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Review Article

GUIDANCE FOR DRUG ACCOUNTABILITY AT CRO SITE

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ABSTRACT

The clinical research industry is struggling to cope with the burden of maintaining Adequate drug accountability documentation for regulatory compliance. Clinical research Regulations require that all investigational drugs are properly accounted for and reconciled from start to finish, however, the majority of drug accountability processes currently being carried out by clinical research organization are done manually and are extremely Laborious.
Proper documentation storage dispensing archival or disposal of IP forms the crux for a good Drug Accountability management.

Keywords: Drug accountability, Principal investigator, Research pharmacist

INTRODUCTION

Currently clinical research Organization carries out their own accountability activities. Traditionally this is a lengthy and complicated procedure involving large paper trials which can result in many errors. Such errors compromise subject safety and will result in heavy penalties for the companies involved and doctors being banned from future clinical trial participation. Drug accountability offering not only enhances our existing product suite but also consolidates its market position as industry leader.

IP Accountability is the process & documentation which we account for time of manufacture until use or archival destruction. Dr. Chinedum describes three MANDRAS which forms the basis of this process. Drug accountability which includes study drug storage, handling, dispensing and Documentation of administration. Any investigational drugs being used in clinical research must be strictly accounted for. It means from its birth – the manufacture till the death – expiry and ultimate destruction[1].

This includes keeping records of

(1) Receipt and inventory of investigational drugs
(2) Storage of investigational drugs
(3) Dispensing of investigational drugs and
(4) Return or disposal of the investigational drugs.

The Research pharmacist must properly store and dispense all investigational drugs and maintain accurate dispensing and inventory records. ICH guide lines stress this in definite words[2]. FDA guidelines also requires that you know where EVERY UNIT of drug is and how it was used from the time it arrived at your site until it was administered to the subject or returned to the pharmacy or sponsor or for destruction[3].

The principal investigator must ensure that the entire research team-which may include a sub investigator, research pharmacist, research nurse, clinical research coordinator-understands the procedures necessary to maintain drug accountability and follow the study protocol[4]. Friedman et al, also stresses the responsibility of the accountability with the Principal Investigator only[5]. Present article discusses the critical information needed for the study drug shipping manifest, importance of drug accountability, the content of the dispensing and return/or destruction documentation at the site.

Acquisition of Study Products

After confirmation of the study, the first step is to procure the study products from manufacturer or sponsor. If the study products are received before the IEC approval of the protocol, receive and store as per the required storage conditions (as in covering letter or container label) under the custody of study personnel

Shipment and Inventory of Investigational Drugs

An exact study drug accountability process commence with sponsor's shipping manifest. Upon receipt of the investigational drug, inventory the shipment ensuring that the information on the packing slip(inside and outside containers) matches accurately with what has been sent to the site, including the amount, batch numbers, manufacturing date, expiry date, name of manufacturer, quantity, strength, storage conditions and document the results of this inventory. Then promptly bring any discrepancies, breakage or evidence of tampering to the manufacturer or sponsor immediately through mail. 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. Retain a copy of the shipping inventory like courier receipt, packing slips and documentation of inventory in the study's records. Once received the investigational products from sponsor, the pharmacist or Principal investigator must acknowledge the same to the sponsor by filled clinical supplies acknowledgement form through mail or courier systems.

Clinical supplies acknowledgement form (CSAF)

Study No:	Received by:
Received date/Time:	Received through (by Courier/ by post):
Storage condition:	packaging condition:
Any special condition:	Number of container received:
Total quantity in test container:	Total quantity in reference container:
Any discrepancy:	

Storing Study Drugs

Drug accountability begins with a secure location to store study drug. According to the ICH Guideline for Good Clinical Practice, The investigational product(s) should be stored as specified by the sponsor[6]. 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 accepted range of temperature for pharmacy is 23 ± 2^0C. The protocol or common sense may suggest other options. Temperature of the pharmacy has to be controlled within the specified limits and humidity has to be monitored. Access to the storage area will be limited to essential research personnel.

Documentation like the following has to be strictly maintained

1. Entry and exit logbook
2. Drug Accountability logbook
3. Environmental conditioning logbook, to verify that the medication was stored under the proper conditions.
4. Study drug storage log book, to record the each movement of study drug.

Drug Accountability at the Study Site

The drug accountability process continues at the investigator site, where the pharmacist is responsible for maintaining

adequaterecords of the disposition of the drug. The Principal Investigator must ensure proper security and storage of the study.

Normally FDA Requires that you know where every unit of drug is and how it was used from the time it arrived at your site until it was administered to the subject or returned to the pharmacy or sponsor for destruction viz CRADLE TO GRAVE POLICY ACCOUNTABLITY has to be meticulously followed. Drug accountability documentation should be completed on arrival of supplies. Each time drugs are distributed and when drugs are returned to the sponsor or destroyed. A copy of all accountability documents will be maintained in the regulatory files.

