice. Compensation to subjects for their time and effort is most often provided in the form of a gift card.

Per GCP 3.1.8, the IRB should review the method, amount and schedule of payment to assure that there are no issues with coercion or undue influence. IRB will also ensure that information regarding payment is included in the consent.

Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject. Gift cards should be for institutions that subjects would typically frequent (e.g., Wal-Mart, Amazon).

When gift cards are used, the PI is responsible for keeping all original itemized receipts for their purchase, making a photocopy of the back of all gift cards to record the number, and submitting the receipts, photocopies and completed and signed Compensation Log for grants accounting purpose.

The original Compensation Log should be filed in your regulatory binder.

ORRA can assist you with creation of a Compensation Log. A template can be found on our website.

OTHER ESSENTIAL DOCUMENTS FOUND IN THE SITE REGULATORY BINDER

In addition to the requirements for research subject records, there are other requirements that apply to regulatory documents essential to the conduct of a clinical trial. Essential documents must be maintained by sponsor and the study team throughout all phases of the study, yet there are no federal or GCP regulations governing their organization.

GCP outlines in detail the documents required for maintenance by both the study sponsor and investigator. Sponsors and investigators should thoroughly review this information and determine which documents are applicable to their clinical trial.

Good Clinical Practice (GCP) 1.22 and 1.23:

- Documentation: *'**All records**, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that **describe or record** the **methods**, **conduct**, and/or **results** of a trial, the **factors affecting a trial**, and the **actions taken**.'*
- Essential Documents: *'**Documents** that individually and collectively **permit evaluation of the conduct of a study** and the quality of the data produced.'*

Storage Method

Sponsor must maintain a trial master file (TMF) that is a 'mirror' of site regulatory binder, including copies of all pertinent documents.

Before your study begins, determine documentation and storage method (paper, electronic, hybrid) that meets requirements of sponsor and the study team while providing 'easy to navigate' document identification, version history, search, and retrieval. After COVID, the majority of teams use a hybrid model with electronic sharing for monitoring purposes (i.e., Box, SharePoint, Veeva Vault).

If study teams struggle with keeping essential documents up to date for multiple studies, one option is to have central binders to maintain department-specific documents. Central binders work well for CVs, licenses, training documentation, lab certifications and normal ranges for frequently used laboratories.

Study-specific essential documentation should be maintained separately.

Electronic-only documents should be limited to documents that are easily accessible by research staff and by a monitor, auditor or inspector during a site visit. The electronic storage location should be controlled and regularly backed up, and processes should be in place to avoid inadvertent deletions of or edits to documents.

General GDocP Tips for Regulatory Binder

- Create NTF indicating filing location of documents.
- Delegate the task of updating, maintaining, reviewing binder.
- Allow access to the binder only to persons delegated to do so.
- File current and retired versions of all documents.
- Use a standardized naming convention (e.g., main folder named 'IRB Submissions' with subfolders for each submission named according to IRB date [e.g., '01JAN2023 Initial Approval Letter']).
- Create sections for 'Current' and 'Retired' documents to avoid use of out-of-date documents.
- File signed and dated versions of documents, as applicable.
- File documents in a timely manner as soon as possible after generation, receipt.
- Store documents in reverse chronological order (i.e., newest document within a section is filed in the front of the section).
- Maintain the binders until said time that they can be sent for long-term storage, then destroyed. Do NOT destroy documents before the end of the compulsory retention period. See UAMS Policy 3.2.01 and 21 CFR 812.28(d) and 21 CFR 312.57 and 21 CFR 312.62(c).

Do Not Add to Binder:

- Financial records; budget documents
- Records related to other studies
- Non-study related personnel records
- Auditing/monitoring reports
- Subject-specific documents (identifiable ICFs, CRFs, source)

Typical Documents Found on File

The following documents are typically found within a regulatory binder (along with those previously mentioned):

Protocol

Your regulatory binder should include a copy of all IRB-approved protocols (both clean and tracked). If the protocol is modified during the course of the study, a copy of each IRB-approved protocol must be stored in this section. Each protocol should be dated and versioned for tracking purposes and to ensure the correct version is utilized.

UAMS IRB has templates for creating your protocol. ORRA will work with you to create and modify your protocol, if necessary.

Consent and HIPAA Forms

Your regulatory binder should include a copy of all IRB-approved consent and HIPAA forms (both clean and tracked). If the consent/HIPAA forms are modified during the course of the study, a copy of each IRB-approved consent/HIPAA form must be stored in this section. Each consent/HIPAA form should be dated and versioned for tracking purposes and to ensure the correct version is utilized.

UAMS IRB has templates for creating your consent/HIPAA form(s). ORRA will work with you to create and modify your consent/HIPAA, if necessary.

Investigator Brochures / Product Package Insert / Device Manual

The regulatory binder should contain a copy of all current and past IBs (for unapproved drugs), PPIs (for marketed drugs) or device manuals (all devices).

If documents are revised or updated during the course of the study, a copy of each version should be stored in the binder.

IRB Correspondence and Letters

This section should include all communication from study team to IRB and from IRB to study team (e.g., submissions, letters, emails, Annual Progress Reports [APRs] for Non-Significant Risk [NSR] IDEs, CRFs, communications, etc.)

Training

If staff are to be delegated tasks, they must be appropriately trained, which is required by sponsor, as well as FDA and GCP.

