Product Accountability *in Clinical Trials:* THE RESPONSIBILITY TO KNOW YOUR REGS

Introduction

In order for a new medical product to reach patients it must first be proven safe and effective and then be approved for use by the governing regulatory body. Clinical trials are the vehicle to bring these innovative technologies to patients and evaluate them in support of regulatory approval. Unless a product is approved under the appropriate regulations for a specific use, it cannot be commercialized for that indication. In clinical research the products are still investigational, and even in a hospital setting, these products are treated differently than those items used in general medical practice. After all, using an unapproved product that is not fully vetted for safety and efficacy outside of the trial protocol requirements could result in risks to patients.

Materials that are unaccounted for, improperly disposed of, or inadequately stored could present potential hazards. Per federal regulations, 100% of investigative products must be accounted for at all times so they are not used for an incorrect indication, in an incorrect way, or by someone who has not been properly trained in its use. **Failure to account for and manage study materials could affect the acceptability of the data collected from a trial, or even termination of a study completely.** Both sponsors and investigators have responsibility over device accountability and can be held accountable if problems are identified.

In a clinical investigation the Sponsor entrusts the Investigator and research site staff to closely control all investigational products and maintain patient safety. Referring to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP), this specifically relates to complete and accurate product accountability. Three essential concepts are:

Accountability:

"Subject to the obligation to report, explain, or justify something; responsible; answerable."[1]

- **The investigator is responsible for the investigational product accountability at the trial site. (ICH GCP 4.6.1)**

Storage:

"A supply or stock of something, especially one for future use."[2]

- The investigational product should be stored as specified by the sponsor and in accordance with the applicable regulatory requirements. (ICH GCP 4.6.4)

Use:

"To employ for some purpose; put into service; make use of."[3]

- The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol. (ICH GCP 4.6.5-6)

The Food and Drug Administration (FDA) regulations also require that the Investigator and Sponsor each maintain control of study products. Knowing the regulations governing who is responsible for what tasks and what documentation is required by the FDA for full accountability is a key aspect of a clinical study. **Taking steps to ensure proper accounting can provide reassurance of patient protection and enhance data integrity.**

What are the Consequences of Incomplete or Improper Product Accountability?

Improper or incomplete product accountability may pose a risk to study subjects, first and foremost. Full accountability of investigational devices in a clinical trial is routinely checked by FDA during an inspection; **failure by a Sponsor or Investigator to maintain accurate, complete and current records related to the receipt, use and disposition of investigational products is frequently cited in Form 483s and warning letters issued by the FDA.** A review of FDA warning letters published on their website will quickly identify some of the shortcomings of sponsors and investigators in this area. Below are some examples of warning letters issued as a result of an inspection where findings violated the Code of Federal Regulations.

Sponsor Warning Letters

- *Failure to maintain adequate records showing the receipt, shipment or other disposition of an investigational drug [21 CFR 312.57(1)]:* There was no documentation of the distribution, return of product from the study subjects and final disposition of the drug.
- *Failure to ship investigational devices only to qualified investigators participating in the investigation [21 CFR 812.43 (b)]:* Replacement parts for the investigational device were shipped to persons other than qualified investigators, namely the subjects. The device shipping log shows replacement parts were sent to the subjects' homes.

PI Warning Letters

- *Failure to maintain adequate and accurate case histories that record the disposition of the drug [21 CFR 312.62 (a)]:* Study subjects were distributed study medication kits not assigned to them by the randomization.
- *Failure to control devices under investigation [21 CFR 812.110(b)]:* Test articles were stored in various offices and the investigators did not have knowledge of exactly when the test articles were removed. Therefore, there was no assurance that non-research physicians, fellows or any other staff did not have access to the devices. In addition, the devices were not labeled as investigational, as required by 21 CFR 812.5.

A warning letter will include a request for a written response including corrective actions the recipient plans to put into place. **If a FDA inspector determines during a follow-up inspection that the deficiencies have not been resolved, the FDA may take further action.** In extreme cases, Investigators may be barred from conducting research studies or a study may be closed. Warning letters clearly illustrate the importance of proper device accountability across a study.

Who is Responsible for Product Accountability?

When it comes to product accountability, regulations and international standards all lay out a set of rules and guidelines as to what should be documented and where the responsibility rests. These include the FDA regulations, the ICH GCP guideline, and the International Organization for Standardization (ISO) standard 14155, which provides international guidance for the medical device industry.

