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ELECTRONIC DRUG ACCOUNTABILITY SYSTEMS: ENSURING COMPLIANCE, SAFETY, AND DATA INTEGRITY IN CLINICAL TRIALS

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Executive Summary

The increased frequency of federal audits, coupled with the complexity of modern clinical trial design, and the growing number of federal regulations governing clinical trials has made drug accountability management more challenging than ever before. The traditional, paper-based methods increase the risk for human error, as well as illicit activity in clinical trials. Failure of an FDA site audit due to insufficient or inaccurate paper-based drug accountability records is common. A failed federal audit leads to costly trial delays to the sponsor, and may result in non-approval of the investigational drug, or criminal liability for the investigator. Electronic drug accountability managed through an IRT system is a cost-effective way to ensure compliance with federal regulations, reduce inefficiencies, preserve the integrity of data and increase patient safety in clinical trials.

Clinical trial sites, both foreign and domestic, have been subjected to an increasing number of FDA audits in recent years. Federal investigators cite non-compliance with federal drug accountability regulations as one of the most common problems found in site audits.[1,2] A failed site audit is a serious problem for a clinical trial, leading to costly delays, non-approval of the investigational drug, or criminal liability.[2,3] Ensuring compliance with federal regulations is key to the success of a clinical trial and the entire drug development program.

Federal drug accountability standards

FDA trial site audits are designed to evaluate the conduct of research and ensure that the rights, safety, and welfare of the human subjects participating in those studies have been protected.[4] During a site audit, federal auditors investigate six areas to determine that a site is in compliance with federal drug accountability regulations.[5] In brief, investigators seek to answer the following questions:

1. Who is authorized to administer or dispense the investigational drug?
2. Has the investigational drug been supplied to any unauthorized person?
3. Can the records for investigational drug inventory be reconciled, i.e., the quantities shipped, received, used, and returned or destroyed?
4. Can drug shipments, dispersals, and returns be verified?
5. Is the drug stored in the manner mandated by the protocol?
6. Does the storage of drugs with the potential of abuse meet the federal regulations for controlled substances?

Consequences of noncompliance with federal regulations

The consequences of non-compliance with federal drug accountability regulations are serious, and can be severe and far-reaching. Sites with inadequate drug accountability management may inadvertently increase safety risks for patients. For example, site staff might disperse the wrong dose or the wrong drug to patients. Insufficient drug accountability records may make it difficult for site staff to determine if a patient is treatment compliant or has returned all unused trial drug.

Managing costs for a drug development program is another motivating factor for complying with federal regulations. Trials found to be non-compliant may suffer long delays, which increases trial costs to the sponsors. In addition, society, as a whole, may suffer from the delay of essential medications.[1] The delays in approval of the cancer agents Herceptin® and Rituxan® serve as stark reminders of the potential costs of postponing a trial. The 1-year delay in bringing these drugs to

market reduced Genentech's earnings by an estimated $730 million and $260 million, for Herceptin and Rituxan, respectively.[6] The loss to society by delaying the availability of potentially life-saving drugs is, of course, incalculable.

Proper drug accountability management is essential not only to ensure patient safety and maintain trial timelines, but also to protect the integrity of clinical trial data. Failing a federal audit due to inaccurate drug accountability records can invalidate efficacy and safety data, which can ultimately lead to non-approval of the investigational drug. The consequences of an audit failure can be serious for investigators, too. Investigators are ultimately responsible for the disposition of investigational drugs on site. If an audit reveals that investigational drugs have been diverted by staff with criminal intent, the investigator could be held criminally liable.[1]

Current challenges of drug accountability management

Most trial sites use a manual process, i.e., paper records, to manage drug accountability. This type of accountability system is difficult to administer and burdensome for busy site staff, as well as clinical trial monitors. Manual accountability systems can also create opportunities for illicit activity by staff as well as patients, such as drug diversion for future use or sale and disregard for randomization assignments.

