10 Tips to Consider when Planning for Accountability, Reconciliation and Destruction of Clinical Trial Material

Monica English* and Amy Ma, PhD

Introduction

All experimental compounds tested in humans during clinical development are under stringent control to ensure that these drugs are administered only to eligible patients participating in approved study protocols. To that end, regulatory agencies worldwide mandate that all investigational products manufactured for clinical trials must have cradle-to-grave tracking for accountability, reconciliation, and destruction.

The lifecycle of investigational product (IP) is complex, transitioning from a manufacturing environment during production to a clinical environment during experimentation. Each of these situations has a unique body of governing regulations, Good Manufacturing Practice (GMP) or Good Clinical Practice (GCP), respectively. Additionally, IP reverts back to GMP when accounted, reconciled, stored, and packed for destruction as waste, creating an additional transfer between these environments. It is critical that you be able to document and demonstrate to regulatory authorities that you are in complete control of the drug supply chain at all times and can account for the whereabouts of all manufactured investigational product, whether consumed or destroyed.

Currently the administrative burden of accounting for and reconciling clinical supplies rests largely on the investigative sites, monitors, and depots who generally perform these tasks manually and without the benefit of a central tool that tracks clinical material from manufacture to dispensation and return [1]. You can reduce this burden and streamline the process by considering and implementing these 10 easy tips, that will ultimately save money, minimize errors, and more efficiently reconcile all IP at study closeout per regulatory requirements.

1) Consider your end-game activities during start-up.

By developing a plan for the accountability and reconciliation of IP before the study starts, you will be able to improve the accuracy of your trial budget and reduce data reconciliation efforts at the end of the trial.

The need for rigorous control over IP progress through the manufacturing and clinical trial processes is apparent for controlled substances, those drugs with high potential for abuse including narcotics, stimulants and hallucinogens. However, in reality *every* investigational product requires a clear and documented plan for accountability and reconciliation, not just those that can create physical or psychological dependencies.

In many instances, the timeline to launch the study and dose the first patient is very tight. Typically there are delays each step along the way. Typical delays include: batch failure during analytical testing, modifications to protocols and lead-time dependencies with labeling and packaging vendors'. The study start date is almost never extended to compensate for these delays. As a result, the narrow focus on study start-up activities often precludes the necessity for considering endgame activities, which can result in significant unexpected costs at the end of a study. Early planning can help studies close out more quickly and efficiently and also bring "hidden" costs to light for inclusion in the overall study budget. Failure to account for closeout activities up-front can result in the

Definitions for terms used in this paper are as follows:

- **Accountability**: The amount of IP dispensed to a patient vs. the amount returned by the patient. This is typically documented by the site at the smallest dosage level, i.e. tablet, capsule, or mL.
- **Reconciliation**: Full accounting for the amount of IP released from the packager, shipped to clinical sites, dispensed to patients, returned from patients, and destroyed. The amount of investigational product left at the site at close-out plus the amount dispensed to patients during the study should total the amount initially received. The following details are generally captured in the IP documentation and serve to track the progress of IP through its cycle from manufacturer to warehouse to site to warehouse and destruction facility:
  - Batch/lot#
  - Kit #
  - Site #
  - Patient #
  - Date assigned
  - Date returned
  - Amount returned
  - Date destroyed
- **Destruction**: The destruction of "all" remaining IP.

need to subcontract the reconciliation tasks out, leading to potential budget overrun.

Figure 1 illustrates the potential paths of IP through its lifecycle from manufacture to destruction and the types of information captured at each step during transit. This information is typically recorded by different users in different formats (supply logs, dispensation logs, and spreadsheet files) as the IP travels through the supply chain. The Manufacturer, Packager, Warehouse, Depot, and Site may all account for and reconcile IP as the study drug flows through their respective location but typically do not reconcile their data with each other. You, however, as the study sponsor, must ultimately be able to trace and document the drug's path through each functional area and resolve any discrepancies in the accounting process.

You need to be aware of your own unique business practices regarding how to handle the remaining IP at the end of a trial and to be mindful of the demands created on resources and budget in order to comply with regulatory requirements. While it is possible to backtrack and collect existing IP data after the fact, proactive planning before the study starts can minimize the time and effort required to gather and clean the information for accurate accounting and reconciliation at the end of the study.

