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Society of Clinical Research Associates
530 West Butler Avenue, Suite 109 Chalfont, PA 18914 USA
Phone: (215) 822-8644 | Fax: (215) 822-8633
Email: office@socra.org | www.socra.org

Proper Documentation of a Clinical Trial: What Are All These Forms and How Do I Complete Them?

Laura Adkins, MAP, CCRP, CCRA, CRS, AdvCRS
Director, Office of Research Regulatory Affairs, University of Arkansas for Medical Sciences

Laura Adkins, MAP, CCRP, CCRA, CRS, AdvCRS

Abstract: *From Case Report Forms to Screening-Enrollment, Delegation of Authority, Adverse Events, Deviation, and Investigational Product Accountability Logs, there is a lot of information to be transcribed when documenting a clinical trial. Both new and experienced clinical investigators and study team members often have many questions when it comes to filling out these essential forms. When the regulations are silent, IRBs, Institutions, Sponsors, Contract Research Organizations (CROs), and clinical investigators are free to develop their own procedures and practices as long as applicable regulatory requirements are met. However, certain elements should be taken into consideration when determining how to record data with integrity (reliable, accurate, complete, consistent, trustworthy, in context). This article presents background information on why the forms are needed and guidance on how best to complete them to comply with regulations and "best research practice".*

Introduction

Although much of our work these days is achieved through electronic means, it still very often feels like we are "buried" under mountains of documents, whether those be in paper on our desk or pending our attention in email or in electronic data capture (EDC) or medical record systems.

The quality of a study and ultimately its results will be determined by the completion and then review of various forms and logs filled out by the study team, so proper documentation is vital to a study's overall success. If you find paperwork (whether paper or electronic) to be tedious, research may not be the right field for you!

Informed Consent Form

Informed consent is the primary ethical requirement underpinning research involving humans, therefore, the informed consent form (ICF) is inarguably one of the most important documents completed in a clinical trial. However, informed consent is not simply a signature on a document, it is a process that continues throughout the subject's participation. U.S. Food & Drug Administration (FDA) regulations and Good Clinical Practice (GCP) guidelines contain specific guidance and instruction on this essential piece of the research puzzle and very often, clinical research sites will have their own Standard Operating Procedures (SOPs) involving this process.

Initial informed consent must be obtained prior to performance of any clinical procedures that are done solely for the purpose of determining eligibility for research. Re-consent may be necessary during the study period (e.g., when an ICF is updated with new information regarding risks and/or benefits). It should be determined by an Institutional Review Board (IRB) (or in some cases, the Sponsor), whether subjects who are still active on the study should be re-consented. In the author's experience, the "willingness to participate" method can be used to make this determination, that is, would updates make subjects less willing to continue in the study (e.g., increase in number

of blood draws, additional visits, more severe risks or side effects).

This consent process continues throughout the subject's participation and should be documented appropriately each time an ICF is completed, meaning a separate consent process note is required for both initial and re-consent(s). Each clinical research site has a specific way of documenting the consent process, either in the electronic medical records or in hard copy notes added to subject binders (see Diagram 1).

Best practice is for the person obtaining informed consent to complete the consent process note in its entirety contemporaneously with consent, ensuring that the **time** of consent is present to document that FDA regulations are met regarding consent being obtained prior to performance of study activities. Per Code of Federal Regulations (CFR) 312.62(b) and 812.140(a)(3)(i), *"The case history for each individual shall document that informed consent was obtained prior to participation in the study."*

When obtaining both initial and re-consent, the subject or legally authorized representative (LAR) and the person obtaining consent should print, sign, and date the document for themselves. From the author's perspective, if the potential subject / LAR takes the ICF home and signs it there, the best practice would be to print a blank copy and ask that the subject / LAR sign and date the document in the presence of the person obtaining the consent.

FDA regulations do **not** require that a clinical investigator personally conduct the consent interview, however, it is essential

Diagram 1

IRB#:
PI:
Study Title:

INFORMED CONSENT PROCESS NOTE

Subject Initials and Subject ID #: _____ _____
Current version of consent: _____
Date consent was signed: _____ Time consent was signed: _____

Note: HIPAA Authorization is included as part of the Informed Consent Form for this study. This Informed Consent Process Note also serves as documentation of HIPAA consent.

Person Obtaining Consent: Add initials to lines below to confirm that each item was addressed during the Informed Consent Process.

__Eligibility was reviewed prior to consent discussion and prospective subject was found to meet all inclusion/exclusion criteria prior to signing.

__Protocol was thoroughly explained to the prospective subject/LAR outlining the risks and benefits, alternate treatment and follow-up requirements of the study.

__Information was given in language understandable to the prospective subject/LAR.

__Prospective subject/LAR was given sufficient opportunity to consider whether or not to participate.

__Prospective subject/LAR was given an opportunity to ask questions about the protocol.

__Prospective subject/LAR was encouraged to take consent home to review and/or obtain family/friends input prior to signing.

__Prospective subject/LAR privacy was maintained.

__Opportunity was given for prospective subject/LAR to read the consent document before it was signed.

__No coercion or undue influence was used in the consent process.

__No research-related procedures were performed prior to obtaining informed consent.

__A copy of the signed consent was given to the subject/LAR.

__All signatures, dates and times were obtained.

__A copy of the consent was sent to Medical Records and the original was placed the subject's research chart.

How was the informed consent process given?

_____

Describe the subject's condition at the time of consent:

_____

Who was present during the Informed Consent process?

_____

Did the subject have any questions? Please list below along with any additional comments about the Informed Consent process._____

_____

Person Obtaining Consent (Signature) _____ Date_____

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that the person obtaining the consent be trained and delegated (i.e., present on the Delegation of Authority Log) to perform this task. Similarly, it is also **not** required by FDA regulations that the clinical investigator sign the consent form.

While FDA regulations do **not** require that the person obtaining consent and performing the consent discussion sign / date the form or that the copy of the form provided to the subject is a signed / dated version, these practices **are** mentioned in the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E6 GCP guidelines under Section 4 "Informed Consent f Trial Subjects":

- *4.8.8: "Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion."*

- *4.8.11: "Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects."*

As always, study teams should follow procedures outlined by their site, sponsor and IRB, in agreement with FDA regulations and GCP guidelines, for completing the consent form and process.

Our assessment of the most common findings on review of ICF and consent process by monitors / auditors is:

- Fields are not filled out/left blank unintentionally
- Subject and/or staff capture information in the wrong field(s)
- Dates are incorrect
- Cross-outs or handwritten corrections made on the original ICF (some clinical research sites/Sponsors consider this an unacceptable practice, recommending Note-to-File [NTF] instead)
- Consent process note does not indicate that the subject was provided with a copy of the form
- Consent is obtained using an outdated version of ICF
- Re-consent was not obtained as required by Sponsor/IRB
- Pages are missing, either from the original document or the scanned medical record submission

The Delegation of Authority Log

Of all the essential forms, the Delegation of Authority (DOA) Log is one reviewed most frequently during visits by both monitors and auditors. Neither FDA nor GCP require clinical research sites to maintain a DOA Log, per se. However, both bodies confirm the need to document the delegation of significant trial-related duties (see **Diagram 2**).

According to 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*

Diagram 2

Delegation of Responsibility and Site Signature Log

Protocol Title:	**IND/IDE#**
IRB Number:	**Sponsor: UAMS**
Site:	**Principal Investigator:**

Study Personnel (Please Print Full Name)	Study Role (Example: PI, Sub-I, CRA, Regulatory, etc.)	Authorization Code(s) (See Legend Below)	Dates Authorized		Staff Initials	Staff Signature and Date	PI Initial and Date
			Start Date	Stop Date			

Authorization Code Legend:

01: Obtain informed consent	07: Randomize subjects	13: Complete source documents	19: Obtain study measurements/collect data
02: Informed consent process note	08: IP administration	14: CRF completion and query management	20: Laboratory specimen collection
03: Conduct subject interviews	09: IP dispensing	15: CRF signature	21: Process sample specimens
04: Obtain/review medical history	10: IP accountability	16: IRB Submissions	22: Shipping hazardous materials (i.e. human tissue specimens, dry ice, etc.)
05: Eligibility assessment	11: AE/SAE/UPIRTSO assessment	17: Update/maintain IRB submissions	23: Concomitant medication review
06: Perform physical exam	12: AE/SAE/UPIRTSO reporting	18: Update/maintain regulatory docs	99: Other:

Principal Investigator's Authorization: I hereby delegate the above significant research–related duties to the aforementioned staff members and certify that they are trained and qualified to perform the specified duties for the protocol listed above. All research procedures related to treatment are conducted within UAMS by licensed and certified clinical staff. I understand that the overall responsibility of conduct of the research remains with me.