However, these challenges are preventable. Advances in technology have rendered paper-based drug accountability records obsolete. Electronic drug accountability, a function that can be added to an existing interactive response technology (IRT) system, can help ensure that trial sites are compliant with federal regulations. In addition, electronic drug accountability can increase the safety of patients in clinical trials, save time and money, and ensure the validity of the data.

Federal clinical trial site audits: 1977 to present day

The FDA began routine clinical trial site audits in 1977.[1] Since then, the number of routine, for-cause, and directed site-level inspections has steadily increased worldwide.[3] Insufficient drug accountability records were found in 25% of sites audited by federal investigators from 1977 to 1990.

Although drug accountability management has improved in the ensuing years, it remains a challenging problem.[2] From 1994 to 2010, federal investigators found inadequate drug accountability records in about 15% of clinical trial sites audited in the United States and Europe. In Western Europe, the percentage was even higher, about 20% of investigated sites were cited for inadequate drug accountability records.

Sites using manual systems typically fail federal audits for two basic issues: inaccurate inventory records and insufficient dispensing records. A failed FDA audit at a Johnson & Johnson clinical trial site in 2008 is a classic example. Federal investigators found drug accountability records reporting that multiple patients received the trial drug at precisely the same time, which was quite simply a physical impossibility.[4]

It is not difficult to imagine how a simple error might occur at a busy clinical trial site that uses a paper-based drug accountability system. Staff must update drug accountability records in a timely manner to avoid lapses in memory, such as the exact time the investigational drug was dispersed to each patient. Investigators, who are responsible for drug accountability at their site, must rely on their staff to keep detailed and accurate records of investigational drugs that correspond to on-site trial supplies. A simple error uncovered during a site audit could invalidate the data, disrupting the trial and possibly the entire drug development program.

Complexities of the paper-based drug accountability system

Paper-based drug accountability systems are inherently complex, making them rife with the potential for error and obfuscation.[7] The process begins upon receipt of the investigational drug at the site. Site staff must verify that shipment records match the contents of the shipping container. Once verified, authorized personnel must sign, date, and file the shipping record in a regulatory binder. Authorized personnel then store the investigational drug in a secure area according to the requirements of the protocol. A staff member must enter the shipment information into the drug accountability log. If IRT is employed in the trial, site staff must place the call to confirm the receipt of the drug shipment, and then return the proof-of-receipt to the sponsor. If a paper-based system is used, site staff must send paper documentation of proof of receipt to the sponsor. When the trial commences, detailed drug dispensing records must be written and updated across multiple documents in a timely manner.

The drug accountability paperwork does not end at study termination. When the trial is complete, the accountability logs must be updated, and discrepancies reconciled. Copies of the accountability logs need to be made and returned along with the original drug shipment record; copies are filed on site, as well. The reconciled log must be included in the shipping container with the returned investigational drug and shipped back to the sponsor. It is easy to understand how one moment of inattention by a staff member can result in an audit failure.

Evolution of clinical trial requirements

In recent years, drug accountability management has become more challenging, simply because overall clinical trial management has become more demanding. This is due, in part, to the complexity of modern clinical trial designs.[8] For instance, the average length of a clinical trial increased by nearly 70% from 1999 to 2005. Not only are trials of greater duration but they also demand a greater number of procedures. From 1999 to 2005, the annual growth rate of unique procedures per protocol increased by 6.5%. Subject eligibility is another area of growth in clinical trial design. The number of eligibility criteria required for subject participation has increased by 58% since 2002. Taken together, these changes have had negative effects on enrollment and retention rates in clinical trials, which can cause delays or early termination. They also increase the duties of site staff, creating a work environment ripe for errors in drug accountability management.

Just as clinical trials have evolved, so has the regulatory environment. Over the past 20 years, federal regulations governing clinical trials have included changes in drug accountability regulations. Drug accountability regulations now extend to clinical and manufacturing practices. The parts of the Code of Federal Regulations (CFR) most affected by change are CFR 21, Parts 50 (Protection of Human Subjects), 54 (Financial Disclosure), 56 (Institutional Review Boards), 312 (Investigational New Drugs), and 314 (New Drug Applications). These regulations charge the FDA with monitoring all aspects of study conduct and reporting for regulated research through a comprehensive program of on-site inspections and data audits. Inspections apply to both non-clinical and clinical research, and all staff involved in regulated research, including institutional review boards, sponsors, contract research organizations, monitors, and clinical investigators.[3] These new regulations add layers of complexity to the innately complex process of accurate, paper-based record keeping.