2) **Determine who will manage the accountability/reconciliation of IP.**

Defined roles and responsibilities for these tasks help to make the process more efficient at the time of reconciliation. Assigning a resource proactively during the planning phase rather than reactively when the need arises ensures that the task will be completed and will be meet all regulatory requirements.

3) Review and understand the local regulatory requirements.

Regulatory agencies globally require documentation of and accounting for all IP produced, but the requirements can vary depending on the country in which regulatory approval is being sought. Individual sites must abide by local authorities, and the sponsor must abide by the local regulations where the drug approval application is being filed. So, it is imperative that you take the time to carefully review all local regulatory requirements before the study starts.

4) Decide who will perform reconciliation. Site vs. warehouse considerations.

Having both the site and the warehouse perform reconciliation on the same IP invariably leads to discrepancies. Site reconciliation is usually more accurate, more efficient, and less costly because the sites typically deal with smaller quantities at any given time, and can reconcile the IP as it is returned. GCP guidelines require that sites account for both used and unused drug at the time of study closeout, and you can leverage this requirement for site-level accountability as part of the overall accountability process. Since site reconciliation is done before the IP is shipped back to the warehouse, the site knows exactly how much study drug was consumed during the study.

Contract warehouses can also perform accountability and reconciliation, but will often charge an additional hourly fee or per-receipt fee to receive, count, report, and prepare IP for destruction. Many also charge a per-pallet per-month fee for storage, starting with the first receipt of a clinical return. Warehouses also may not have resources immediately available to perform ongoing reconciliation as the returns arrive. Shipments may begin to accumulate before reconciliation is performed, and the accumulation can then translate into additional storage fees.

Warehouses do not operate under GCP; consequently their reconciliation activities are often performed with unregulated documentation procedures (often using simple spreadsheet programs). To maintain compliance with with 21 CFR Part 11 (FDA's requirement for electronic record keeping and maintaining an audit trail around investigational products), the warehouse tracking spreadsheets must be printed and signed because they are generally neither validated nor controlled electronically. These hard copies must then be used as data to maintain the audit trail. Further, warehouses can often only track kit numbers because they do not have access to study data from the sites, and thus cannot map kit numbers to patient numbers. This gap becomes the responsibility of the sponsor to fill, reconciling warehouse spreadsheets with the site accountability records to track assignments and returns at the level of the medication kit.

5) Decide ahead of time on how you will re-distribute supplies.

Determine in advance what regulatory requirements are in place and what your policy will be in terms of redistributing supplies. By documenting your own internal requirements and those of external agencies in advance, you can help ensure that supplies can be distributed quickly to the necessary site, while at the same time maintaining a sufficient audit trail.

It is common that not all IP allocated to a site is consumed due to poor recruitment or low enrollment. To maximize the use of available study drug, sponsors often redeploy supplies to other sites with true demand. This practice can help prolong the supply of study drug but can also introduce uncertainty and complexity in accountability due to the difficulty of tracking all the locations where the IP has been and the route taken. While re-distribution is a fairly common practice, regulatory agencies typically discourage site-to-site and site-to-warehouse-to-site shipments because storage cannot be confirmed once the initial shipment leaves the warehouse, and these subsequent shipments may not have QA inspection and release processes. By clearly documenting what your policy and requirements are in advance, you can prevent a significant amount of confusion once the study begins.

6) Decide where the IP should be destroyed.

Typically IP must be destroyed by a licensed incineration facility that can issue a certificate verifying destruction. For non-controlled substances, you also have the option of having the sites destroy unused drug themselves. However, many sponsors elect not go this route due to the risk of the drug being diverted and ending up on the street, creating legal and liability issues. Outline the process for returned IP to travel from the warehouse to the destruction facility and establish your vendor agreements with the destruction facility prior to the accumulation of IP.

7) Ascertain the timeline for IP destruction.

Again, it is important for you to engage your shipping and destruction vendors early in order to understand the lead times required and the costs associated with freight and transport. Often transport-runs to the destruction facilities must be scheduled a month in advance to ensure that a full load is being delivered. This time should be incorporated into your planning process. Additional considerations include inventory storage and warehousing while waiting to acquire a full-load for destruction.

