Welcome to Online Training for Clinical Research Coordinators

Role of the Research Coordinator

Safety for the Research Subject: Adverse Event Reporting

May 2016

Important Note

For this training, be sure you have completed the course entitled CFR Role Adverse Event Definitions and Documentation.

Objectives

- Understand that reporting adverse events is important to both a study hypothesis and is key to keeping subjects safe while on a clinical trial
- Know the various time points for reporting adverse events
- Identify when an adverse event requires immediate reporting to the Sponsor
- Know the various agencies involved in receiving immediate or expedited reports

Subject Safety

- Protecting safety is a Federal mandate requiring investigators to report certain adverse events (see investigator commitments on FDA form 1572).
- Protecting safety is an institutional mandate from the UCLA IRB.
- Safety is often one of the protocol objectives when testing new therapies so adverse event data must be collected and reviewed by the Principal Investigator.
- Stopping rules are often clearly identified in terms of types and frequency of SAE's; the risk versus benefit ratio is a key variable on whether enrollment to a study can continue.

Subject Safety

- **All** adverse events that the subject experiences must be assessed and documented in case report form supplied by the sponsor, or entered into the correct page of an electronic clinical trial management system…or both. This will determine later analysis.

- **Unexpected** adverse events and/or **serious adverse events** determined by the investigator to be related to study drug will have additional reporting requirements to the study's sponsor, the FDA if the investigator is the sponsor and holds the Investigational New Drug (IND) approval, the institutional review board (UCLA IRB and possibly other agencies involved in sponsoring the study or collecting safety information for the trial. 21 CFR 312.32

Subject Safety

What are the responsibilities of the research coordinator in reporting adverse events for the study they are managing?

1. Collect pertinent clinical source documentation
   **Principal Investigator is responsible for all assessments and must sign forms as required.

2. Begin completing the case report form or entering into electronic database
3. Read the protocol and know who would be receiving an expedited report of adverse events that are related, unexpected and/or serious:
   - Investigator holds IND – FDA MedWatch 3500a
   - Pharmaceutical/Industry-Notify sponsor with report or phone call as required by protocol
   - Cancer center cooperative groups- AdEERS online
   - UCLA IRB iRISs form

4. Deadlines for reports vary depending on the agency. Meet deadlines to remain compliant and avoid violations.

Subject Safety

after a subject is off-study….

- Reporting requirements for newly identified adverse events or serious adverse events usually exist for 30 days after the end of protocol treatment. However, whenever an investigator believes the adverse event is related, unknown and is considered serious, he/she should report it even if after the 30 days.
- For patient safety, all ongoing adverse events determined to be related to research participation, is usually followed until it is resolved or patient begins another therapy.

Subject Safety

- Reporting timelines and conditions for reporting can vary between agencies so **keep a tracking log**, examples on next two pages.
- **Before the study begins**, it is the responsibility of the research coordinator to read this section in the protocol, set up a checklist for who to report to and what forms are needed.
- Reporting is so important that missing deadlines become a protocol violation for the Principal Investigator.

SAE Reporting to IRB Tracker

Project Title:			Principal Investigator:			
			IRB Project #:			
Patient Number or Identifier	Serious Adverse Event (SAE)	Date of SAE	Date Research Team Learned of Event	Date Reported to Sponsor (if applicable)	Date Reported to IRB	IRB Response Received (Y/N)

Unanticipated/Unexpected Adverse Event Tracker

UNANTICIPATED PROBLEMS TRACKING LOG

Study Title:

Principal Investigator: **Study Coordinator:**

	Subject ID	Start Date of Event	Description of Event	Serious	Expected	Related	"Is this a UP involving risks to subjects or others?	CPHS Communication	
								Submission	Outcome
1				☐ Serious ☐ Not serious	☐ Expected ☐ Unexpected	☐ Possibly related ☐ Unrelated	☐ Yes, this is a UP ☐ No, this is not a UP		
2				☐ Serious ☐ Not serious	☐ Expected ☐ Unexpected	☐ Possibly related ☐ Unrelated	☐ Yes, this is a UP ☐ No, this is not a UP		
3				☐ Serious ☐ Not serious	☐ Expected ☐ Unexpected	☐ Possibly related ☐ Unrelated	☐ Yes, this is a UP ☐ No, this is not a UP		

- Those Investigators who are also the Sponsor and hold an IND – the CRC will assist in preparing the reporting forms to the FDA based on the following guidelines.