Investigator

Investigators are liable for maintaining strict control over investigational products under their supervision to ensure use is only for consenting subjects enrolled in the study. In fact, when they sign the Investigator Agreement or a Form 1572, they have agreed to do so! The Investigator also agrees to ensure that only qualified and trained study staff use or administer investigational products. The Investigator is thus responsible for ensuring that site staff members have proper training prior to conducting any delegated tasks. A site must maintain adequate records of use and disposition to demonstrate compliance with the regulations, ICH GCP and ISO standards. **While certain responsibilities can be delegated to others qualified on the research team, controlling the product is ultimately the Principal Investigator's responsibility.** In order to effectively meet this responsibility it is critical that the Investigator has a working knowledge of the regulations to which he or she will be held accountable. The table below outlines the many regulations and standards that mandate investigator oversight for investigational products.

Table 1: Investigator Responsibilities for Investigational Products

Responsibility for investigational product(s) accountability at the trial site(s) rests with the ***investigator***/institution. **ICH 4.6.1**
The *Investigator is responsible to ensure control* of investigational product. Drug/device will be administered only to those subjects enrolled in the clinical study and under investigator or designee's supervision. **21 CFR 812.110 • 21 CFR 312.61**
The investigator should ensure that the investigational product(s) are ***used only in the clinical investigation and in accordance with the approved protocol***. **ICH 4.6.5 • ISO 14155 6.9**
Where allowed/required, the investigator/institution may/should ***assign*** *some or all of the investigator's/institution's duties for investigational product(s) accountability* at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution. **ICH 4.6.2**
The Investigator is required to *maintain adequate records of the disposition* of the product. **21 CFR 812.140 • 21 CFR 312.62 • ISO 14155 6.9**
The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include ***dates, quantities, batch/serial numbers, expiration dates***(if applicable), and the ***unique code numbers*** *assigned to the investigational product(s) and trial subjects*. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. **ICH 4.6.3 • ISO 14155 6.9**
The investigational product(s) should be ***stored as specified by the sponsor*** and in accordance with applicable regulatory requirement(s). **ICH 4.6.4**

Sponsor

The Sponsor is often the manufacturer of the investigational product, and is therefore the first set of hands on the product. **Even if the Sponsor is not the direct manufacturer, the responsibilities for product accountability remain the same.** A Sponsor is also charged with selecting experienced investigators and monitors, providing investigators with complete information necessary to conduct the investigation properly, and ensuring proper monitoring is arranged, among other important tasks (21 CFR 312.50, 21 CFR 812.40). The Sponsor dictates when a study team can receive materials related to the research study. However, per federal regulations, Sponsors can only ship investigational products to qualified investigators participating in the trial. How does a Sponsor determine when an Investigator is fully qualified to handle the investigational product? This involves a complicated balance of factors, beginning with evaluation of the Investigator's credentials, and including training, contract negotiations and the site's IRB approval status.

When a site receives study products, significant responsibility is then shared with the site, but the Sponsor still maintains responsibility for tracking all products throughout the study (ISO 8.2.3 (a)). Truly, out of sight does not mean out of mind - or responsibility! Sponsors must:

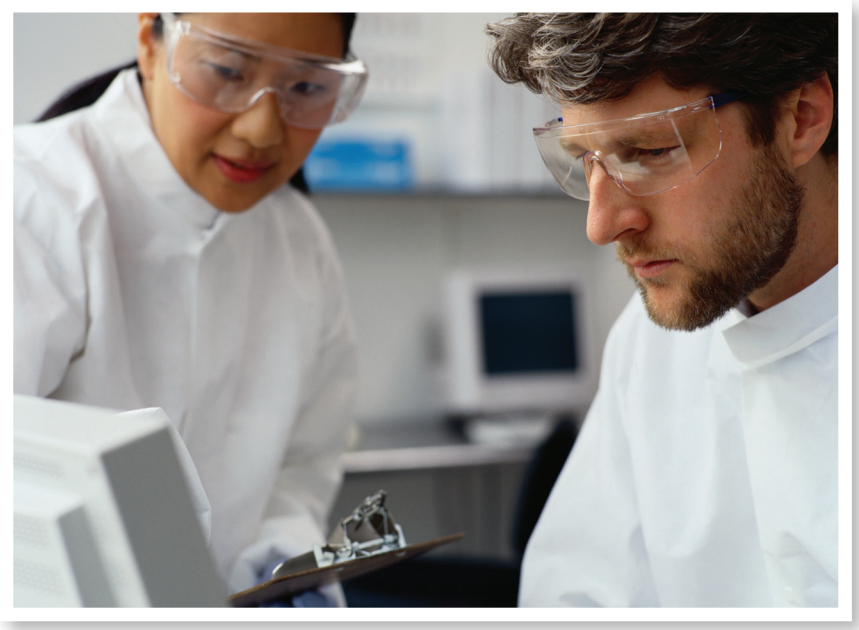
- Keep records to document the physical location of all investigational devices from shipment to the sites until return or disposal (ISO 14155: 6.9)
- Ensure the return of all unused investigational drug/device from individual investigators, or to authorize alternative disposition of unused product
- Maintain constant contact with the site and monitor to ensure their storage and accountability logs are accurate and up-to-date.