Principal Investigator: (printed name)	Signature	Initials	Date

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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."

This practice is reinforced in GCP guidelines:

- 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, the DOA Log should include all key staff members who make a direct and significant contribution to the clinical data and/or perform any duty or task that could significantly impact subject safety, protocol compliance, or data quality and integrity. Ultimately, the clinical research site and the Sponsor will determine who should be included. Most often, the log includes the:

- Clinical Investigator
- Sub-Investigators
- Research nurses
- Coordinators (both data and regulatory)

In the author's experience, the primary clinical research pharmacist and the medical monitor, key staff members whose oversight could impact significantly on subject safety, protocol compliance or data quality and integrity, should be included on the main DOA log.

Regarding the primary pharmacist, this person is delegated by the Investigator as the one ultimately responsible for the work being performed by the staff under their direct supervision. Clinical research sites may find it beneficial to create a pharmacy-specific DOA Log along with a NTF to document that the primary clinical research pharmacist has delegated a portion of their study-related duties to other individuals selected by the primary pharmacist.

Regarding the medical monitor, the University of Arkansas for Medical Sciences (UAMS) asks that study teams include the medical monitor along with other key staff members. In addition to simply proving that the clinical investigator has delegated a vitally important task to a specific person, if this staff member ever had to weigh in regarding a consent waiver, Adverse Event/Serious Adverse Event evaluation or any other important trial-related decisions, the signature on the log can be used to validate the signature on the report/documentation.

Staff (e.g., nurses and technicians) functioning in the scope of routine practice and staff who are not making a direct or significant contribution to data should not be added to the DOA Log. It is necessary, however, to use caution when allowing these staff members to complete study forms, as some Sponsors may consider these "significant trial-related duties".

Depending on the site, different ideas may exist about who should be included on the DOA Log, so it would be best to check the site's SOPs, speak to the site's managers, and consult the Sponsor when determining the appropriate staff to include on the log.

Responsibilities on the DOA Log must be assigned accurately and appropriately, with staff delegated to roles based on their training (e.g., perhaps physical exams must be performed by physicians or nurses).

The start date refers to the date that the individual has been delegated tasks by the clinical investigator. 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. Prior to delegation of the task, all study training appropriate to the role should be completed. At UAMS, it is expected that IRB acknowledgement should also be received prior to staff's participation in study activities.

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

If a staff member's role changes or responsibilities are added or removed, best 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 and/or responsibilities. Rather than using strikethrough, initial, date, this method is easier to follow visually.

Outside providing evidence of clinical investigator delegation, another function of the DOA Log is to capture the signatures and initials of the delegated staff, allowing for verification of study documentation attributed to these individuals. While electronic logs are becoming

more common and increase efficiency, they do not allow for this handwriting comparison. This has brought about the use of individual signature pages (see Diagram 3). In this situation, the main DOA Log is electronic, with each study member completing an individual signature page in hard copy, which is then filed in a central location.

The clinical investigator must confirm their approval and oversight of delegation by initialing or signing and dating each entry on the DOA Log. Depending on the log required by the clinical research site/ Sponsor, the clinical investigator may sign/initial and date each entry either only at the beginning of a staff member's participation or at both the beginning and end of participation. Although lapses of days, weeks, or months in clinical investigator initial/signature and date have been noted, obtaining this documentation prior to the staff performing delegated duties is best practice.

Overall clinical investigator authorization is found at the bottom of each log, where the clinical investigator can sign prior to consenting the first subject or at the conclusion of the study, based on the processes of the clinical research site, the Sponsor, and the log's format.

If the clinical investigator changes during the study, a new DOA Log can be created or the original log can be revised.

If a new log is created, the old log should be finalized and retired by following these steps:

- Add stop dates to active staff
- Obtain former clinical investigator's initial and date for all entries
- Former clinical investigator should complete the authorization field, if not already done
- Stop date on old log and start date on new log should coincide with IRB confirmation of the clinical investigator change

Diagram 3

Individual Signature Page

This form is applicable for all research personnel that are
1) Conducting study activities through [study site], and
2) Documented on any study's Delegation of Authority Log via electronic signature.

This form is used for validating research personnel's handwritten signature and initials that may be used on any study related documents.

This document may be uploaded to an electronic regulatory file as a Certified Electronic Copy.

First Name *(print or type)*	**Last Name** *(print or type)*

Handwritten Signature	**Handwritten Initials**	**Date**

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If the current DOA Log is kept:

- Strikethrough clinical investigator's name at the top of each page and add the new clinical investigator's name
- New clinical investigator should review the log and sign/initial and date beside the previous clinical investigator's signature/initials to confirm acknowledgement
- Create NTF to document the details of the change, including the IRB approval date

See Table 1 (on next page) for more information on completion of the DOA Log.

Our assessment of the most common findings on review of DOA Logs by monitors / auditors is:

- Study tasks have been carried out by staff not listed on the DOA Log
- Staff being delegated tasks without the appropriate education, training, and level of experience
- Staff responsibilities are improperly documented
- No DOA Log is on file, or log is filed but blank
- Log has not been completed in a timely manner as staff changes
- Responsibilities or tasks are updated without an audit trail

Documentation of Training
As just discussed, if staff are to be delegated tasks, they must be appropriately trained. Training and its documentation are supported by both FDA regulations and GCP guidelines. They emphasize that staff members must be qualified for their study tasks by education, training and experience.

Per FDA regulations:

- 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."*

And GCP guidelines:

- 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…"*

This training should be documented, either on overall or individual logs (**see Diagrams 4 and 5 on next page**) and filed in regulatory binders.

TABLE 1
The Delegation of Authority Log

- Study personnel and roles to include:
  - Principal Investigator
  - Sub-Investigators
  - Research nurses
  - Coordinators (data and regulatory)
  - Primary research pharmacist
  - Medical monitor
- Responsibilities:
  - Ensure responsibilities are assigned:
    - Accurately
    - Appropriately
    - Clearly
  - If responsibilities change:
    - Enter the stop date for the initial entry
    - Create a new entry
- Review often and make edits in a timely manner
- Include start and stop dates:
  - Start date should precede performance of any study-related tasks
  - Start date should be after training is complete and staff member is knowledgeable about role
  - Start date should not precede IRB approval
  - Stop date should be added when role(s)/task(s) change or when staff member is not serving in role and no further study-related activity is planned
- Staff signatures and initials:
  - Handwritten signatures or initials allow validation of documents
  - If electronic log is used, create individual signature pages to capture signature/initials
  - Clinical investigator signature/initials confirm approval and oversight of delegation

Eligibility Checklist
The Eligibility Checklist is another essential component of research documentation that all monitors and auditors will review.

Eligibility criterion ensure that subject population is uniform (e.g. age, type/stage of disease, general health), risks are minimized to persons who might be harmed by the research and finally, that the results of the

study are conclusively related to the intervention and not other factors. Therefore, their verification is leaned on heavily during regulatory visits and inspections. See this excerpt from an FDA Warning Letter as proof of the importance of verifying eligibility: *"Enrollment of subjects who do not meet eligibility criteria…jeopardize subject safety and welfare and compromise the validity and integrity of the data collected at your clinical research site."*

The checklist used should be study-specific, matching the current version of the protocol, and listing all criterion separately (see Diagram 6 on next page). Each criterion should be verified prior to the performance of any study-specific activities (including randomization) by direct comparison with source documentation (e.g., pathology or laboratory test results, physical exams, outside records). In other words, it is not enough to rely on "yes" and "no" check boxes with a general "blanket" statement such as, "The subject does/does not meet the inclusion or exclusion criteria outlined in the protocol." You must have proof to confirm **each** item on the checklist.

