

Drug accountability in clinical trials

Manejo y control de los productos y medicamentos empleados en ensayos clínicos

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Clinical trials are important vehicles for validating new research findings and outcomes to improve the science of oncology treatment. Ultimately, however, patient safety and quality of care must always come first and can be achieved through this attention.¹⁻⁴

Therefore, protecting human research subjects is the single most important duty when conducting clinical trials. In order to ensure that, it needs a complete adherence to Good Clinical Practice (GCP),⁴⁻⁷ adherence to regulatory requirements and adherence to the protocol.^{8,9} Besides, a qualified Institutional Review Board (IRB),¹⁰ an informed consent from each patient enrolled,¹¹⁻¹⁷ a qualified team of investigators,¹⁸⁻²⁴ and an accurately manage and document drug accountability are necessary.²⁵⁻²⁷

This article focuses on the last task, with critical information needed for the study drug shipping manifest and with specific steps you can modify to your practice. It discusses the importance of drug accountability records with respect to study data integrity and describes the role of clinical trial sponsor, clinical researcher pharmacist, the whole staff of investigators and study monitors.

When drug accountability records are well designed and error-free, and appropriately reconcile from initial shipment to the site through final disposition, any individual should be able to perform drug reconciliation in half hour.²⁸

According to the regulations governing the use of investigational drugs, failure to account for and manage study drug is considered noncompliance and could affect the acceptability of the trial data you generate.^{9,26} In addition, if you are not in compliance with the protocol, that can result in termination of the trial, suspension of all research activities at the site, and possibly fines. But most importantly, noncompliance compromises patients' safety.^{4,8}

What is means drug accountability?

Drug accountability includes: study drug storage, handling, dispensing, and documentation of administration, return and/or destruction of the drug.

A drug accountability process should be initiated for any study that uses study-supplied drug. Study drug can be an investigational agent or an approved drug that is being tested for a currently unapproved use. When testing investigational drugs, clinical trial sponsors and investigators must follow the rules of conduct established by the US Food Drug Administration (FDA) and Cuban Regulatory Agency (Center for Drug Quality Control [CECMED]).^{4,7-9} These rules describe sponsor and investigator responsibilities, recordkeeping and record retention, inspection of records and reports, control of the investigational drug, disposition of unused drug, assurance of Institutional Review Board (IRB) review, handling of controlled substances, and reasons for disqualifying a clinical investigator.^{4,8}

Drug accountability at the sponsor site

An accurate investigational drug accounting process begins with the sponsor's shipping manifest. The regulations require control of investigational medications, and the safety reasons alone justify these restrictions. One must be able to confirm that investigational medication has not been dispensed to non-study subjects, and that subjects have not been exposed to doses in excess of protocol-defined regimens.^{8,9,29} Therefore, all investigational medication documented as shipped to the site should reconcile with the documentation of used and unused supplies and the handling of investigational drug must be adherence to GCP. Moreover, federal regulations restrict investigational drugs to research use. Marketing and commercialization are prohibited. Hence, chain of custody and strict accounting, as well as secure storage conditions at the site, must be in place for all investigational medications.

Drug accountability at the investigative site

At the investigative site the drug accountability process continues. Here, the principal investigator (PI) is responsible for maintaining adequate records of the disposition of the drug. The PI must also ensure proper security and storage of the investigational drug.²⁶

This person (or designated individual) is charged with maintaining complete and accurate records about drug received, dispensed, and disposed of, including quantities used and last disposition. The PI must ensure that the whole research team (sub-investigator, research nurse, research pharmacist, or clinical research coordinator) understands the procedures necessary to maintain drug accountability and follows the study protocol.^{24,26,28} Even when research pharmacists are involved, the clinical investigator retains this responsibility.^{4,8,9,18,19,30}

What steps should be carried out with the investigational drug?

1. Receiving investigational drug shipments.

Be sure that the sponsor's instructions about receipt of the study drug are followed. Upon opening the package:

- Check the shipment and confirm that the contents are intact.
- Compare the invoice to the lot number, expiration date, quantity and dosage.
- If there are any discrepancies, report the sponsor immediately.

2. Storing study drug.

Securely lock study drug in a temperature-controlled drug storage place separate from the other medicines. The drug store should be according to the conditions specified in the protocol or the shipping invoice. Keep temperature record, in order to verify that the drug was stored under the proper conditions.

3. Dispensing according to clinical trial protocol.

This document provides detailed information about dosing, including instructions for dose modification and discontinuation; how to prepare, administer and/or dispense study drug; and how to manage and report side effects.

Drug may be dispensed to patients according to the protocol. The study-provided drug should only be used for the patient enrolled in the study and the drug should only be distributed to the assigned patient. Never change the medication from one patient to another! If the drug requires admixture, only a specific nurse or clinical pharmacist can be to dispense and prepare that drug.