When Does Product Accountability Start for an Investigation?

The answer is before the first patient is even enrolled! **The sponsor needs to provide product to sites, and the site staff is responsible for maintaining records as soon as the site receives the first shipment of materials.** Documentation of receipt is important as well as inventory of the shipment's contents. If there are any damaged, missing, or additional materials present, the Sponsor or relevant party should be notified. Documentation of any follow-up action is also important as the products may need to be returned or destroyed.

There are quite a few more regulations and guidelines in effect for the Investigator than the Sponsor in clinical trial research. This makes sense, since the investigative site will have the most direct interactions with the product and the public. Since the Investigator is charged with the medical care of the patient and overseeing the use of an investigational product, more regulations exist to govern practices, protect patients, and limit risk. A lot rests on the Investigator's shoulders to maintain product accountability. This obligation is most clearly stated in ICH GCP 4.6.1: "Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution." However, the sponsor is not off the hook, since the sponsor must ensure that the investigator is maintaining compliance with the regulations (21 CFR 812.40, 21 CFR 312.50), which of course, includes product accountability!

How is Adequate Product Accountability Assessed? Bring in the Monitor!



The FDA describes monitoring as the act of overseeing an investigation. The International Organization for Standardization (ISO) further describes monitoring in the ISO 14155 standard as ensuring that a study is "conducted, recorded, and reported in accordance with the Clinical Investigational Plan, written procedures, this International Standard, and the applicable regulatory requirements."[4]

As mentioned above, certainly the monitor's role includes product accountability, which is why it is an important part of a monitoring visit at a research site. A monitor can help assess site compliance by reconciling what was sent to the site, versus what was used, versus what is still in stock at the site. A monitor can also verify the site's received, used, destroyed and returned products documentation (i.e. packing slips, product stickers in patient charts, the product log) and physical inventory.

Going a step further, a monitor can ask questions and observe:

- Does the study team have access to an adequate number of investigational products? (ISO 14155 8.2.4.4b)
- Have the investigators and study team been trained in the use of the products? (ISO 14155 8.2.4.4c)
- What is the process when a shipment of products is received?
    - Who is responsible for documenting and record keeping regarding the product?
    - Is an evaluation done to document the condition of the product upon receipt, i.e. product that requires refrigerated handling sat on the receiving dock at room temperature over a weekend or the shipping carton containing the product arrived damaged or water-logged?
- Where/how is the investigational product stored?
    - Are products stored according to manufacturer's recommendations in the Instructions for Use (IFU) or as specified in the protocol? Is the product storage area temperature regulated? (if applicable)
    - Are the products kept secure? If a controlled substance, is the product kept in a locked area? Who has access to the keys?
- What are the site's requirements or the protocol's requirements for storage of investigational products? I.e. - products stored separately from non-research products, are investigational products for multiple studies all stored in the same cabinet? Who has access to these products?
    - Do the person(s) delegated for product use have documentation of training?
    - Do non-research personnel have access to the products or the area where the products are kept?
- Who is maintaining the product log?
    - Have they been delegated this responsibility and has it been properly documented?

The Monitor should have access to a product log in order to conduct product accountability. Using a device log like the one below, the Monitor will verify that the sponsor's shipment records match the products that were sent to the site, as well as products the sponsor received as returns from the site, if any.