As with the completion of the ICF, the staff member reviewing subjects for eligibility and completing this checklist should be qualified, delegated, and trained. Depending on the clinical research site and Sponsor, the checklist may have multiple signature lines as a "check and balance" multi-layer validation system (i.e., coordinator, nurse, Investigator, etc.). Often, the clinical investigator is required to sign/date the checklist for confirmation of eligibility, as well as documentation of oversight.

Diagram 4

Training Log

Investigator Name:	Protocol:	Site Number:

Printed Name	Signature	Title of Training	Date of Training

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Diagram 5

INDIVIDUAL PROTOCOL TRAINING ATTESTATION STATEMENT

MUST be signed before any work on study activities can begin

By signing this form, you affirm that you personally have read **Version** _____ of the protocol and reviewed the Training Slides, if applicable. Further, you affirm that you are aware of your roles and responsibilities on the study titled "***STUDY TITLE***".

Staff Member

Print Name: _____

Signature: _____

Date: _____

Sponsor Official

Print Name: _____

Signature: _____

Date: _____

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A fully verified Eligibility Checklist with complete supporting source documentation can prevent queries from monitors/auditors about whether a subject meets inclusion/exclusion criteria, and more importantly, avoid major issues with the FDA and/or the Sponsor.

The Screening and Enrollment Log(s)

Documentation of Screening and Enrollment is recommended as best practice for all studies. Along with offering a snapshot of current subjects, the Screening and/or Enrollment Logs also track information such as reasons for screening failures, withdrawals, or terminations. This information is helpful in the completion of IRB continuing review submissions, as well as the design of future studies.

GCP defines Screening Logs and Enrollment Logs separately, however, many clinical research sites combine them into one document with specific codes or status to indicate the final placement of subjects (e.g., failed screening/screening failure, subject withdrawal/consent withdrawal, clinical investigator withdrawal, died/death, completed) (**see Diagram 7**).

Regarding the regulatory definition of "enrolled", the author refers to ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies, which states *"'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, consented equals enrolled.

As with all essential documents, the Screening and/or Enrollment Logs should be created prior to study start-up and completed in a timely manner.

Diagram 6

IRB#:
PI:
Study Title:

ELIGIBILITY CHECKLIST

Subject ID #: __________ Date: __________

Inclusion Criteria (circle 'Yes' or 'No')
(All items must be marked 'Yes' for the subject to be eligible)

1.	Yes	No
2.	Yes	No
3.	Yes	No
4.	Yes	No

Exclusion Criteria (circle 'Yes' or 'No')
(All items must be marked 'No' for the subject to be eligible)

1.	Yes	No
2.	Yes	No
3.	Yes	No
4.	Yes	No
5.	Yes	No
6.	Yes	No
7.	Yes	No
8.	Yes	No
9.	Yes	No
10.	Yes	No
11.	Yes	No
12.	Yes	No
13.	Yes	No

The subject is:
☐ Eligible for the study
☐ Not eligible for the study

CRF completed by: ____________________ Date: ______________

PI Signature: ______________________ Date: ______________

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Diagram 7

Study Title:
IRB #: **Principal Investigator:**
Sponsor: **Study Site:**
IRB Approved Enrollment number *:

Subject ID and Initials		Subject Demographics		Date Subject signed ICF	Subject eligible? (yes/no)	If not eligible, Reason for Exclusion/Comments	Subject final status **	Additional comments
		Gender	Age					
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
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		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	
		M☐ F☐			Y☐ N☐		C☐ WS☐ WP☐ S☐	

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Case Report Forms
Case Report Forms (CRFs) are crucial elements of clinical trial documentation, as they are the last point of data entry, ultimately influencing the outcome of the study. While the study protocol outlines specific hypotheses and objectives, CRFs support the final steps of data analysis, collecting the specific information needed in order to answer the questions proposed by the research. Therefore, the creation and design of these forms should be protocol-driven and all documents must be approved by clinical research site and Sponsor prior to enrollment.

CRFs are defined clearly in GCP guidelines and may be either paper or electronic. Per GCP 1.11: *"Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject."*

CRFs must meet all ALCOA+ standards (i.e., attributable, legible, contemporaneous, original, accurate AND complete, consistent, enduring, available, accessible, credible, corroborated) in order to be verifiable by monitors, auditors, data analysts, etc.

The Medical History Form is useful as a tool to capture relevant conditions that establish health at baseline. Information documented here can be later linked directly to conditions noted on the Physical Exam Form, indicating changes from baseline leading to investigation of possible Adverse Events (AEs) (see Diagram 8).

Many forms serve as checklists, acting as reminders to ensure that all procedures are completed per protocol and reported or documented appropriately. For example, checking of "Yes" to a change in concomitant medications (Con Meds) or signs/symptoms could lead the coordinator to investigate whether the appropriate forms (Con Med or AE Logs) should be updated and

Diagram 8

Physical Exam

STUDY NAME

Protocol Number:_____ Visit Date: __ __ / __ __ __ / __ __ __ __
Pt_ID:_____ d d m m m y y y y

Visit Type: ☐ Screening ☐ Baseline ☐ Visit 1 ☐ Visit 2 ☐ Visit 3 ☐ Visit 4 ☐ Visit 5 ☐ Completion Visit

Category	Normal or Abnormal	If abnormal, describe below	Change from baseline
General Appearance	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
HEENT (Head, Eye, Ear, Nose, Throat)	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Neck	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Chest and Lungs	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Cardiovascular	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Abdomen	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Genitourinary	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Rectal	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA

Physical Exam 1 of 2 Version 1.0

Category	Normal or Abnormal	If abnormal, describe below	Change from baseline
Musculoskeletal	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Lymph Nodes	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Extremities/ Skin	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Neurological	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Other, specify: _____	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA

Note: *For follow-up PE, if a body system category changes from "Normal" at baseline to "Abnormal" at follow-up due to a new disease/condition or if a preexisting disease/condition worsens from the baseline, an adverse event form should be completed to report the change.*

Physician Signature: _____

Date signed: __ __ / __ __ __ / __ __ __ __
d d m m m y y y y

Physical Exam 2 of 2 Version 1.0

whether the IRB should be notified (**see Diagram 9**).

As previously discussed, only qualified, delegated and trained personnel should complete forms.

Table 2 provides an overview of how to create and complete these forms.

Our assessment of the most common findings on review of CRFs by monitors/auditors is:

- Data recorded on CRFs do not match source
- Fields left incomplete/ questions unanswered
- Extraneous writing outside dedicated fields
- Data are recorded without being signed/initialed and/or dated
- Forms completed by non-delegated staff members

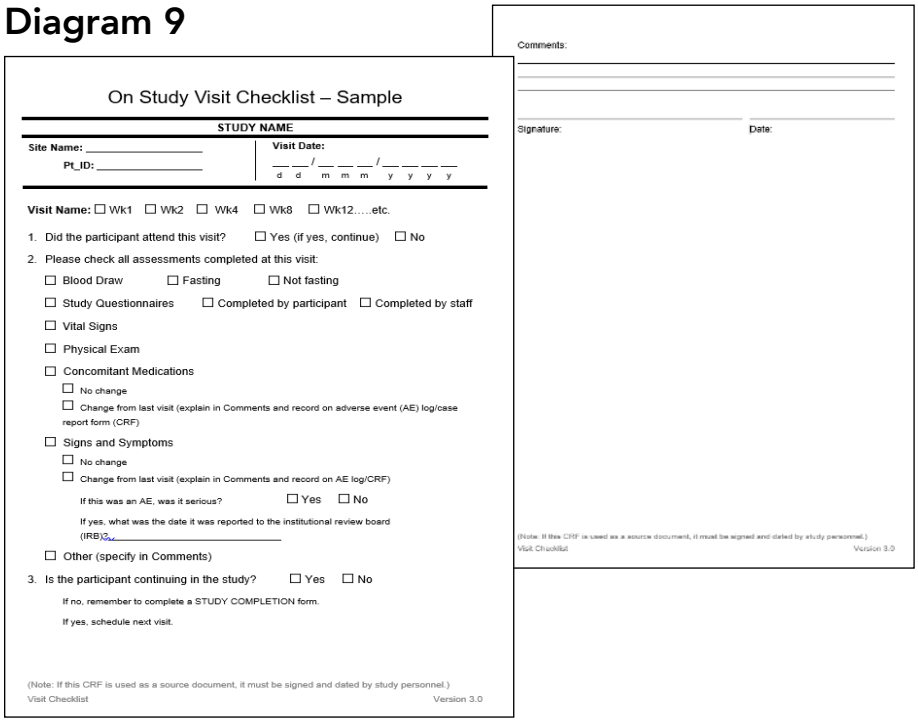
Note-to-File and Phone Call Summary Templates
Other forms useful in the documentation of clinical research are the Note-to-File (NTF) and phone call summary templates.