Drug Accountability Form (DAF)

Use a separate drug accountability form for each protocol

Fill in:

Protocol No:	Received date:
Product Name :	Batch Number:
(Test/Reference)	Dosage form:
Brand Name:	Manufacture Date:
Description:	Expiry Date:
	Strength:
Total quantity sent by sponsor:	Quantity found after counting:
No. of units for study purpose:	No. of units for Retention:
Stored in:	Storage conditions:
Accountability done by:	Checked by:
Comments:	

PREPARATION/DISPENSING

1) Investigational drugs must be properly packaged in accordance with all applicable standards and regulations

2) Randomization

There are various types of randomization including simple and block forms. Simple randomization involves use of a random numbers table or computer-generated number sequences e.g. even numbers (treatment A) vs. odd numbers (treatment B). A potential disadvantage of simple randomization is that the balance of trial subjects taking either drug may be heavily distorted. Block randomization avoids this and ensures that if the trial is stopped at any point approximately equal numbers of subjects receive A and B Randomization request is given to statistician mentioning about IP, No. of subjects, No. of periods & get a confirmed randomized schedule duly approved by the Principal Investigator[7].

All investigational drugs must be signed out on Investigational Drug Accountability Forms by the pharmacist dispensing the drug. These records are maintained for a minimum of five years after the drug has been FDA approved or for at least two years after the study is discontinued and FDA is notified. For studies involving international sites, records shall be maintained for 15 years after study closure.

3) All used and unused investigational drugs (i.e. bottles, vials) must be saved unless otherwise specified by the sponsor.

4) If a volunteer is to receive the study drug at another institution, suitable arrangements for its transfer must be made.

DRUG DISPENSING FORM

Use a separate drug dispensing form for each protocol, and each dosage of an agent.

Fill in:

Name of the investigational product: Test/Reference							
Batch Number:				Expiry date:			
Period	Date	Line clearance Yes/No	Initial balance Of drugs	No. of units dispensed	No. of units dosed	Remaining Units	Allotment of subjects as Per Randomization Schedule
Dispensed by:				Checked by:			

LABELING

1) Investigational drugs must be properly labeled in accordance with all applicable standards and regulations to ensure their safe use.

2) The following represent the minimum labeling requirements for investigational drugs dispensed and administered to subjects.

A Model Unit Dose Label

Protocol number:	For as clinical research Use only"
Name and location of the patient	Name of investigator:
Name and strength of drug (if applicable)	Product type: T/R
Dosage form:	Dispensing date:
Expiration date	Dosing date:
Dispensed by:	Check

DRUG ARCHIVAL OR DESTRUCTION

The final step in the drug accountability process is drug archival or destruction. Ascertain the time line for destruction. Throughout the study, drug return and destruction should be properly documented, including protocol and drug identifiers, units, and lot numbers. If applicable, the returned IP's should be attributed only to specific subjects. In addition, the records should distinguish between unopened (not dispensed) and unused (by the subject) supplies, identify broken or lost supplies, and show that 95–100% of supplies are accounted for. Any larger discrepancies must be investigated and explained.

Drug archival logs should be orderly and clear, though often this is not the case. Common findings include medication amounts or lot numbers that do not reconcile with receipt documents or dispensing logs. 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. Sometimes the archival form does not distinguish between used and unused supplies, complicating both compliance assessments and matching of the amounts and specific supplies the subject used.

Retention period

- A representative sample of the drug supplies used in the study will be retained for a period of 05 years (pivotal

study) and 02 years (pilot study) from the date of completion of the study.

- 300 units of drugs or 5 times of the drugs are required for regulatory retention purpose.

DESTRUCTION

Disposal of drugs by destruction can be done as follows

1. As per local policy of the CRO who have sops dealing with destruction guidelines. The CRO can destroy the IP and can format a document like below:
   Record of Destruction
   Name of the product:
   Batch No./Expiry Date:
   Actual quantity of IP Received for study:
   No. of Subjects involved in the study:
   Method of destruction

DONE BY	**VERIFIED BY**
PHAMACIST	QA/PI

   Send one copy of this to sponsor and put one in the TMF.
2. Licensed professionals who are authorized for IP destruction can also be utilized for disposal purposes.

WHAT AUDITORS SHOULD OBSERVE

An investigative site audit tests the drug accountability process and can help gauge the readiness of the records for an FDA inspection. Thus, an auditor should carefully assess drug accountability. The accountability documentation should fully comply with for all supplies received, dispensed, and returned. There should be evidence that entries on logs were made in real time (at the time the action took place). Documentation should support proper storage and security of the drug. Moreover, dispensing logs should be complete. The auditor should confirm that the monitor reviewed drug accountability periodically and that final drug reconciliation was performed. Copies of drug labels should be attached to the original CRF pages, and returns should be completely documented. In all, the documentation should provide a full and accurate explanation of drug handling from receipt through final disposition. Good documentation and records maintenance will definitely facilitate in facing any regulatory compliance.

CONCLUSION

Investigational 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. The study drug should be inventoried and prepared to be returned to the sponsor in accordance with the requirements of the sponsor. All documentation regarding receipt, storage, dispensing, and return of used containers must be complete and accurate.

KEY POINTS OF DRUG ACCOUTABLITY

1. Principal Investigator (PI) is responsible for full drug accoutablity
2. PI should delegate the activities to other in heirarky like pharmacist
3. Maintain systematic practice of storage as per regulatory rules
4. Investigational Product (IP) is to be utilised only for particular clinical study which is approved by the iec.
5. Ensure that IP is administered only to the elegible subjects participating in the approved sudy protocal.
6. Unused IP's to be completely reconciled and either returned to sponser or disposed. this is an important event.
7. Ensure that clear cut guide lines are utilised for destruction – disposal process as per regulatory requirements
8. Cradle to grave policy has to be scruplously followed in all cases of study medications.

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