PEER REVIEWED

Automated Accountability: Maintaining a Chain of Custody from Release to Destruction

New solutions are proliferating to improve the efficiency of the clinical research function within pharmaceutical companies and contract research organisations (CROs). One work stream, in particular, that has been ripe for transformation is the process by which sponsors demonstrate to regulatory authorities that all investigative products (IP) have been handled in accordance with Good Clinical Practices (GCPs) and Good Manufacturing Practices (GMPs).

The accountability and reconciliation process is noted for being time-consuming and error-prone, two characteristics that result in it adding significantly to trial costs and timelines. The onerous task of reconciling discrepancies in supply records that have accumulated over the course of a trial often adds as much as two years to the study closeout phase.

In many cases, accountability and reconciliation are still paper-based, and in others they are supported by fragmented solutions that do not completely solve the problem. For example, accountability solutions that do not prevent discrepancies from creeping into data sets do little to improve reconciliation. Solutions that fail to link the drug assignment to the chain of custody records don't provide a continuous, unbroken lineage of what was assigned, dispensed and returned, so they cannot confirm study compliance with regard to IP consumption.

In contrast, chain of custody software that is integrated with the trial's interactive response technology (IRT) system provides visibility to, and an audit trail of, product conditions and movement throughout the trial. This improves patient safety, reduces trial risks, and strengthens monitoring and compliance, while cutting costs and shortening timelines.

In the following pages we review the challenges that sites and sponsors/CROs face in complying with good practices and explain how accountability can be improved to reduce trial risks and all but eliminate the dreaded reconciliation process.

The Regulatory Requirements: Accountability — and Proof of It

As is often the case with regulatory guidance, worldwide regulatory bodies like the FDA, EMEA, etc., document on maintaining an auditable chain of custody for drug products, stipulate what must be achieved, but not how it should be achieved. Nor do regulators specify how requirements can/should vary with different forms of IP packaging, across therapeutic areas, or by study design (open label, double blind or single blind).

The requirements for maintaining a chain of custody are governed by GCPs (which relate to the protocol and the treatment and protection of the study subject) and GMPs (which pertain to the manufacture, distribution, and quality of the investigational product). Essentially, the sponsor must be able to prove that the IP administered to patients was in a safe condition and that it was used only by subjects and according to the prescribed dose. All unused IP must be accounted for at the end of the trial, and any discrepancies in records must be documented and explained.

A Necessary Evil

Capturing accountability data and reconciling any discrepancies in it has been called a "necessary evil." It is important, but it is also painful, time-consuming, and costly.

Site staff are required to record the movement and dispensation of IP at every step of the way through a trial, whether it is in accepting a shipment, administering a drug to a patient, or accepting an unused drug kit back from a patient. But, this seemingly simple requirement is difficult to meet because site staff are busy with their first priority: patient care. Maintaining records is made cumbersome with a variety of fragmented solutions, variations among vendor products and standard operating procedures (SOPs) that complicate the site's work. Different aspects of the chain of custody are recorded in different systems, and often accountability work needs to be duplicated on paper records to adhere to site SOPs.

Complying with expectations – both those of the sponsor and of their own internal processes – is commonly a struggle for patient-facing site staff. Consequently, their records are often incomplete and contain errors (many caused by having to transcribe information from multiple fragmented systems into one).

Some sponsors have sites record accountability information in the electronic data capture (EDC) system. However, *because the EDC is not used for randomisation and trial supply management (this is performed in the IRT), this method creates a gap in the chain of custody record*. It cannot automatically be used to help ensure – or validate – that the drug assigned is the same one that was administered, returned, and destroyed. This problem is exacerbated by the fact that sites update EDC records retroactively, causing further delays in detecting errors early, let alone correcting them.

It then falls to CROs and sponsors to correct these errors, complete missing data, and resolve discrepancies in the records. The work is so laborious that it is typically not addressed until the end of the trial. This reconciliation process can add months and even years to the trial timeline, delaying the approval of a new therapy.