NTF are not necessarily a CRF, but they are a useful tool to keep in the clinical research site's arsenal to clarify or add information to document specific requirements or standards, or to address complicated issues or discrepancies (**see Diagram 10 on next page**). NTF can and should be used in the context of explaining errors, however, overuse of NTF is a red flag to any monitor or auditor, possibly leading them to dig deeper into files, so use sparingly.

Our best practice recommendations for use of NTF:

- Print on letterhead
- Generate on a case-by-case basis

Diagram 9



On Study Visit Checklist – Sample

STUDY NAME

Site Name: _____ Visit Date: __ __ / __ __ __ / __ __ __ __
Pt_ID: _____ d d m m m y y y y

Visit Name: ☐ Wk1 ☐ Wk2 ☐ Wk4 ☐ Wk8 ☐ Wk12…..etc.

1. Did the participant attend this visit? ☐ Yes (if yes, continue) ☐ No
2. Please check all assessments completed at this visit:
   - ☐ Blood Draw ☐ Fasting ☐ Not fasting
   - ☐ Study Questionnaires ☐ Completed by participant ☐ Completed by staff
   - ☐ Vital Signs
   - ☐ Physical Exam
   - ☐ Concomitant Medications
     - ☐ No change
     - ☐ Change from last visit (explain in Comments and record on adverse event (AE) log/case report form (CRF)
   - ☐ Signs and Symptoms
     - ☐ No change
     - ☐ Change from last visit (explain in Comments and record on AE log/CRF)

       If this was an AE, was it serious? ☐ Yes ☐ No

       If yes, what was the date it was reported to the institutional review board (IRB)? _____
   - ☐ Other (specify in Comments)
3. Is the participant continuing in the study? ☐ Yes ☐ No

   If no, remember to complete a STUDY COMPLETION form.

   If yes, schedule next visit.

(Note: If this CRF is used as a source document, it must be signed and dated by study personnel.)
Visit Checklist Version 3.0

Comments:

Signature: Date:

(Note: If this CRF is used as a source document, it must be signed and dated by study personnel.)
Visit Checklist Version 3.0

TABLE 2
How to Create and Complete Case Report Forms

- When creating forms:
  - Ensure consistent formatting (e.g. date format, font, spacing)
  - Define all units (e.g., Fahrenheit for temperature, pounds for weight)
  - Include reminders to ensure that procedures follow the protocol and are reported or documented appropriately
- When completing forms:
  - Use subject IDs, not protected health information (PHI) (e.g., name, date of birth)
  - Use checkboxes, not circles
  - Include dedicated fields for signature or initial of person completing the form
    - For a form to serve as its own source, it should be signed and dated by the person completing it, even if that is the subject
  - Include version number/date in the footer
  - Follow CRF completion guidelines, if applicable
  - Ensure data entries are consistent with source data
  - Complete in a timely manner
  - Write legibly
  - Avoid abbreviations and acronyms
  - Complete all fields, unless otherwise indicated; strike through empty fields
  - Enter reason for missed data (e.g., not done, unknown, not applicable)
  - Do not write outside designated boxes; if necessary, write comments separately in NTF
  - Use Good Documentation Practice (GDocP) to correct errors
  - Form must be completed by qualified, delegated and trained personnel

- Use "one-size-fits-all" **only** for recurring oversight/ erroneous practice
- Include subject and protocol IDs
- Explain clearly and specifically the error/ omission/discrepancy
- Include any corrective action or follow-up, when applicable
- NTF should be initiated/ authored by the person responsible for its content (coordinator, research nurse, pharmacist, clinical investigator, etc.)
- File with related documents in subject file or behind appropriate study binder tab

Often, a nurse or study coordinator needs to call subjects to give or gather information, such as how to take the study drug as prescribed or to follow up on AEs. The source (the first place something is recorded) documentation of these conversations can be achieved through either paper or electronic methods but should be done in a way that routinely captures all relevant information to allow for an audit trail that can be followed by monitors and auditors when reviewing files. The Phone Call Summary Template is an ideal document for use in this situation (see Diagram 11).

Documentation of Investigational Product Accountability (i.e., Device and Drug Accountability)
For all studies that involve an investigational product (IP), an accountability log is a requirement per FDA regulations and GCP guidelines. These logs serve to document shipment, receipt, disposition, use and return of IP throughout

Diagram 10

Sample Note To File:

PROTOCOL #: DMS1001

TITLE: The Evaluation of Efficacy and Safety of "Investigational Drug Q" on recurrence of "Disease"

From: Joe Brown, research coordinator
[Insert staff name, include role on study}

To: Subject File

Re: Subject# 11202-02
[insert subject identification]

Date: March 31, 2010

This subject was consented by Dr. Smith on March 31, 2010. Dr. Smith, in error dated the consent form March 30, 2010. The dating discrepancy is not representative of an inappropriate consent process, but the result of a typographical error. Dr. Smith has been reminded to confirm the correct date in the future.

Signature: _____ Date: _____

Diagram 11

IRB#:
PI:
Study Title:

PHONE CALL SUMMARY REPORT

For documentation of phone calls related to the clinical conduct of the study.

Date:

Time:

Study staff member:

Subject ID:

Summary of phone call:

Signature: _____ Date:_____

a study (see Table 3). The Sponsor should communicate their preferred method of documentation prior to enrollment.

Device Accountability Log format can fall into two categories: Combined, with receipt, use, return, repair, and destruction on one page OR the logs can be separated into two or more documents (see Diagrams 12 & 13). The author prefers the separate documents, where more space is allowed for the "Use" section, including fields for subject ID, date of use, start and stop times (i.e., exposure), name and signature/ initials of person administering the device and comments.

Electronic investigational drug systems (IDS) are used at most clinical research sites, including UAMS, for purposes of documenting drug accountability (i.e., Drug Accountability Log). These systems are more user-friendly and efficient at documenting inventory, accountability, dispensing, and compliance than paper logs and allow for review, if necessary, between and during monitoring and auditing visits.

No matter the version of log used, they should be completed immediately following each instance of dispensation/use or return to ensure that documentation meets ALCOA+ standards of contemporaneous, accurate and complete.

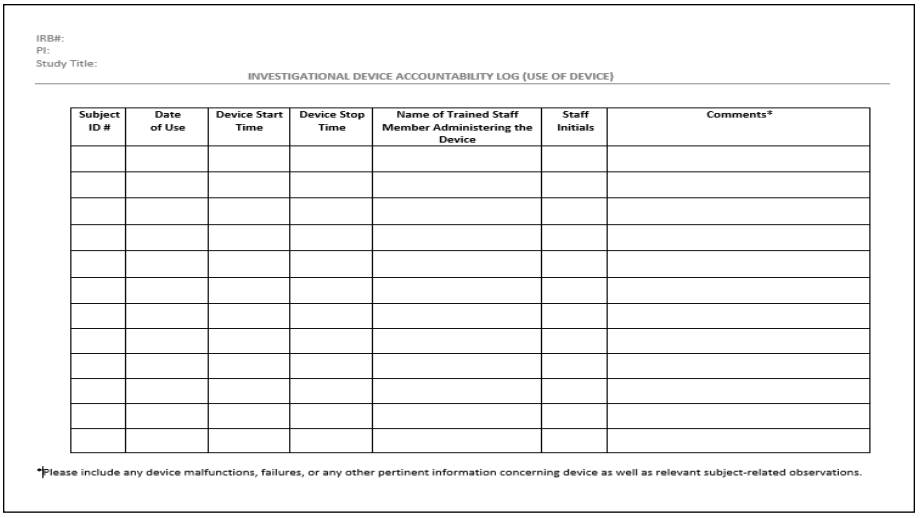
For unblinded studies, maintaining the IP Accountability Log in the regulatory binder is suggested. However, to maintain the blind in blinded studies, the log should be stored in a separate location, such as the research pharmacy for drugs or the laboratory for devices.