8) Outline the disposal procedure for the sites.

In the event that the sites are authorized to destroy returned IP, what documentation is required? What is the disposal procedure? Many sponsors elect not to have sites destroy IP directly due to the risk of the drug being diverted from a controlled environment. Having the sites return drug to the warehouse serves as an internal check to ensure that all drug stays within your control. However, if you decide to allow the sites to destroy material, make sure they are adequately trained and all documentation is provided on how you want the material to be destroyed. Once the IP concludes its lifecycle in the realm of the site, it transitions out of GCP and back to GMP, so ensure that the destruction process meets the requirements of the correct guidelines.

9) Proactively consult with your waste management vendor to understand the cost implications of destruction.

If you would rather the site not destroy the IP, you must proactively engage your waste management vendor to understand all “hidden” costs and transport requirements. Again, return activities are often not considered when the study budget is being developed and can lead to cost overruns during close-out. There are additional charges for hazardous material, regulated waste, medical waste, or any other materials that require special handling and transport. Check with your waste management vendor early on in the process to avoid surprises and plan accordingly. You should also discuss with your waste management vendor what types of material can be destroyed locally and the impact that has on transport requirements and freight charges. Many vendors will require full-loads to be destroyed at a time. This needs to be considered during budgetary planning. Additional storage and warehouse costs will need to be accounted for while you wait for a full-load to accumulate at the warehouse.

10) Optimize your IVR data stream to streamline data collection

As described previously, packagers, warehouses, and sites all touch IP as it flows through each location and use different tools to account for and reconcile materials that they handle. However, because these processes are disparate and largely manual, there is no easy way to follow the progress from one environment to the next.

One way to streamline the data collection of the accountability and reconciliation process is to incorporate the IP return function into a centralized database such as an interactive voice response system (IVRS). Typically, an IVRS is already being used to track IP release through clinical distribution and dispensations to patients. An IVRS can significantly minimize the administrative burden on the site when used for randomizations and drug assignments, and with proactive planning the IVRS can also be leveraged to facilitate site accountability of returned IP. In addition to investigative sites, warehouses and depots can also use the tool to enter which IP a patient has returned and capture the date the IP was destroyed.

Figure 1 illustrates the areas that can be easily consolidated into an IVRS to provide users with a central tool for accounting and reconciling study drug. The IVR houses all the data that would otherwise be captured separately by the sites and warehouses in a single database. You can easily access this database to stay on top of closeout progress. Most commercially available IVR systems are fully validated and developed in compliance with 21 CFR 11, eliminating the sponsor's need to piece together incongruent data in order to meet regulatory requirements. As some data is still captured through handwritten documentation, using an IVR also eliminates the need for data entry and verification required for transcription into an electronic tracking file.

Importantly, an IVRS does not eliminate the need to count unconsumed medication, but it can consolidate all information from release to destruction in one system. The entire reconciliation can be easily accessed at any time through IVRS-generated reports either by request or on a scheduled basis; Figure 2 shows a sample of a report summarizing return activity. An IVRS can also help consolidate cost and reduce or eliminate the per-hour fees associated with warehouse reconciliation and per-receipt return fees. This approach can reduce many hours of reconciling various reports and documents manually, which also reduces costs.

Conclusion

By following these 10 easy tips, you will be able to address all your major accountability, reconciliation and destruction issues before your trial even starts. Investing in proactive study planning with early consideration of endgame activities can save time and reduce the risk of cost overruns. While it is often difficult to establish concrete plans while a protocol is still being developed, thoughtful planning and consideration in conjunction with the clinical study manager and clinical supply manager can prevent the surprises of unforeseen tasks and hidden costs. Leveraging readily available tools such as IVRS not only during the study itself but after the last patient out can streamline many labor-intensive activities and minimize errors.

Reference

1. Dowlman, N., Kwak, M, Wood, R, Nicholls, G. "Managing the Drug Supply Chain with eProcesses," Applied Clinical Trials, **15** (7):40-45 (2006).

Monica English and Amy Ma are Project Managers with Covance IVRS, 210 Carnegie Center, Princeton, NJ 08540, (609) 452-8550. *To whom all correspondence should be addressed, email monica.english@covance.com.

