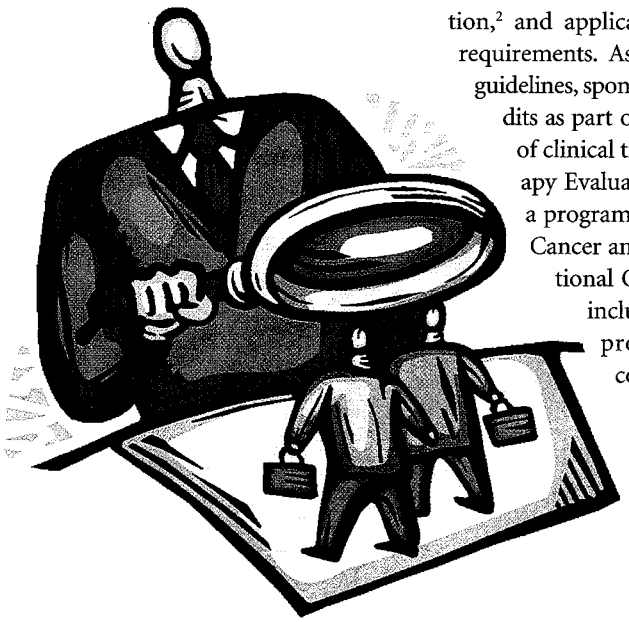
Management Consultation

Understanding and preparing for clinical drug trial audits

Q: We know very little about the procedures regarding audits for clinical drug trials. Can someone explain the audit process and suggest ways to prepare for these inspections?

A: Investigators who conduct clinical trials are routinely audited by the study sponsor or a contract research organization and the Food and Drug Administration (FDA). The purpose of these audits is to ensure the protection of human subjects and the quality and integrity of the study data.[1] An audit is accomplished by evaluating compliance with the protocol, standard operating procedures, Good Clinical Practice (GCP) guidelines established by the International Conference on Harmonization,[2] and applicable federal regulatory requirements. As specified by the GCP guidelines, sponsors should conduct audits as part of the quality assurance of clinical trials. The Cancer Therapy Evaluation Program (CTEP), a program within the Division of Cancer and Diagnosis of the National Cancer Institute (NCI), includes an onsite auditing program as one of the components of its quality assurance program.[3] An important step in this auditing program is verifying that procedures for drug accountability meet the requirements of federal regulations and correspond to CTEP procedures. Pharmaceutical companies audit study sites regularly and often have an outside firm conduct audits of trials that are pivotal for a new drug application. FDA also conducts inspections of clinical trial sites.[1,4-6] The most common audits conducted by FDA are routine surveillance inspections of high-enrollment sites or sites that have participated in a pivotal study that is critical for product approval. The other type of audit conducted by FDA is the "for cause" inspection of a site, which investigates a suspected regulatory or ethical deficiency.



An audit of the study site by the sponsor or FDA includes a review of the drug accountability records. Drug accountability by the study sponsor and the investigator is specified by the GCP guidelines[2] and mandated through the Code of Federal Regulations.[7-9] Maintenance of adequate records on the shipment of the drug product to the trial site, the receipt of the drug product by the trial site, the inventory at the site, the use of the product by the subject, the return of unused product to the sponsor, and the disposition of unused product are required. The records should include dates, quantities, batch numbers, expiration dates (if available), and unique code numbers assigned to the trial subjects and, if applicable, to the drug products. Accountability records must be accurate and clear. Black ink must be used, and corrections must be made by crossing out erroneous information with a single line, supplying the new information, and initialing and dating the correction.

All procedures for drug accountability must comply with federal regulations and the specific requirements of the study sponsor. As outlined by the GCP guidelines, the investigator or study institution

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The Management Consultation *column gives readers an opportunity to obtain advice on common management problems from pharmacists practicing in health systems.*

AJHP *readers are invited to submit questions for this column. Selected questions will be forwarded to one or two experts in the field, who will prepare brief responses for publication. Questions should be narrow in scope, such that they can be answered in approximately 500 words. Responses will be sent to the inquirer before publication. Readers are also invited to comment on the answers of consultants; such comments will be considered for the* Letters *column.*

Suggestions for topics should be submitted to AJHP, *7272 Wisconsin Avenue, Bethesda, MD 20814 (301-657-3000 or ajhp@ashp.org).*

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is responsible for the proper storage and accountability of the investigational product.[2] This responsibility should be delegated to a pharmacist working under the supervision of the investigator.[2,10] The American Society of Health-System Pharmacists provides guidance to pharmacists for drug management in clinical research.[10] Pharmacists who are involved in the dispensing of investigational drug products are responsible for the completeness and accuracy of the drug accountability records.

The Investigational Drug Service (IDS) at the University of Michigan Health System (UMHS) was established in July 1984. Currently, the IDS staff coordinates about 260 active protocols that involve the use of an investigational drug. The IDS manages industry-sponsored studies, investigator-initiated protocols, and NCI-sponsored cooperative group trials. The IDS is staffed by 2.5 full-time-equivalent (FTE) clinical pharmacists and 3 FTE pharmacy technicians and is located in the UMHS central pharmacy in an area dedicated to investigational drugs. Investigational drugs are sent to the IDS pharmacy by study sponsors. The IDS pharmacy dispenses the majority of investigational drugs and maintains central inventory records of drug receipt and disposition. Investigational drugs for inpatients and patients treated at the UMHS Comprehensive Cancer Center are dispensed by satellite pharmacies. The IDS staff supplies investigational drugs, inventory records, and dispensing information to these satellites and trains the satellite pharmacy staff to dispense and maintain accountability records for the drugs.