Study: XYZ

Site Name/Number: Research Hospital - Site #5				Site Name/Number: Research Hospital - Site #5			
Date Reciveived	Batch/Lot Number	Product Identifier	Expiration Date	Subject ID	Date Used	Product Disposition	Signature
21 Feb 12	001002	XYZ1234	04 May 13	JLF 0501	12 Mar 12	Used	XXX
23 Feb 12	001003	XYZ1233	04 May 13	--------	--------	Returned	XXX

Practical Examples

In order to ensure proper product accountability the research team needs to go beyond "x=x and y=y" when comparing source documents with study documents. **Only through good record keeping can study staff rest confident in compliant, accurate accountability.** Simple clerical errors, omissions, or gaps in documentation can have serious implications; take into consideration the following examples where unintentional mistakes can occur during a research study.

Medical Device Case Study:

In the mid-1990's, metal bone screws were commercially available as devices used to fix orthopedic hardware to long bones for repairing fractures. Several sponsor companies were investigating the use of identical devices, labeled as pedicle screws, under IDE studies for spinal fixation – a new application for the same device. Hospitals who were participating in these spinal fixation IDE studies could have potentially had two sets of identical metal bone screw devices on their shelves: one in commercial use for approved indications and the other labeled "Investigational for spinal IDE studies." Nonetheless, the investigational inventory had to be 100% accountable and stored in a controlled manner so that only those investigators trained and authorized to use them had access.

Pharmaceutical Drug Case Study:

In pharmaceutical trials product accountability has a large role in impacting the overall integrity of data and the well-being of study subjects. Drug accountability is more than just counting pills and vials; site staff must insure that the study subject receives the right allocation to study drug or placebo and the correct dosage[5]. Many investigational drugs are administered in varying titrations, and in these cases complete and accurate records are crucial to prove that drugs were administered as specified in the protocol.

An Onsite Case Study:

Using study subjects' medical records the Monitor is able to confirm the date the product was used and by which study team member. Documentation that they are qualified by training and experience and delegated this responsibility by the Principle Investigator will also be verified. The monitor will review that the patient study identification number is written correctly in the log and follows all Good Documentation Practices.

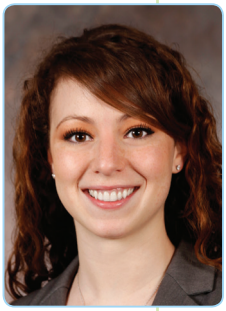
During device accountability at a site, a monitor identified the following issues:

- *A site's device log was incomplete:* A device was missing on the log. The monitor noted the devices on the packing slip did not match the devices recorded on the product log the site maintains.
- *A site's device log was not current:* The log was not updated with current disposition information for a recent study procedure.
- *A Sponsor's device log was incomplete:* The log was not updated to note a returned device.

In Conclusion

Product accountability discrepancies should never be taken lightly, as "missing" product poses risks to subjects. The Monitor should address the findings with site personnel during the visit whenever possible. Most often a discussion with the coordinator makes sense, as many tasks are delegated from the Investigator to the Research Coordinator. If this is the case, it would then be the Research Coordinator's responsibility to update the device log to note the missing device, note the disposition details for the recent study subject, and provide an updated copy for the sponsor. The Monitor should request that the Sponsor update their device log to note the returned device. The primary responsibility to ensure product oversight is maintained still remains with the Primary Investigator, but the Research Coordinator likely handles the day-to-day details of documenting product accountability.

By understanding the regulatory requirements for the Investigator and the Sponsor, and the roles of each in running a trial, the Monitor can ensure that both are meeting the requirements and following good clinical practices. It is important to note that, regardless of one's role on the clinical research team, running a compliant clinical trial and maintaining product accountability should be a priority and team effort.



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Jessica joined IMARC Research in 2011 from the Cleveland Clinic were she worked in a clinical research lab investigating translational and human genetics and genomics. Jessica understands the importance of product accountability from a unique perspective having worked in personalized genomic medicine, culturing patient cells and genetic material. After joining the Medical Device CRO team at IMARC, her interest in product accountability compliance remains a topic of important focus. Jessica appreciates that in clinical research having a working knowledge of the regulations and exceptional documentation skills is key to ensure that patients are protected and that the resulting data has integrity.

Jessica holds a Bachelor of Science degree in Biology from the University of Alabama at Birmingham. She is a member of the Society of Clinical Research Associates (SoCRA).

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