Community Healthcare System

The Review

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Reporting Adverse Events and Protocol Deviations

IRB Policy 11: Internal Adverse Event, Protocol Deviation/Violation, Unanticipated Events: Reporting and Review

The Code of Federal Regulations requires the "prompt reporting of any unanticipated problems involving risks to subjects or others". (CFR 21 §312 and §812, CFR 45 §46)

Causality refers to the probability that the event was caused or occurred as a direct result of participating in a study. When in doubt, define the study intervention, i.e., data collection, test the safety of a new drug or device, to guide the decision.

	Definition	Example – Drug	Example - Device
Unrelated	Event ***clearly not related*** to the investigational agent	The subject is admitted to ED with a broken ankle and just happens to be neutropenic. The admission for a broken ankle is the reportable event and is clearly not related to the study medication. The neutropenia should be reported separately.	The subject is admitted to ED with a broken ankle and just happens to have had an investigational peripheral stent inserted into the opposite leg the week before. The admission for a broken ankle is the reportable event and is clearly not related to the study intervention.
Possible	Event ***may be related*** to the investigational agent	Neutropenia is a symptom of the disease process but it is also a possible side effect of the investigational drug. The investigator would need to determine if the subject was neutropenic prior to their first dose of study drug.	The subject is admitted to the ED with pain to the leg where the investigational peripheral stent was inserted one week before. The stent is intact on x-ray and distal pulses remain good. Given the fact that the stent is intact and the subject has a history of severe PVD, the pain may be related to his history and not to the investigational stent.
Probable	Event is ***likely related*** to the investigational agent	Neutropenia is a symptom of the disease process but it is also a possible side effect of the investigational drug.	The subject experiences clot formation near the lesion where the stent under investigation was placed immediately

		The subject was not neutropenic prior to receiving the study drug.	following the percutaneous procedure. This is a known potential adverse event or risk of a percutaneous procedure with stent placement. The study, however, is testing the performance of the stent during deployment. The subject was scheduled to undergo this procedure with that particular stent even if he was not enrolled in the study. The clot could be related to the non-investigative procedure or to the insertion of the stent under investigation. Therefore, it is likely related to the investigative agent.
Definite	Event is ***clearly related*** to the investigational agent	The neutropenia was the direct result of having taken the investigational drug. The subject may have an illness with numerous symptoms but the list of possibilities did not include neutropenia. The list of possible side effects from the study drug included neutropenia.	During the procedure, the stent under investigation failed to deploy and had to be surgically removed. The event is clearly related.

A Registry Study does not "fit" neatly into any of the previous examples. The investigator must understand that the "intervention" for the registry is ***to collect data*** regarding the effects of a drug or device. In a registry study, a breach of confidentiality during the collection and reporting of PHI would "definitely" be related to the study but the fracture of the stent would be "unrelated" since the purpose of the registry was to collect data on the use of the stent not to test the investigational stent.

Event Severity Classification refers to the magnitude of the event and whether or not the investigator expected the event to occur as a direct result of their participation in the study. In other words, was the event identified as expected in the current IRB approved research protocol or consent as a potential adverse event? The event is considered *serious* if it is fatal or life threatening; requires prolonged hospitalization; produces a disability or congenital anomaly or may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in the consent. The event is considered to be *moderate* if it requires medical evaluation and /or other medical treatment.

Protocol Deviation: An unintended or unapproved change to an IRB approved protocol. It generally does not have a significant effect on the subject's rights, safety, or welfare, or on the integrity of the resultant data. Example: Obtaining a protocol required test one day outside the acceptable window.

Protocol Violation: Those events that were caused by or could have been prevented by the investigator and which materially affect the study results. Violations generally do affect the subject's rights, safety, or welfare, or on the integrity of the resultant data. Example: Enrolling a subject who did not qualify for the study without obtaining the sponsor's permission or repeatedly failing to obtain a protocol required test.

Protocol Deviation/Violation reporting: Tips to improve communication of deviations and violations include:

1. Provide a statement of the facts as to what deviation/violation occurred. Do not include adjectives such as "inadvertently", etc. Example: the subject did not receive an ABI prior to discharge.
2. Provide an explanation as to what was done to remedy the deviation. Be as specific as possible. Example: The subject was contacted within 24 hours and the ABI was completed at the research site.
3. Provide as much detail as possible regarding any action taken to ensure that similar deviations will not occur in the future. Example: Implemented a checks and balance system within the department. Better: Implemented a system in Outlook to notify the regulatory staff of date to submit a request to renew a protocol. Reminders appear as a "Red/Important" category on their calendar.
4. Carefully consider the safety of the subject before replying that the deviation did not affect their safety. A missed appointment or test may appear to have only a minor detrimental effect on the subject however 1) they were assured of receiving this care during the consent process and 2) the protocol demands that the investigator follow the protocol exactly as it is written for a reason which is subject safety.
5. Some deviations do affect the integrity of the data. An appointment that was scheduled one week out of the window probably does not affect the overall data for the study. A test or procedure that is missed, inadequate consent discussion, enrolling a subject who does not fit the inclusion/exclusion criteria, or substituting a different piece of equipment than the one called for in the protocol does affect the data and may be grounds to exclude all the data previously obtained about that subject.

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A Hallmark Holiday? The second Friday in November has been designated as "Human Subjects Protections Day"!