4. Disposing of or returning drugs.

During the study, follow the sponsor's instructions concerning drug return and/or disposal. Document all activities, including protocol and drug identifiers and units and lot numbers. If applicable, returned supplies should be attributed to specific study participants. In addition, the records should:

- Distinguish between unopened (not dispensed) and unused (by study subjects) supplies.
- Explain broken or lost drug supply.
- Account for all supplies.

5. Inventory.

Ensure patient treatment schedules against drug supply and monitor expiration dates. If the drug is not available at the investigative site, do not substitute from the office stock. Request the treatment immediately to the sponsor. If by any chance office stock is used inadvertently, you have to document deviations from the protocol. Never use study-supplied drug to replace office stock or vice versa.^{26,28}

What should be documented about investigational drug?

Accurate drug accountability records demonstrate that the study drug was dispensed and administered according to the protocol.

The site should document drug receipt, subject dispensing and return, returns of used and unused supplies to the sponsor (or on-site destruction), and should maintain a current accounting of all supplies in inventory. The site should document receipt of each drug. The receipt has to contain the name and ID number of patient, date, name of the drug, amount, doses, batch, name and signature of the doctor.²⁸

When dispensing drug to a subject, clinical pharmacist should record the date, subject number, number of doses and amount dispensed. When a patient returns a drug, the amount used and unused should be documented, as should an explanation for any inadvertent loss or destruction of supplies. A well-maintained balance-on-hand log allows the study monitor to efficiently assess drug accountability during routine site visits, and at the final drug reconciliation.

The final step in the drug accountability process is drug return or destruction. This action should be properly documented, including protocol and drug identifiers, units, and lot numbers. If applicable, the returned supplies should be attributed to specific subjects. In addition, the records should distinguish between unopened (not dispensed) and unused (by the subject) supplies. Any larger discrepancies must be investigated and explained. Often, medication amounts or lot numbers do not match with receipt documents or dispensing records. Incomplete listings of returned supplies or replication of returned supplies (returns of the same supplies on different dates) are also common. Such errors result in drug supply amounts that do not reconcile.²⁸

In order to do a good work, the site needs a qualified personal. Therefore, every year the sponsor gives courses and training to the entire personal that works with the drug handling.

What do the study monitors do in their visits?

The study monitor is the key to ensuring accurate drug accountability. During routine visits, monitors should assess the site's drug preparation and dispensing procedures, as well as subject compliance, and ensure proper drug storage and log maintenance.

The monitor should also verify that the clinical investigator or an authorized personal (such as, research pharmacist) is dispensing the supplies. Besides, monitors should confirm that all supplies are accounted for and returned or destroyed report and investigate any discrepancies, and resolve all items before site closure. By periodically reviewing drug accountability documentation throughout the study, monitors can identify inappropriate practices as they occur and retrain site staff as needed. Problems detected early are more easily resolved. Proper review of drug records could uncover poor subject compliance with drug administration, incorrect supplies at the site, errant drug preparation, incorrect randomization, and potential un-blinding of subjects who were dispensed coded labels. Upon noting problems, monitors should immediately implement corrective action plans to prevent future occurrences.^{4,31,32}

Drug accountability documentation should be simple and useful, and it allows:

- Document the handling of the study drug from receipt to dispensing to return or disposal.
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- Display inventory, lot numbers, dose sizes, quantities in stock, and expiration dates.
- Include shipping invoices, confirmation of receipt, condition upon receipt, and a running tally of when the drug was received, dispensed, disposed of, and returned to the sponsor.
- Help verify patient clinical records and detect possible lot variations.
- Help verify patient case report form and detect any non-compliance.
- Help identify patients who may have received the drug, as well as the quantities that they may still have in their possession, should recovery of any unused drug become necessary to minimize health risks.
- Support the validity of study data and conclusions drawn from those data.

Attention!

Drug accountability records are part of the regulatory documents. If the PI or the person that he designed (research pharmacist) adequately maintains the study drug accountability documentation, and the monitor conducts ongoing reviews, then the records should reflect that the researcher maintained proper control of administration and distribution of the study drug. The records, when kept according to the recommendations presented here, should also indicate that the clinical trial is according to regulatory obligations.

The paper trail should show the receipt of the supplies at the site, the dispensing to each subject, the amount the subject used or did not use, the amount the subject returned, and the amount the research pharmacist returned to the sponsor or destroyed on-site. Accurate drug accountability records provide assurance that the drug was dispensed and/or administered according to the protocol, and support study data validity and conclusions drawn from those data. At any stage of the study, the site staff, the monitor, and the sponsor should know where their drugs are.

In summary

Managing drug accountability demands attention to detail but can be achieved with a trained research team dedicated to following GCPs, standardized procedures and the study protocol. Accurate drug accountability enhances patient safety throughout the clinical trial.

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Recibido: 25 de mayo de 2011.

Aprobado: 30 de junio de 2011.

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