Despite there being a number of solutions on the market, the problem persists. One sign that accountability issues have not been adequately addressed is the number of warning (483) letters that the FDA issues to site investigators concerning the chain of custody and specific processes around accountability and protocol compliance at sites. In fact, inadequate record-keeping and

inadequate accountability for IP are two of the most common issues cited in FDA warning letters.[1]

The Current State, by the Numbers
An informal poll of Almac Clinical Technologies' clients shows that:

- About HALF rely on a combination of paper and electronic solutions for tracking supplies returned for destruction.
- 52% had chain of custody issues that caused data problems, short supplies, or delayed timelines.
- 65% had dispensing errors that impacted patient treatment, safety, and/or data validity.
- 30% use EDC systems to collect accountability data from sites.
- 65% use an IRT system to collect accountability data from sites.
- 85% still use some form of paper records for accountability and reconciliation.

Envisioning the Ideal Solution
Currently, there is no standardisation or best practice that will guide sponsors on how to collect, present, and maintain accountability data. This disparity of approaches has led to the problems just described.

In order to overcome these persistent challenges, the industry needs a solution that:

- **Provides end-to-end traceability.** For the chain of custody to be complete, the IRT and accountability functions *must* be handled in the same system (see Figure 1.) This then can satisfy both internal and external auditors.
- **Is configurable.** Any solution must work with all protocols and supply designs *without adding to start-up time*. In other words, the size, complexity, and design of the IP should not affect the ability of the system to function. The system should also be flexible enough to work with multiple IP destruction strategies with different site, country, or study-level parameters. Ideally, the solution should be configurable even if certain study details (such as whether IP must be accounted for at the unit or kit level) have not yet been determined at the time of the system build.
- **Prevents errors and omissions.** Problems should be prevented to the extent possible and if they do occur, the system should make it easy to catch them quickly before they multiply.
- **Delivers real-time visibility to all IP-related events.** Users should be able to analyse and cross-reference patient records with supply records, all on a single screen. They should be able to assess and report on the progress of the entire chain of custody, again in real time. And, they should be able to perform root-cause analysis of issues relating to any IP event so they can address them as soon as possible
- **Is easy and intuitive for users.** For site staff to use a system when and how intended, it must make their jobs easier and guide them through the steps they're asked to perform instead of being an obstacle in their daily work.

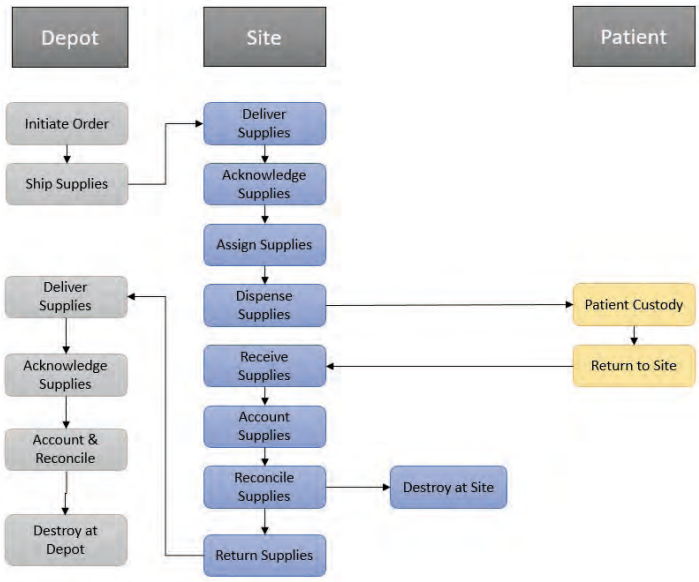

Figure 1: An End-to-End Chain of Custody

Recommendations
Companies wishing to maintain a complete, electronic chain of custody will need to:

- **Capture accountability and reconciliation data in the IRT system.** This is the only way to leverage both clinical and supply events in the process. Companies that attempt to track chain of custody from within their EDC system cannot realise the benefits discussed here unless they transfer the chain of custody functions into the IRT (this is because it is the IRT that stores the randomisation and dispensing information).Continued use of the EDC system for accountability will only perpetuate the problem of data fragmentation and transcription errors. At the same time, continuous feeds from IRT systems to EDC can keep the two systems in sync so that sites can continue realising the patient-centric information and benefits that EDC systems offer.
- **Engage supply and distribution vendors early.** To avoid having the supply strategy, packaging design and accountability procedures developed as an afterthought, be sure to involve your vendors when you are still discussing the protocol. All of these considerations should be addressed in parallel, not sequentially so that the best protocol and supply cost-saving strategies are taken into account up front for maximum trial benefits.
- **Train and motivate site staff to use the chain of custody tool throughout the trial.** An electronic chain of custody solution is designed to be used as the trial progresses, not sparingly or at the end. A well-designed

system will guide users through steps to ensure complete collection of data and will provide error-correction workflows – benefits that can only be realised when the system is used routinely.