TABLE 3

Documentation of Investigational Product Accountability

- Document when and how IP is used throughout the study
- Required for both drug and device studies, per the regulations
- Document shipment, receipt, disposition, use and return of IP
- Complete logs immediately following each instance of dispensation/use or return to ensure accurate and complete documentation
- Documentation storage location:
  - Separate from essential documents (blinded studies)
  - Regulatory binder (non-blinded studies)
- Device Accountability Log:
  - Format may be combined with receipt, use, and return/repair/ destruction on one page OR separated into two documents
- Drug Accountability Log:
  - Complete a new line each time study product is dispensed and/or received
  - Utilize IDS system, if available

Diagram 12



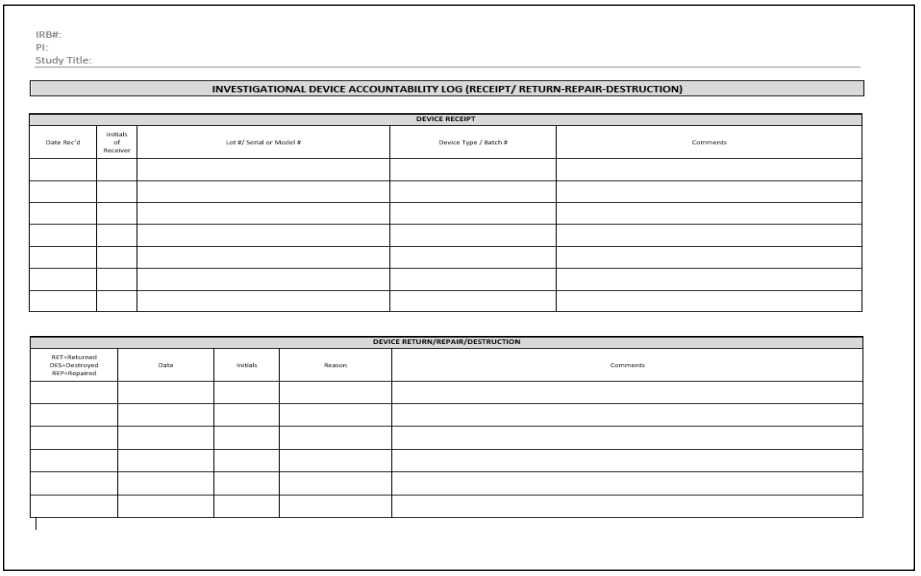
IRB#:
PI:
Study Title:

INVESTIGATIONAL DEVICE ACCOUNTABILITY LOG (USE OF DEVICE)

Subject ID #	Date of Use	Device Start Time	Device Stop Time	Name of Trained Staff Member Administering the Device	Staff Initials	Comments*

*Please include any device malfunctions, failures, or any other pertinent information concerning device as well as relevant subject-related observations.

Diagram 13



IRB#:
PI:
Study Title:

INVESTIGATIONAL DEVICE ACCOUNTABILITY LOG (RECEIPT/ RETURN-REPAIR-DESTRUCTION)

DEVICE RECEIPT

Date Rec'd	Initials of Receiver	Lot #/ Serial or Model #	Device Type / Ratch #	Comments

DEVICE RETURN/REPAIR/DESTRUCTION

RET=Returned DES=Destroyed REP=Repaired	Date	Initials	Reason	Comments

The Concomitant Medication Log

Concomitant Medications (Con Meds) are medicinal products (i.e., prescription and over-the-counter [OTC] products, dietary supplements) that a subject takes while participating in a study. These may be drugs for the same indication being studied OR for pre-existing or concurrent conditions. Ideally, the protocol should specify concomitant medications that are and are not allowed if drug-drug interactions are expected.

Like DOA Logs, there are no regulations governing the filing and/or maintenance of Con Med Logs. FDA guidances do, however, mention "Concomitant Medications", "Concomitant Therapy", and "Concomitant Treatments," and GCP guidelines mention reporting Con Meds as per the protocol on the CRFs.

Documentation of Con Meds is imperative for many reasons. Con Meds may interact with the study treatment, leading to faulty conclusions regarding safety and efficacy and impacting a subject's ability to complete the trial or meet trial obligations. Con Meds may also indicate a condition (like hypertension) which potentially affects the pharmacokinetics of the study drug. The earliest indication of an adverse event (AE) or serious adverse event (SAE) may have been self-treatment with an OTC medication

Table 4 provides an overview of the Concomitant Medication Log.

TABLE 4
The Concomitant Medication Log

- Record all medications the subject is taking, beginning at baseline/screening
- At subsequent visits:
  - Record new medications
  - Record changes or discontinuation of previous medications
- Record the drug's generic name:
  - If unknown, record the brand name
- Include only one medication per line
- For fixed dose combination medications:
  - Indicate the strength
- For multiple indications:
  - List medication again with each indication as a new line or row
- Record the reason for use:
  - If unknown, enter "unknown"
- For each medication and administration, record:
  - Dose
  - Unit
  - Route
  - Frequency
- Record changes in dose, unit, route or frequency on a new line
- Start, stop, and ongoing:
  - Medications with lengthy historical use may have incomplete dates
  - Medications taken during the study should have complete start dates
  - Prior medications that are exclusionary should have start and stop dates
  - For medications where the exact date is unknown:
    - If day is unknown: Enter the first day of the month (e.g., 01MAY2022)
    - If day and month are unknown: Enter the first day of the first month for both fields (e.g., 01JAN2022)
    - If day, month and year are unknown: Use the best estimate for the year
- Indicate whether the drug is ongoing at the end of the study

Beginning at baseline/screening, use the Con Med Log to document all medications the subject is currently taking, using one line per medication (see Diagram 14). At subsequent visits, record new meds, and document changes in or discontinuation of previously listed meds, adding a new entry/row, if necessary, to capture changes.

In order to eliminate confusion, it is recommended to document medications using generic names (e.g., ibuprofen). If the generic name is unknown, record the brand name (e.g., Advil, Midol, Motrin). For fixed dose combination medications, indicate the strength if known.

It is important to record an accurate indication (reason for use), as this could be tied to AEs. **Indication**, defined as, *"A medical condition that a medicine is used for; a sign, symptom, or medical condition that leads to the recommendation of a treatment…."* should not be confused with **intended use**, which is synonymous with labeling of the product. If the reason for use is truly unknown, enter "unk" or "unknown" to avoid a blank field. For multiple indications, some recommend listing the medication again with each indication as a new line or row.

For each medication and administration, record:

- Dose and Unit - amount of medication taken at one specific time, it is most often expressed in metric mass units (e.g., milliliters, milligrams) vs. the apothecary system (e.g., teaspoons, ounces).
- Route - the way by which a substance is taken into the body
- Frequency - number of times something should be administered/taken

Just as indication should not be confused with intended use, dose should not be confused with dosage, which is the broader term to encompass intended use, specific amount, route and frequency (i.e., instructions).

