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Study Drug Accountability

By Paula Smailes

Accurate drug accountability records help ensure that study drugs have not gone astray and help find them if they do. Site monitors, auditors and FDA investigators all perform their own drug accountability inspections. Any discrepancy is a big problem, not just because of the regulatory violation, but because it potentially endangers the integrity of the study and even public health.

Drug Receipt, Storage and Labeling

Drug accountability begins with a secure location to store study drug. According to the ICH Guideline for Good Clinical Practice (E6 (4.6.4)), "The investigational product(s) should be stored as specified by the sponsor…and in accordance with applicable regulatory requirement(s)." However, the regulations require only:

- An investigator is responsible…for the control of drugs under investigation. (CFR 312.60)
- If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution. (21 CFR 312.69)

A good approach is to store study drug in a double-locked location, i.e., in a locked cabinet in a locked room accessible only to study staff. However, the protocol or common sense may suggest other options. The cabinet, freezer or refrigerator should not be used for storing anything else, e.g., blood samples or staff lunches. If the only option is to store study drug and blood samples, for example, in the same storage unit, compartmentalize the unit and label the compartments clearly. Sponsors may have certain requirements, so check with them if there is uncertainty. (It is beyond the scope of this article, but it is good practice to use min/max thermometers or computer-based systems to record storage temperatures, since deviations are most likely to occur outside office hours when nobody is available to record temperature excursions. The easiest way to ensure stable temperatures in a freezer or refrigerator is to pack the empty space with two-liter bottles of water.)

Figure 1. Study Drug Accountability Checklist

Receipt
- ❑ Verify contents match shipping records
- ❑ Sign and date shipping records and place in regulatory binder
- ❑ Store drug in a secure area
- ❑ Log shipment onto Drug Accountability Log
- ❑ Call into IVRS, if being used
- ❑ Return proof-of-receipt material

Return
- ❑ At study end, make sure Accountability Logs are updated
- ❑ Reconcile discrepancies
- ❑ Photocopy Log, return original with drug shipment, copy for site
- ❑ Once monitor tapes box, it is ready for return

When study drug is received from the sponsor, process it immediately or move it to a secure location until it can be processed. Use a standardized process. A checklist will help avoid skipping any steps. (Figure 1)

Verify that the drug labels, quantities and lot numbers match the paperwork. Acknowledge receipt through the IVRS system, assuming there is one. Initial and date any associated paperwork that arrives with the drug. File the paperwork in the regulatory binder behind the Drug Accountability tab. If the sponsor includes proof-of-receipt material, send it in as soon as possible. Drug shipments may include temperature recording systems. If so, transmit this information to the sponsor. Make sure that all personnel handling the study drug have the necessary delegation on the Delegation of Authority Log.

Place the drug in its own distinct area. Color-coding bottles, etc., by study helps prevent errors, especially when conducting more than one study for the same sponsor on the same drug. Put the investigator's name and telephone number on the drug package, in the event of emergency or in case the subject loses the drug, especially when traveling.

Drug Dispensing

The first step in dispensing study drug is to obtain the baseline, randomization or allocation number for the subject that identifies which drug (or placebo) to dispense. For drug assignments made by IVRS, wait, if possible, for confirmation of the number via email or fax before dispensing the drug. It is a research coordinator's worst nightmare to dispense the wrong drug, especially when there is a placebo arm in the trial. As an extra precaution, ask the subject or a coworker to verify that the numbers on the fax/email confirmation match those on the bottles.

Before dispensing drug to subjects, count the pills with the subject if the medication is in pill form. Aside from double-checking the count, this process will minimize later claims by the subject that he or she received the wrong number of pills.

Educate the subjects to avoid discrepancies caused by taking too many or too few doses. Make sure they understand how often, by what route, and in what quantity they should take the drug. Write it down for them, since subjects often forget verbal instructions before they walk out the door. It is easy for study personnel to underestimate the complexity of these instructions, so ask the subjects to repeat what they've heard. Follow up with subjects by telephone a few days after they start the drug, to find out if there are any uncertainties or immediate side effects.

When first dispensing the drug, stress that all medications and empty containers must be returned to the study site. Too often, subjects will throw out empty bottles. They may even save unused pills for future use or give them to a "friend in need." Subjects may use a weekly pill organizer to help manage their medications. If so, it is normal for them to add the study drug to the organizer. Doing so increases compliance but requires subjects to bring their pill organizer to study visits.

If the bottle has a tear-off sticker, collect it prior to dispensing the bottle to the subject and place it in the subject's chart or the Drug Accountability records. The sticker becomes part of the paper trail that shows the correct bottle was dispensed.

At each visit, with the subject present, if time allows, count the pills and attempt to reconcile any discrepancies. Obtain the dates of any missed doses by subject memory or a diary card, if available. If the subject forgot to bring his or her pill organizer, assume there is one missing pill for each remaining day of the week (if the supply was adequate).

Drug Return or Destruction

U.S. regulations state:

> If the investigation is terminated, suspended, discontinued or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under §312.59. (21 CFR 312.62 (a))

Update the drug accountability log and file an initialed and dated copy of the shipping documents in the regulatory binder. If you are destroying study drug on-site, follow your standard operating procedure, which will require additional documentation by the personnel involved with the destruction. If a third party destroys the drug, obtain the appropriate documentation.

Drug Accountability

U.S. regulations state:

> An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects. If the investigation is terminated, suspended, discontinued or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59. (21 CFR 312.62 (a))

FDA's Compliance Program Guidance Manual specifies how its investigators should conduct test article accountability inspections:[1]

- Determine who is authorized to administer or dispense the test article.
- Determine whether the test article was supplied to a person not authorized to receive it.
- Compare the amount of test article shipped, received, used and returned or destroyed. Verify receipt date(s), quantity received, and condition upon receipt; date(s), subject number(s), and quantity dispensed; and date(s) and quantity returned to sponsor or other disposition of the test article.
- Determine where the test article is stored, whether it is stored under appropriate conditions, as specified in the study protocol, and who has access to it.
- If the test article is a controlled substance, determine how it is secured and who has access.
- Determine whether the test article is appropriately labeled.

Site monitors and auditors normally follow the same procedures to ensure that they catch any problems prior to an FDA inspection. Research sites can conduct their own drug accountability audits, especially if they have had previous accountability problems, there is a new study coordinator, the drug is a controlled substance, or accountability is a challenge because two studies are using the same drug.

Keep drug accountability logs current. Recent discrepancies are hard enough to reconcile without waiting until memories fade or additional discrepancies compound the problem. If a subject or study personnel accidentally loses or destroys study drug or a drug container, document it on the Drug Accountability Log. Notify the site monitor immediately of any discrepancy that cannot be resolved.

Sponsors normally supply drug accountability logs, but sites can create their own to avoid dealing with multiple forms.

At the conclusion of the study, review all previous documentation to make sure it is complete. Document any missing or incomplete records. Conduct a final inventory and document any discrepancies that cannot be resolved.

Conclusion

Study drug accountability is simple in theory but can be challenging in practice. Without adequate attention, it is easy for mistakes to occur at a busy research site and then grow exponentially over time. Think of your drug accountability log like your tax return. Nobody wants to complete a tax return with old, jumbled records and no memory of the events that occurred. Neither the IRS nor the FDA will be amused.

Reference

1. Food and Drug Administration. (2008). Compliance Program Guidance Manual (Program 7348.811, Chapter 48 Bioresearch Monitoring, Section J).

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