- These guidelines also apply to industry sponsors of drug trials when they hold an IND or IDE.

FDA Reporting for Sponsors and Investigator-Sponsors of an IND - 21CFR 312.32

What and When to Report Serious Adverse Events (SAE)

- Any **unexpected (unanticipated) SAE** defined as **death or life-threatening** and is **related** to study drug:
  - Call or fax a written Medwatch 3500a to the FDA division that is responsible for the IND **within 7 days** upon receiving the information about the event.
- Any **other event defined as an SAE** and unexpected and is **related** to study drug:
  - **Mail a written Medwatch 3500a to the FDA division responsible for the IND within 15 days upon receiving the information about the event.**

FDA Reporting for Sponsors of an IND

21CFR 312.32

Instructions for completing FDA 3500a are found at the following website:

http://www.fda.gov/safety/medwatch/howtoreport/downloadforms/ucm149238.htm

FDA Reporting for Sponsors of an IND

21CFR 312.32

- ✓ Reporting directly to the FDA is the responsibility of the party otherwise known as ‘sponsor’ of the IND.
- ✓ In industry trials or trials sponsored by the NCI/cooperative group, they are the sponsor. You report the reportable SAE to them on a timeline usually described in the protocol, usually within 24 hours from the time the investigator was notified of the event. That gives their safety office time to report to the FDA when needed.
- ✓ When the principal investigator files an IND and thereby becomes a sponsor, it is his/her responsibility to report directly to FDA using the information on the previous slide.

FDA Reporting for Sponsors of an IND

21CFR 312.32

MedWatch as described is used for drugs, devices and most biologics.

- ✓ Use the VAERS form (available at http://www.vaers.org) to report vaccine adverse events.

- ✓ Gene Therapy IND Sponsor / Principal Investigator Letter from the FDA (available at http://www.fda.gov/CbER/ltr/gt110599.htm)

NCI CTEP

Adverse Event Reporting Requirements

http://ctep.cancer.gov/reporting/adeers.html

- Adverse Event Expedited Reporting System (AdEERS) ONLINE
- NCI's web-based system for submitting expedited reports for serious and/or unexpected events forwarded to designated recipients and the NCI for all trials using a NCI-sponsored investigational agent.
- Each NCI protocol, will have a table which reporting timelines based on the severity of the event, and its relatedness to the study product.

Human Research Protection Program (HRPP)
Committee on Human Research (IRB)
Internal SAE/AE 10-day report

Internal also known as On-site* adverse events defined as follows:

- Meet the definition of both unexpected and an SAE
- Meet the causality definition of possible, probable or related
- Happen during the course of Gene Therapy research
- Result from an overdose of study medication
- Result from a protocol violation
- Causes subject to withdraw from study participation
- Change the risk/benefit ratio as written in the protocol
- All deaths occurring in interventional studies (while the study remains open) must be reported regardless of study relationship

*On site refers to subjects who are enrolled at a UCLA facility or facility under the review of the UCLA IRB.

Committee on Human Research (IRB) Internal SAE/AE 10-day report

External also known as **Off-site*** adverse events defined as follows:

- Changes the risk/benefit ratio.
- Unexpected event that is not listed in the consent form or Investigator's Brochure or protocol.
    - Triggers modifications to protocol, consent form, or IB.
- Can be SAE or unexpected AE significant enough to trigger modifications.
- Included as '**off-site**' would be IND safety letters sent to the PI by the sponsor/manufacturer of the study drug, reported to them for studies being conducted throughout the US and outside the USA for global studies.