Diagram 14

STUDY ID HEADER: PI Name, Protocol or IRB Number, and/or Protocol Short Title

Subject Initials ___ ___ ___ **Subject ID#** ___ ___ ___-___ ___ ___ **Page** ____ **of** ____

Concomitant Medication Log

Medication/ Non-drug Therapy	Indication	Dose (per admin)	Dose Units[1]	Schedule/ Frequency[2]	Dose Form[3]	Route of Administration[4]	Start Date*	End Date	Baseline Med (Y/N)	Continuing at end of study (Y/N)

Dose Units[1]	Schedule (frequency)[2]		Dose Form[3]		Route of Administration[4]	
1 - g (gram)	1 - QD (once a day)	7 - QOM (every other mo)	1 - Tablet	9 - Gas	1 - Oral	8 - Inhalation
2 - mg (milligram)	2 - BID (twice a day)	8 - QH (every hour)	2 - Capsule	10 - Gel	2 - Topical	9 - Intravenous
3 - µg (microgram)	3 - TID (three times a day)	9 - AC (before meals)	3 - Ointment	11 - Cream	3 Subcutaneous	10-Intraperitoneal
4 - L (liter)	4 - QID (four times a day)	10 - PC (after meals)	4 - Suppository	12 - Powder	4 - Intradermal	11-Nasal
5 - mL (milliliter)	5 - QOD (every other day)	11 - PRN (as needed)	5 - Aerosol	13 - Implant	5 - Transdermal	12 - Vaginal
6 -IU (International Unit)	6 - QM (every month)	12 - Other	6 - Spray	14 - Chewable	6 - Intraocular	13 - Rectal
7 - Other			7 - Suspension	15 - Liquid	7-Intramuscular	14 - Other
			8 - Patch	99 - Other		

- *Medications taken during the study are expected to have a complete start date*
- *Prior medications that are exclusionary should have both a start and end date*

If the subject has been taking the medication for a considerable amount of time prior to the start of the study, it is acceptable to have an incomplete date. In the event that the DAY is unknown, it is recommended to enter 01 (e.g. 05-01-1965). In the event that both the day and month are unknown, enter 01 for both fields (e.g. 01-01-1965). A best estimate should be used to capture the year.

Diagram 15

ADVERSE EVENT *CTCAE or Diagnosis* * = Present at study baseline (Lilly I3Y-MC-JPCF)	GRADE 0-5	SAE? Yes or No	START DATE	STOP DATE	STATUS A = Active R = Resolved G = Grade Changed	CAUSALITY: RELATIONSHIP TO STUDY DRUG 1 = Definitely Related 2 = Probably Related 3 = Possibly Related 4 = Probably Not Related 5 = Definitely Not Related	ACTION TAKEN WITH STUDY DRUG 1 = continued same dose 2 = dose decreased 3 = IP held 4 = IP discontinued	CONMED	CONMED START DATE	CONMED STOP DATE
*Insomnia	2	No	06-Mar-2017	n/a	A	5	n/a	zolpidem (Ambien) 10 mg po HS daily	06-Mar-2017	n/a
*Constipation, intermittent	2	No	07-Mar-2017	n/a	A	5	n/a	OTC senna prn	07-Mar-2017	n/a
*Hot flashes	1	No	15-Jun-2017	n/a	A	5	n/a	n/a	n/a	n/a
*Neuropathy LUE	1	No	30-Jun-2017	n/a	A	5	n/a	n/a	n/a	n/a
*Fatigue	1	No	20-Jul-2017	n/a	A	5	n/a	n/a	n/a	n/a
*Pain, left arm & axilla	2	No	06-Nov-2017	19-Jul-2018	G	5	n/a	n/a	n/a	n/a
*Joint range of motion decreased	2	No	17-Nov-2017	19-Jul-2018	G	5	n/a	n/a	n/a	n/a
Macular rash	1	No	05-Jul-2018	07-Jul-2018	R	5	n/a	n/a	n/a	n/a
Pain, left arm & axilla	1	No	19-Jul-2018	n/a	A	5	n/a	n/a	n/a	n/a
Joint range of motion decreased	1	No	19-Jul-2018	n/a	A	5	n/a	n/a	n/a	n/a

V# - MM/DD/YYYY

Page ___ of ___

Collecting information on Con Meds considered to be unrelated to the study treatment (e.g., prophylactics) or an AE is a gray area in the regulations. The industry standard, however, is to record all medications that a subject takes in the interest of safety evaluations and potential drug interactions. Focus should be placed on collection of Con Meds related to AEs, both treatment and non-treatment related (see Diagram 15).

If subjects take a medication while on study, include complete information about the medication. If necessary, the study team should call the subject for details. For example, if the subject notes that they took an OTC medication for a headache, the recorded information should include the name and amount of medication and when it was used. This is a perfect use of the phone call summary form!

If the exact date cannot be determined, enter information as closely as possible, narrowing down to the day or the month or at least the year. If a medication has been taken for a considerable amount of time prior to a subject starting the study, it is acceptable for an exact start date to be unknown. However, a stop date is absolutely necessary for exclusionary medication (i.e., wash-out). Always indicate whether the drug remained ongoing at the time the subject went off the study.

Depending on the clinical research site and Sponsor, the Con Med Log may have a field for the signature and initials of the person completing the form.

The most common findings on review of Con Med Logs by monitors/auditors are:

- Baseline/Historical medications not captured
- Medications, especially OTC, missing from log
- Unknown indications
- Incomplete start/stop dates
- Vague unit, route, frequency
- Information captured does not match source
- Dose out of range/nonsensical
- Medications not confirmed as ongoing at end of study

The Adverse Event Log

The Adverse Events (AE) Log is both vitally important and very often misunderstood and not completed appropriately. Unlike other logs, specific FDA regulations and GCP guidelines speak about the collection and documentation of AEs that allows for reporting to authorities. These logs facilitate the capture of data that is then used to meet the regulatory requirements and most importantly, monitor the safety of subjects.

AE Logs (see Diagrams 16 and 17) are the dedicated space for recording AEs that may be documented in multiple places throughout the subjects' records (e.g., physician notes, nursing / coordinator notes, lab or procedure reports, subject diaries, phone calls or emails). Through careful documentation, it can be determined whether conditions, including those present at baseline, are worsening and whether events across the subject and/or study are becoming more frequent, severe, or prolonged.

The protocol will determine when official AE collection begins. Some protocols will indicate that collection begins at consent and continues throughout study participation. Others will call events that occur between consent and administration of IP "Pre-Treatment Events," with AE collection coinciding with first IP administration. This is an important delineation, as evidenced in a study conducted at UAMS, in which AE documentation began at consent. There was a significant delay in the study procedure, so for many months, the study team was forced to record all AEs, including surgeries and hospitalizations unrelated to study participation.

Diagram 16

IRB#:
PI:
Study Title:

Subject ID:_____

ADVERSE EVENTS

Description of Adverse Event	Start Date	Stop Date	Severity Grade	Relationship to Study Drug	Action Taken	Outcome	Expected?	Serious*?	PI Initial and Date

Severity Grade	Relationship to Study Drug:	Action Taken	Outcome	Expected	Serious
1=Mild 2=Moderate 3=Severe 4=Life-threatening/urgent intervention indicated/ disabling 5=Death related to AE	1=Not Related 2=Unlikely Related 3=Possibly Related 4=Probably Related 5=Definitely Related	1 = No change (continued same dose) 2 = Dose Decreased 3 = Drug held 4 = Drug discontinued 5 = Other	1 = Recovered/resolved, no sequelea 2 = Recovered/resolved with sequelea 3 = Recovering/resolving 4 = Not recovered/resolved 5 = Unknown 6 = Death/Fatal	1 = Yes 2 = No	1 = Yes 2 = No **Complete SAE CRF**

*Serious = death, life-threatening, requires hospitalization (initial or prolonged), results in disability or permanent damage, results in congenital abnormality birth defect, or other serious important medical event (based on medical judgment)

V# - MM/DD/YYYY

Page _____ of _____

Diagram 17

ADVERSE EVENTS

Description of Adverse Event	Start Date	Stop Date	Severity Grade	Relationship to Device	Action Taken	Outcome	Expected?	Serious*?	PI Initial and Date

Severity Grade	Relationship to Device	Action Taken	Outcome	Expected	Serious
1=Mild 2=Moderate 3=Severe 4=Life-threatening/urgent intervention indicated/ disabling 5=Death related to AE	1=Not Related 2=Unlikely Related 3=Possibly Related 4=Probably Related 5=Definitely Related	1 = No change 2 = Device Stopped Temporarily 3 = Device Stopped Permanently 5 = Other	1 = Recovered/resolved, no sequelea 2 = Recovered/resolved with sequelea 3 = Recovering/resolving 4 = Not recovered/resolved 5 = Unknown 6 = Death/Fatal	1 = Yes 2 = No	1 = Yes 2 = No **Complete SAE CRF**

*Serious = death, life-threatening, requires hospitalization (initial or prolonged), results in disability or permanent damage, results in congenital abnormali birth defect, requires intervention to present permanent impairment of damage, or other serious important medical event (based on medical judgment)

V# - MM/DD/YYYY

Page _____ of _____

If not otherwise specified in the protocol and/or ICF, consider subjects to still be on study during their final study visit, meaning that events noted at this time should be added to the log for assessment. Further follow-up would depend on the seriousness and relatedness of the AE.