Federal audits can reveal that illicit activity with investigational drugs has occurred among both clinical site staff and patients. Paper-based drug accountability systems make it difficult to prevent such activities, because records are easily altered to obscure illicit actions, and it can be difficult to track patient compliance with protocol (e.g., discerning whether all unused drug was returned).

Interactive response technology: an e-solution to drug accountability management

A technological solution to the problems central to paper-based drug accountability already exists. Interactive response technology (IRT) systems are used in many clinical trials for a myriad of tasks, from patient randomization to drug supply management and allocation. IRT is ideal for drug accountability because it tracks drug dispensing units by warehouse, depot, and site location, and by batch, bulk lot, packaging step, label group, and patient allocation.

All trials can benefit from using IRT for drug accountability management. However, some types of trials may realize greater benefit than others. A longitudinal, home-based trial with a regimen of multiple doses stands to benefit the most from IRT-driven drug accountability. The sheer number of drug accountability requirements in a lengthy trial with a complex regimen increases the opportunities for human error and drug diversion among site staff and patients. Conversely, hospital-based trials typically have less drug accountability requirements. The benefits of IRT in hospital-based environments are comparatively fewer than with a home-based trial, but no less important.

IRT is an ideal system for management of drug accountability because it was designed with safeguards that reduce the risk of human error. It automatically time-stamps dispensing information, automatically flags entries that do not adhere to protocol, enforces compliance by mandating that staff write summary statements for potential protocol deviations, and creates an audit trail with electronic signatures that helps preserve the integrity of the trial data. IRT also allows for remote, site-level monitoring of drug accountability logs. Finally, to meet the unique needs of every trial, some vendors offer a fully customizable IRT.

These inbuilt features give electronic drug accountability many advantages over the manual, paper-based process. The safeguards involved with electronic drug accountability management make it a more accurate and efficient method than its paper-based counterpart. For instance, IRT links records, eliminating time-consuming collating of files at the end of the trial. This timesaving feature is also cost-effective, because it reduces the necessity for costly site visits by the clinical trial monitor. On-site monitoring can account for up to 35% of the overall cost of a Phase III trial.[9]

IRT centralizes information, reporting it in a uniform format that is available for review at any time. This is a vitally important feature for trials investigating drugs with the potential for abuse. For such trials, the FDA mandates that sponsors provide all information, including case report forms and final outcomes, on all instances of drug diversion, discrepancies in inventory of the clinical supplies of the study drug, and noncompliance and protocol violations.[10] Complying with this federal mandate requires a substantial increase in the administrative burden on clinical site staff when paper-based methods for drug accountability are used. The availability of centralized trial information afforded by an IRT system is invaluable for this and other tasks, including reconciling inventories of investigational drug supplies at study termination.

A centralized accountability system allows sponsors to easily track trial drugs from manufacture to shipping, and use, return, or destruction. IRT also provides site-level, real-time tracking of investigational drug supplies. This reduces the possibility of drug diversion or inappropriate drug assignment by clinical staff, as well as patient noncompliance.

Implementing electronic drug accountability

Although electronic drug accountability software has been available since 1990,[11,12] the clinical trial industry has been slow to adopt it. Resistance to change is a common phenomenon among individuals, as well as organizations, and even across entire industries. Change can be difficult to accept, even when the benefits of change are clear.

Organizations should expect and plan for some resistance to change before undertaking the switch from a paper-based drug accountability system to an electronic drug accountability system. High-level stakeholders within the organization should develop an implementation plan for the change. Standard operating procedures (SOP) for adoption and use of electronic drug accountability must be written. The new procedures should ensure that electronic accountability can fully replace the paper process when implemented.

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