Every three years, the Children's Oncology Group, the National Surgical Adjuvant Breast and Bowel Project, and the South West Oncology Group perform routine audits of drug studies at UMHS. All three audits require the IDS to prepare drug accountability records for a large number of studies in a short period of time. In addition, clinical trial monitors from the pharmaceutical industry also routinely audit the drug accountability records. These records are also reviewed by FDA and NCI.

At UMHS, study coordinators, data managers, and pharmacists assist investigators in managing clinical studies. When the study sponsor or FDA informs the investigator of an upcoming audit for a clinical drug trial, the coordinator or data manager contacts the IDS. To prepare for the audit, an IDS technician obtains the pharmacy study file and pharmacy records. If the drug was distributed to satellite pharmacies, the technician obtains the satellite's current inventory records. The technician sorts by date and location the drug inventory records, drug receipt records (invoices), records of drugs returned to the sponsor or disposed of onsite, records of the transfer of drugs between protocols, and all other records, such as randomization information or drug preparation worksheets. The technician checks all records for completeness, accuracy, and clarity. If any problems are identified, the technician consults with the pharmacist to determine what action should be taken. When the initial preparation of records by the technician is completed, the IDS pharmacist reviews the records. For open or ongoing studies, inventory is physically counted in the IDS and satellite pharmacies.

To prepare for an audit of a clinical trial, a checklist was developed based on a review of the GCP guidelines,[2] the CTEP *Investigator's Handbook*,[3] FDA inspection instructions,[11] and records from past IDS audits (see figure on page 2308). The use of the checklist allows the pharmacist, who coordinates the audit, to distribute the workload of preparing the records among the IDS staff. In addition, the checklist ensures that all files are prepared in a timely, standardized, and complete manner. Once the records have been prepared, the pharmacist reviews the completed checklist to identify issues that require further investigation or intervention. Since all files are organized in the same manner, reviewing files before the auditor arrives and presenting the information during the audit are efficient. The checklist has proven to be a timesaving tool that has contributed to the success of audits conducted at UMHS.

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5. FDA inspections. In: Iber FL, Riley WA, Murray PJ, eds. Conducting clinical trials. New York: Plenum Medical; 1987:315-23.
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7. 21 C.F.R. 312.59.
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9. 21 C.F.R. 312.62.
10. Guidelines on clinical drug research. In: Deffenbaugh JH, ed. Best practices for health-system pharmacy: position and guidance documents of ASHP 2001–2002. Bethesda, MD: American Society of Health-System Pharmacists; 2002: 294-300.
11. Food and Drug Administration. Compliance program guidance. Manual for FDA staff. Part III—inspectional. www.fda.gov/ora/compliance_ref/bimo/7348_811 (accessed 2002 May 5).

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Checklist developed at the University of Michigan Health System for preparing a pharmacy for a clinical trial audit.

University of Michigan Health System
Department of Pharmacy Services
Investigational Drug Service

Audit Checklist

Drug name _____ Protocol # _____ Audit date _____
Audit company _____ Principal investigator _____
Data manager/study coordinator _____ Phone _____

___Gather the pharmacy file, notebook, and records pertaining to the above protocol.
___If the study is closed, obtain the closed file.
___If the study is open, obtain the current inventory records from the satellite pharmacies. Inventory the drug in the satellite pharmacy and provide a new inventory sheet.
___Sort invoices by date (be sure that invoices were signed and dated by IDS personnel).
___Sort central and satellite pharmacy inventory records by location and date.
___Sort return forms by date.
___Sort transfer forms by date.
___Sort all other records by date (e.g., randomization information, worksheets).
___Check that all invoices were signed in on the central inventory sheet (make sure lot numbers and expiration dates are on sheet).
___Check that all returns were signed out of the central inventory sheet.
___Check that all transfers were signed in or out of the central inventory sheet (for sponsors that allow transfers between protocols, make sure a transfer form was filled out).
___Check the central inventory sheets against satellite inventory sheets. Was everything logged in and out correctly? (Check that dates match and lot numbers and quantities match.)
___Was central inventory sheet filled out properly?
  ___Was the top of the inventory sheet filled out (e.g., page numbers, study title, drug name and strength, investigator name, location of dispensing site)?
  ___Were all entries filled out properly? Check for the following:
    ___Patient's initials (not name)
    ___If the study requires a patient study identification number on the inventory sheet, check that the number is filled and is correct
    ___The dose and frequency of administration
    ___Initials of recorder and pharmacist
    ___Lot numbers and expiration dates
___Was satellite inventory sheet filled out properly?
  ___Was the top of the inventory sheet filled out (e.g., page numbers, study title, drug name and strength, investigator name, location of dispensing site)?
  ___Were all entries filled out properly? Check for the following:
    ___Patient's initials (not name)
    ___If the study requires a patient study identification number on the inventory sheet, check that the number is filled out and is correct
    ___The dose and frequency of administration
    ___Initials of recorder and pharmacist
    ___Lot numbers and expiration dates
___Inventory the drug in the IDS central pharmacy. Make sure that the book inventory matches what is on the shelf. If not, try to resolve the discrepancy by checking the math, comparing prescriptions to inventory records, and consulting with the individuals who dispensed the drug.
___For closed studies, verify that all drugs were returned or transferred or discarded and verify that the records that indicate the disposition of the drugs are available.

Remember: Ditto marks are not allowed on accountability records. Only use black pen. Do not use correction fluid. Make corrections by putting a single line through the item and writing in the correct item. Initial and date the correction.

List issues that require further investigation or intervention by the audit coordinator

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_____

Initial preparation of file _____ Name _____ Date

Reviewing pharmacist _____ Name _____ Date