When documenting the AE description, report a diagnosis rather than a list of symptoms, if possible (e.g., upper respiratory infection vs. runny nose, coughing and shortness of breath; C. Diff vs. diarrhea, fever and abdominal pain). If you can only report individual symptoms, that is acceptable, as long as you record final diagnosis once determined. See Table 5 for an overview of the documentation of AE start/stop dates and description.

Depending on the protocol, the clinical research site and the Sponsor, the study team may not be required to report abnormal laboratory values unless they are deemed to be "Clinically Significant". As with all research, "not documented, not done," so, the clinical investigator or designee should review the lab report/values, record their assessment and add this source documentation to subject files.

As discussed, our clinical research sites use the Medical History CRF exclusively to document baseline conditions at screening, however, other clinical research sites add these baseline events to AE Logs as well, allowing for grading/assessment for future comparisons. Each clinical research site should comply with the procedures indicated by the Sponsor.

If baseline events worsen during the study, best practice is to add the event to the AE Log as a new event with the start date as the date severity increased. This also applies to AEs that worsen during the study. Add the end date for the previous grade and create a new event with the start date as the date the condition worsened. Always enter AEs to the highest possible level of detail or granularity.

When determining severity of an event, it is important to remember that "severe" does **not** equal "serious". Severity is equivalent to intensity or grade, while seriousness, based on outcome of the event or the action taken, is the driver behind reporting to the Sponsor and the FDA.

The assignment of "serious" is usually associated with events that threaten life or functioning. For example, visiting the emergency department for a laceration, receiving stitches, and going home might be severe in terms of intensity/grade, however, it does not meet the threshold for a "serious" event. If, however, that laceration also came with fractures and significant blood loss requiring surgery and an overnight hospital stay, this event would become serious

TABLE 5
The Adverse Event Log (Start-Stop-Description)

- Follow AE collection period outlined in the protocol
- Start of AE collection will either begin at:
  - Consent
    or
  - IP administration
    - Some studies define a Pre-Treatment Event as: *"Any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study [treatment]."*
- Final AE collection will continue through the end of the study period as stated in the protocol
  - Final study visit is considered on study, so events discovered during this visit should be documented
  - If event is stable and/or unrelated, no further follow-up is required
- Description of AE:
  - Document the diagnosis or syndrome, not the sign or symptom
  - If the constellation of signs and/or symptoms cannot be characterized as a single diagnosis or syndrome, document the information currently available
  - If diagnosis is subsequently established, report as follow-up
  - Use consistent terminology, based on the protocol
  - Document abnormal laboratory results if clinically significant (some studies), along with evidence of clinical investigator review, assessment and determination; add to subject file/source

and should be reported to the Sponsor.

In terms of safety reporting (21 CFR 312.32(a)), FDA defines SAEs as those that, in the view of either the Investigator or Sponsor, result in any of the following outcomes:

- Death
- Place the subject at immediate risk of death (i.e., life-threatening)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect **or**
- Important medical events (as determined by clinician) that may jeopardize the subject and may require medical or surgical intervention to prevent outcomes listed above

Table 6 provides an overview of AE severity.

In terms of grading, non-oncology and device studies often use a 5-point mild, moderate, severe, life-threatening, death scale, based on signs, symptoms, and the effect on activities of daily living (ADLs).

For oncology studies, UAMS most often utilizes the NCI Common Terminology Criteria for Adverse Events (CTCAE) grading scale, which breaks down conditions by system organ class, term and grade, stratified from least to most severe (i.e., Grades 1–5).

All AEs must be assessed for their relationship to study

TABLE 6
AE Severity

- Severity: *"Intensity of an event; based on investigator's clinical judgement"*
- Grading scales:
  - Non-oncology and device studies often use a mild, moderate, severe, life-threatening, death scale, based on signs and symptoms and effect on activities of daily living (ADLs)
- Grades:
  - Grade 1: Mild:
    - Easily tolerated, minimal discomfort, not interfering with ADLs
  - Grade 2: Moderate:
    - Sufficiently discomforting to interfere with ADLs
  - Grade 3: Severe:
    - Prevents normal ADLs
  - Grade 4: Life-Threatening:
    - Specific parameters according to the organ system involved
  - Grade 5: Death
- Oncology studies often use the NCI Common Terminology Criteria for Adverse Events (CTCAE):
  - System Organ Class
  - Term
  - Grade
    - Grade 1: Asymptomatic or mild symptoms; no intervention indicated
    - Grade 2: Minimal, local or non-invasive intervention indicated
    - Grade 3: Medically significant but not immediately life-threatening
    - Grade 4: Life-threatening consequences; urgent intervention indicated
    - Grade 5: Death

treatment (Table 7). Relatedness is an assessment regarding the causal relationship between the study intervention and/or IP and an AE. When determining relatedness or causality, a qualified, delegated and trained clinician should ask the following questions:

- Was the condition present at baseline and can it be explained by the underlying disease?
- Is the event a known reaction documented in the Investigator Brochure (IB), protocol, or ICF?
- 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?
- Can any other potential causes explain the condition?

It is also helpful to refer to the Bradford Hill Criteria for Causation.

The most common 'Relationship' categories are:

- Definitely (clearly) related
- Probably (likely) related
- Possibly (may be) related
- Unlikely (doubtfully) related
- Unrelated (not) related

Choices for 'Action Taken' **regarding study intervention,** depending on the log used, include:

- No change/None
- Regimen increased/ decreased
- Regimen held
- Drug/Device discontinued and re-introduced
- Drug/Device stopped permanently

TABLE 7
Relationship of AEs to Study Treatment

- Relationship and causality: *"Relatedness is a term intended to indicate that a determination has been made that event had a reasonable possibility of being related to exposure to the product."*
  - Questions to ask when assessing causality:
    - Was the AE present at baseline assessment or in recent medical history?
    - Can the AE be reasonably explained by subject's clinical disease status?
    - Is the AE a known reaction of the intervention?
    - Is the AE similar to others listed in protocol, consent, or safety documents?
    - Has the AE occurred before in this study?
    - Is the AE reasonably temporally related to the intervention?
    - Does the AE improve or disappear when intervention is discontinued; re-tested?
    - Are there other potential causes for the AE?
- Relationship categories:
  - Definitely Related:
    - The AE is clearly related to study treatment
    - Onset occurs in a plausible time relationship to study treatment and other contributing factors can be ruled out
  - Probably Related:
    - The AE is likely related to study treatment
    - Onset occurs in a plausible time relationship to study treatment and the influence of other contributing factors is unlikely
  - Possibly Related:
    - The AE may be related to study treatment
    - Onset occurs in a plausible time relationship to study treatment; though, other factors may have contributed to it
  - Unlikely Related:
    - The AE is doubtfully related to study treatment
    - Onset does not occur in a plausible time relationship to study treatment, and other contributing factors are likely
  - Unrelated:
    - The AE is clearly NOT related to study treatment
    - There is no causal relationship between the AE and the study treatment

- Concomitant medication treatment
- Medical intervention
- Hospitalization
- Other

Similarly, 'Outcome' categories also depend on the log used, including:

- Subject recovered and the event resolved with minor, major, or no aftereffects
- Event is ongoing or recovering (based on severity)
- Subject did not recover
- Event resulted in death
- Outcome is unknown

Expected AEs are those that may be anticipated as documented in Reference Safety Information (RSI) such as the protocol, ICF, IB, package insert, or device manual. Expectedness is **not** determined by what could happen in the regular course of the treated disease. For example, in an oncology study, nausea, vomiting, and diarrhea may be expected as side effects from the chemotherapy but should not be labeled as "expected" AEs **unless these symptoms are thought to be IP-related.**

Unexpected events would not have been documented in RSI or their nature, specificity, severity, or outcome is not consistent with RSI. Unless the event is mentioned in the RSI, it is most likely to be classified as unexpected. Bottom line in determining expectedness: Focus on the treatment, **not** the disease.