Supporting Clinical Operation's Compliance and Operational Efficiency

A chain of custody tool that functions within an IRT would be more than a "housekeeping" tool for managing and monitoring supplies. It would support the clinical operation's dual goals of compliance and operational efficiency. Almac Clinical Technologies' Accountability & Reconciliation Tracking (ART™) within IXRS® 3 (our IRT system) is native, extended functionality that:

- **Supports compliance with GCP.** Because the software captures both the drug assignment (within the IRT) and details on the IP that was dispensed and returned, it serves as an extra step to ensure that the protocol was followed. Non-compliance is both reduced and highlighted for remediation.
- **Makes it easy for monitors to do their job.** The toolkit provides one consolidated view of clinical and supply information that enables clinical research associates (CRAs) to plan their work up front and immediately assess compliance and identify problems. Then they can correct them equally and easily.
- **Produces correct and complete records.** Intuitive workflows guide site users through all required steps so that they produce correct records. Validations stop users from committing wrong data, ensuring accurate capturing of information.
- **Increases patient safety.** Real-time validation checks at the time of dispensing and system back-end checks on the eligibility and condition of drug supplies throughout the supply chain reduce the opportunity for patients to be given the wrong treatment or a treatment that has expired or experienced a temperature excursion.
- **Speeds study closeout.** Due to the electronic accountability function, the system catches most discrepancies before they're recorded, and those that do occur can be addressed at once. User errors are eliminated due to system validation checks. So, discrepancies don't accumulate, and reconciliation at the end of the study should be just a formality that doesn't extend the study timeline. It is well known in the industry that every day that a study is extended a sponsor can lose anywhere from $600,000 to $8 million in sales opportunity costs.[2] Slashing study closeout times will significantly impact a sponsor's/CRO's margins and profitability.[3]

End-to-End Visibility/Accountability for Supply Management

Almac's paperless chain of custody user interface provides real-time traceability of clinical supplies as the study progresses, making compliance with GMP routine and reconciliation and at study close a mere formality. For supply managers, the tool provides:

- **Full Traceability, On-Demand Assessment.** Supply managers have 100 per cent visibility to supplies throughout the supply chain, at any point in time. A barcode-enabled platform provides reliable traceability of supplies as they move through the trial, recording their whereabouts and condition.
- **Immediate Reconciliation Capabilities at the Depot.** The system guides site users through the process of managing and documenting returned IP (unused, damaged, or expired drugs and empty containers), forcing them to complete all of the required fields. Logic checks prevent basic data entry errors. Thus, the information that is passed on to depots is cleaner and more complete than what is delivered via paper-based systems, so depots can close their records at once. When depots receive returned shipments from sites, they can easily compare the kit contents to the full accountability details provided in the shipment manifest.
- An audit trail. At any time, users can access a complete and auditable trail of the physical chain of custody for all clinical supplies. These records can be produced for auditors, indicating that 100 per cent of lots and returned shipments were successfully destroyed.

Conclusion

An electronic chain of custody solution that incorporates all IP events — from IP release all the way through to product destruction — in a single system is the only way to comply thoroughly with GCPs and GMPs. When this solution is armed with validations and flexible, configurable workflows, then one will gain maximum efficiencies and streamlining in the accountability and reconciliation processes.

The right system will help sponsors and CROs realise time savings that come from easy setup, streamlined site ops, error reduction, and discrepancy resolution. Additionally, real-time validation checks at the time of dispensing and ongoing visibility to the condition of drug supplies throughout the supply chain improve compliance, reduce risk to patient safety, and safeguard against trial delays.

REFERENCES

1. "Top 3 Reasons an FDA Warning Letter is Issued to a Study Investigator," imarc, accessed at http://www.imarcresearch.com/3-reasons-fda-warning-letter-issued
2. http://blog.covance.com/2013/02/clinical-trial-challenges/
3. https://social.eyeforpharma.com/clinical/slashing-cost-clinical-trials

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