- CFR:
  - 21 CFR 312.53(a): *'A sponsor shall select only investigators **qualified by training** and experience as appropriate experts to investigate the drug.'*
  - 21 CFR 312.53(c)(2): *'A curriculum vitae or other statement of qualifications of the investigator showing the education, **training**, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.'*
  - 21 CFR 812.43(a): *'A sponsor shall select investigators **qualified by training** and experience to investigate the device.'*

- GCP:
  - 2.8 The Principles of ICH-GCP: *'Each individual involved in conducting a trial should be **qualified by** education, **training**, and experience to perform his or her respective task(s).'*
  - 4.1.1 Investigator's Qualifications and Agreements: **'***The investigator(s) should be qualified by education, **training**, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s)....'*
  - 5.6.1 Investigator Selection: *'The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be **qualified by training** and experience...'*
  - 8.2.10 Essential Documents for the Conduct of a Clinical Trial - Curriculum Vitae and/or Other Relevant Documents Evidencing Qualifications of Investigator(s) and Subinvestigator(s): ***'To document qualifications** and eligibility **to conduct trial and/or provide medical supervision** of subjects.'*

Sponsor requirements for documentation of training include current versions of:

- Curriculum Vitae (CV), signed and dated within 2 years, for each PI and Sub-I; CVs of other staff members may be added per site SOP
- Clinical license for all staff, as appropriate (MDs, DOs, APNs/RNs, psychologists, etc.)
- CITI Human Subjects Protection Training for all research study staff, per UAMS IRB
- CITI Good Clinical Practice Training for each PI and Sub-I; GCP Training of other staff members may be added per site SOP

Documentation should also include study-specific training for all research staff. At a minimum, the training documentation should include the protocol title, training date, trainer's name, signatures of attendees and training agenda/summary. This training should be documented, either on overall or individual logs, and filed in regulatory binders.

Expired documentation must be retained as these demonstrate qualification for the duration of the study.

Any lapses in training should be explained with NTF filed with other training documentation in the regulatory binder.

Lab Certifications and Normal Ranges

For studies that use clinical laboratories for specimen testing, the regulatory binder should contain documentation of laboratory certifications/accreditations (e.g., CAP, CLIA), normal values/ranges for medical/ lab/ technical procedures and tests (updated at least every 2 years), SOPs and/or procedure manuals.

Expired certifications and outdated reference ranges must be retained as these demonstrate qualification for the duration of the study.

Rather than filing normal values/ranges every two years, many study teams create a NTF and place in a central location with details of where the most current (electronic) lab documentation can be located.

Specimen Tracking Log

The regulatory binder should contain a copy of the Specimen Tracking Log, if used.

The log should contain a comprehensive list of all specimens obtained including minimum information: subject ID, type of specimen (e.g., stool, blood, saliva) and dates of collection, shipment and receipt.

To ensure completeness and accuracy of the data, record specimens in the tracking log as they are collected, and update shipment information as specimens are shipped or received. If consent for future use is withdrawn, document on the log and notify the lab immediately, adding documentation of communication to subject files.

ORRA can assist you with creation of a Specimen Tracking Log. A template can be found on our website.

Conflict of Interest Management Plan / Notice of Significant Financial Interest

For studies with research staff that have a conflict of interest (COI), this section should include the management plan and emails from the UAMS COI Office notifying the research team of the conflict. The COI Office can provide guidance on the implementation of a management plan.

Data and Safety Monitoring Board Documentation

The regulatory binder should include from the Data and Safety Monitoring Board (DSMB), if applicable:

- Data and safety monitoring plan, if not incorporated into the protocol.
- Study reports generated for the safety monitors.
- Minutes from the safety monitor meetings.
- Recommendations and correspondence from the safety monitors.

Subject-Related Communications

Verbal and written communications pertinent to research data collection must be documented in the research record in enough detail to support the data collected, such as actual or attempted contacts, emails, letters, etc.

The communications must have appropriate identifiers to verify that they correspond to the specified subject (e.g., subject ID, date of communication and name of research team member documenting the communication).

Where applicable, follow local SOPs for documentation of communication.

Central Filing

The regulatory binder should include memorandums or NTFs regarding the location of documents that are stored centrally (e.g., study team qualifications, laboratory reference ranges, any documents stored in a location other than the main regulatory binder).

Standard Operating Procedures / Manual of Procedures

The regulatory binder should include site and sponsor Standard Operating Procedures (SOPs) and Manual of Procedures (MOPs), as applicable.

Sponsor Correspondence

Important communications (fully signed, as applicable) between sponsor and the study team throughout the conduct of the study should be added to the regulatory binder. If these documents need to be revised during the conduct of the study, all signed versions with original signatures must be retained.

- Monitoring:
  - Study Initiation Visit (SIV) (e.g., monitoring plan, confirmation letter, agenda, slides, report, follow-up letter, 'green light' email)
  - Interim Monitoring Visit (IMV) (e.g., confirmation and follow-up letters)
  - Close Out (COV) (e.g., confirmation and follow-up letters, logs, sponsor forms)
- Regulatory:
  - Sponsor-Site Agreements (required for each PI) *(all studies)*
  - Form FDA 1572 (required for each PI) *(drug studies)*
  - Investigator Agreements (required for each PI) *(device studies)*
  - Financial Disclosure Forms (required for PI and Sub-Is) *(all studies)*
- Approval of document revisions (e.g., protocols, consents, CRFs)
- Select communication between ORRA Regulatory Unit and study team
- Select communication between ORRA Monitoring Unit and study team

FDA Correspondence

The site regulatory binder should include a complete record of all correspondence to and from the FDA (e.g., initial submission, protocol amendments, APRs, response to FDA request for information, requests for meeting, etc.

The sponsor is responsible for ensuring that all FDA correspondence is provided to each study group.