UAMS requires study teams to use AE Logs that allow for clinical investigator oversight to be confirmed with signature and/or initial. The clinical investigator should be periodically reviewing the log for trends over time to look for systemic problems with the study and/or IP.

The Deviation Log

A written protocol is at the heart of every scientific investigation, especially in the context of clinical trials. The importance of following the protocol can be seen by referring to the outcome of FDA Bioresearch Monitoring (BIMO) program inspections, in which lack of protocol compliance is consistently the number one finding. It is important to note, although "**protocol** deviation" is common terminology, deviations can involve events that fall outside the confines of the protocol.

Deviations, whether intentional or unintentional, big or small, affect the strength of the results, the data integrity (e.g., completeness and accuracy) and possibly the safety of the subjects. It is therefore natural that tracking, recording and reporting deviations is a major concern in clinical development. Ongoing and repeated deviations could signify the need for protocol updates, logistical / workflow changes or additional staff training.

Deviations are mentioned in FDA regulations, guidance documents and GCP guidelines. See FDA Guidance for Industry E3 Structure and Content of Clinical Study Reports Questions and Answers (R1):

Deviation: *"Any change, divergence, or departure from the study design or procedures defined in the approved protocol."*

Violations (aka "Important Protocol Deviation") may be considered a 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.

The content of the Deviation Log (**see Diagrams 18 and 19 on next page**) depends upon who is providing the document. Most often, logs include fields for subject ID, dates the deviation occurred and was identified, a description and reporting (to whom and when). Another field commonly seen is "Description of Corrective Action". The author encourages the inclusion of a number field, which can then be cross-referenced on AE Logs, IRB submissions, monitoring reports, and other study-related documentation.

Less common contents for Deviations Logs may be fields for protocol version (helpful when determining whether a missed lab or test was indeed required at that time point) and whether the deviation resulted in an AE or subject drop-out (helpful when tracking safety, outcomes and Unanticipated Problems Involving Risks to Subjects or Others [UPIRTSOs]).

Often, codes are used to record the type of deviation, with provided logs having built-in legends, allowing space for additional codes specific to the clinical research site or study.

Table 8 (on page 58) provides an overview of the Deviation Log.

Common types of deviations are:

- Informed consent/ Randomization
- Eligibility
- Study procedures/Visit schedules
- Safety
- Prohibited medications or therapy

- Other, to be specified in the log

Common codes for "Informed Consent/Randomization" are:

- Failing to obtain or document informed consent prior to initiation of study procedures
- ICF used was not the current IRB-approved version
- Non-delegated staff member performs the informed consent process
- ICF is not signed and/or dated by subject
- ICF is not signed and/or dated by staff member (if required)
- Failing to provide subject with a copy of the ICF
- ICF is missing from files
- Other, to be specified in the log

Common codes for "Eligibility" are:

- Subject did not meet eligibility criteria(on)
- Randomization of an ineligible subject
- Subject randomized prior to completing baseline assessments
- Randomization and/or treatment of subject prior to IRB approval of protocol
- Other, to be specified in the log

Common codes for "Study procedures/Visit schedules" are:

- Subject received the wrong treatment
- Conducting a study visit outside of the required timeframe
- Missed assessment or visit
- Performing a study procedure not approved by the IRB
- Failing to perform a required test
- Exceeding approved enrollment numbers

Diagram 18

IRB#:
PI:
Study Title:

DEVIATION LOG

This log is to be used to record all deviations and violations, regardless of reporting requirements. Report deviation/violations that are unanticipated/ unexpected, related to the research, and that involve new or increased risk to subjects or others (UPIRTSO) to the IRB within 10 days of the event. Deviations/ Violations leading to events that are life-threatening or that have resulted in death are to be reported immediately to the IRB. All others may be reported at Continuing Review.

Subject ID (or N/A)	Date of Deviation/ Violation	Date Identified	Description of Deviation/Violation	Dev. Type*	Corrective Action(s)	Increased Risk to Subject or Others? (Y/N)	Expected? (Y/N)	Date Reported to IRB	PI Initials/ Date

*Deviation Type: (A-) See codes below – enter the appropriate deviation code from the list.

A – Consent Procedures
B – Inclusion/ Exclusion Criteria
C – Randomization Procedures
D – Laboratory Assessments/ Procedures
E – Study Procedures
F – Visit Schedule
G – Investigational Product
I – Other (specify): _____

V# - MM/DD/YYYY

Page _____ of _____

Diagram 19

Protocol ID/Number:						Site Name/Number:			
Protocol Title (Abbreviated):									
Principal Investigator:						Page number [1]:			
Ref No.	**Subject ID**	**Date of Deviation**	**Date Identified**	**Deviation Description**	**Dev. Type [2]**	**Resulted in Adverse Event?**	**Did Subject Continue in Study?**	**Meets IRB Reporting Req. (Yes/No)**	**IRB Reporting Date**
1									
2									
3									
4									
5									
6									
7									

Investigator Signature: _____ Date: _____

V# - MM/DD/YYYY

Page ___ of ___

- Implementing unapproved recruitment procedures
- Other, to be specified in the log

Common codes for "Safety" are:

- Dispensing or dosing error for study medication
- Prescribed dosing outside protocol guidelines
- AE/SAE/UADE not reported to the IRB within protocol-mandated timeframe
- Failing to report UPIRTSO to the IRB and Sponsor (if applicable)
- Other, to be specified in the log

Common codes for "Prohibited medications or therapy" are:

- Use of unallowed concomitant medications/ treatments
- Other, to be specified in the log

As with AE Logs, UAMS asks that study teams use Deviation Logs that allow the clinical investigator to confirm oversight with their signatures and initials. The clinical investigator should periodically review deviations to track and trend events over time to look for systemic problems with the study.

Good Documentation Practice
Good Documentation Practice (GDocP) is an important concept with which to be familiar, as mistakes are bound to be made during the transcription process.

Among other best practices, GDocP describes how to properly correct errors. First, the person recording data should correct the error. If this is not possible, the supervisor should make the correction (if supporting data is available) or Sponsor procedures should be followed.

Steps include:

- Single line through incorrect entry (i.e., no write overs, no scribbling) to permit reading of original information
- Write correct entry near the error
- Record concise explanation for correction, if necessary (e.g., date/spelling error, late entry)
- Initial and date correction
- Ensure that there is a clear audit trail for all changes/ revisions

TABLE 8
Deviation Log Contents

- Common contents:
  - Reference number
  - Subject ID
  - Date of deviation
  - Date identified
  - Deviation description
  - Description of corrective action
  - Reporting to Sponsor and IRB
- Less common contents:
  - Protocol version
  - Whether the deviation resulted in an AE
  - Whether the subject continued in the study
  - Impact:
    - Study validity
    - Safety
    - Outcome measures
    - No Impact
- Deviation Log codes include those related to:
  - Informed consent procedures
  - Randomization procedures
  - Eligibility (Inclusion/Exclusion criteria)
  - Study procedures
  - Visit schedules / Intervals
  - Drug/Device regimen
  - Reporting of SAEs/UPIRTSOs/UADEs
  - Prohibited concomitant medication/Therapy
  - Other

Remember that the ALCOA+ principles should always be followed!

In closing, ***"It is important to understand that proper documentation of a clinical research trial is not just a means of organized filing for a multiplying mound of paperwork. It is a tangible trail that tells the story of the trial from conception to completion, reflecting adherence to applicable regulations and demonstrating trial integrity through transparency."***

— Maddock & York, 2012

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