***Off-site** refers to subjects who are enrolled in a UCLA study but the site is also being reviewed by another IRB.

Reporting to the UCLA IRB
Take home points for 10 day reports

Within 10 working days – From the time the investigator becomes aware of an AE meeting any of the following criteria:

1. On-site occurring AE that meets the definition of a Serious (SAE) or an Unexpected AE and is related, probably related, or possibly related to the study drug/device or research participation.
2. **Some additional On-site events such as overdose, gene therapy study, protocol violation, changes risk/benefit ratio, causes patient to withdraw.**
3. Off-site occurring AE that results in a change to the study risk or requires modifications to the study protocol, informed consent or investigator's brochure document.
4. All 10-day reports summarized on the iRIS IRB renewal application.

Post Approval Reporting Requirements can be found here

Reporting to the UCLA IRB Using the AE Summary Log

At the Time of Renewal -All AEs that do not meet the 10-day reporting criteria are required to be reported to IRB by sponsor and summarized in log. Actual reports are not required to be submitted.

- Death determined to be unrelated to research participation in an interventional study is summarized in log.
- It is the responsibility of the investigator to assess causality and make the determination that the subject death is unrelated to study participation.

Reporting to the UCLA IRB

Use forms found on the HRPP website

http://www.research.UCLA.edu/IRB/Guide/IRBA_AE1pg.asp

What Adverse Events Not to Report to UCLA IRB

1. Subject deaths occurring in non-interventional studies (i.e., surveys, interviews and observational-only studies) do not need to be reported.

2. Any other AE related to research participation (i.e., AE that is both expected and non-serious).

3. All off-site occurring AEs that do not change the consent, protocol, or risk-benefit ratio.

4. All AE's clearly not related to Research, except death on an intervention study

Adverse Events Reporting at UCLA

Other UCLA Departments that require extra reporting of expedited, identified SAEs and unanticipated AEs

- Oncore 'e-research' is a real time database that requires AE and SAE entry, and reporting for some programs utilizing this for data entry and reports.
  - Enter adverse events as instructed by your program.
- If managing your study in these departments, they will also want to know what events get reported to IRB.
  - General Clinical Research Center (GCRC)
  - Pediatric Clinical Research Center (PCRC)
  - Biological Safety Committee (BSC)

Data and Safety Monitoring Plans (DSMP)

NIH Requirement (10/00) for all human subject “interventional” studies.

- Principal Investigator is responsible for including this DSMP in any grant going to NIH and any human subject clinical trial protocol.
- This is required for studies that frequently are not an FDA protocol but still enrolls human subjects.
- Data Safety Monitoring Board (DSMB) is required for all Phase III by law due to the large number of subjects who will be enrolled.
  - Members of a DSMB are knowledgeable in the science or disease but are independent of the protocol outcomes.

Elements of the DSMP Help to Ensure Patient Safety

- Description of anticipated adverse events and their frequency
- Plan for AE reporting and procedures for communicating to the local IRB and federal regulatory authorities when applicable.
- Safety Risk Assessment and description of who will perform the safety reviews and with what frequency
  - Monitoring plan using staff members or other investigators because there are no industry monitors for this type of study.
  - Interim analysis by DSMB to determine risk versus benefit and data to analyze the hypothesis are in good shape and do not indicate a compromise to subject safety.

Takeaways……

The Principal Investigator is ultimately responsible for reporting adverse events to the sponsor and the IRB.

Understand and Follow protocol-specific reporting requirements for immediate and ongoing adverse events

Understand and Follow the protocol Sponsor reporting requirements for immediate and ongoing adverse events

Know and Follow the Federal regulations governing Safety reporting on human subject clinical trials

Understand and Follow the UCLA IRB requirements for reporting immediate and unexpected adverse events

It's the Law! And it protects human subjects participating in clinical trials!