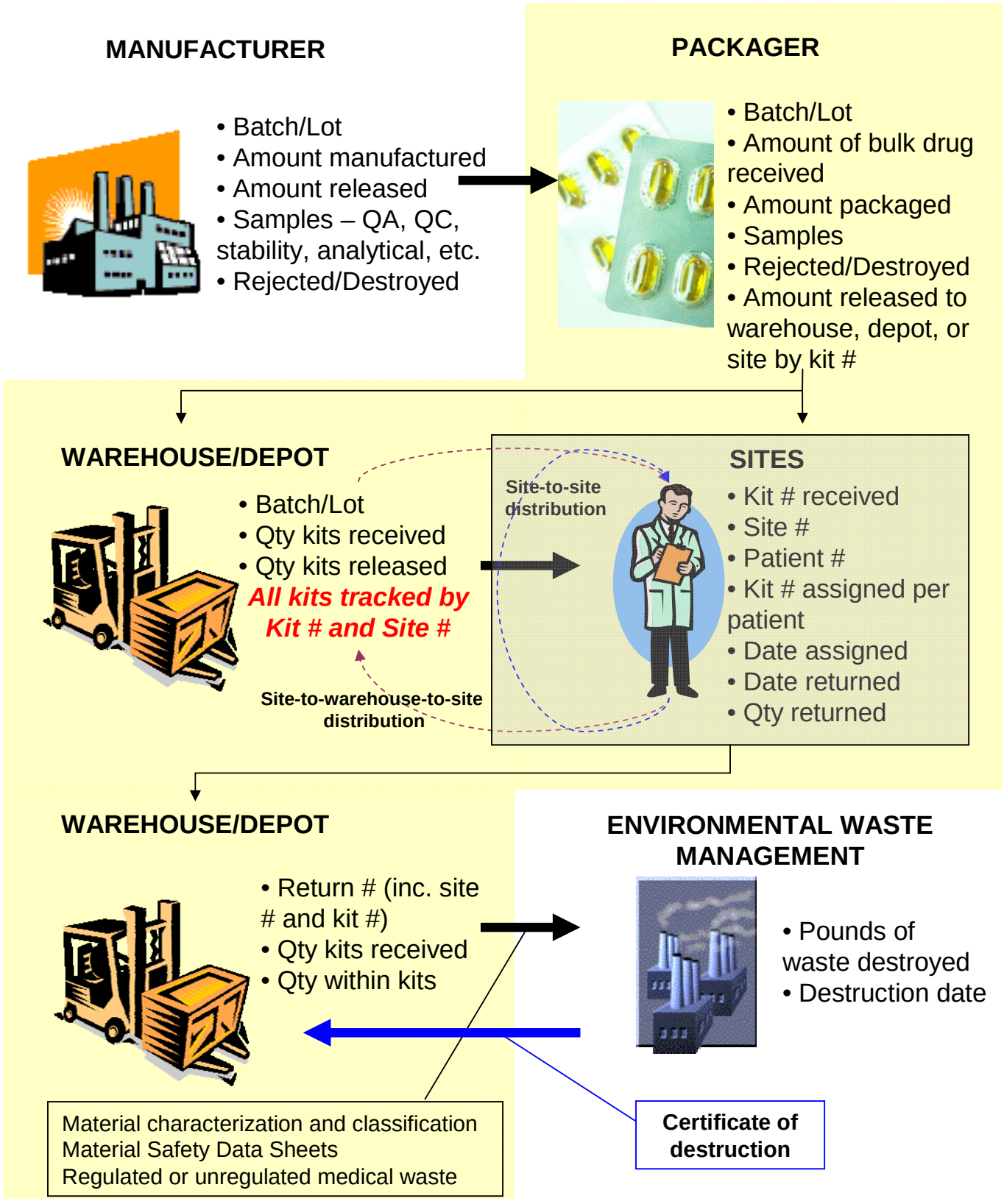

Figure 1. Potential paths for progress of investigational product through its lifecycle from manufacturing to destruction. Different information is tracked by different users types as it touches each area. Data captured by all of the areas shaded in yellow can be consolidated into a single system such as an IVRS which is easily accessible to all users and provides the sponsor with convenient access to complete oversight of these areas of the supply chain.

ABC Therapeutics

Protocol: ***ARD 101***

Inventory Returns at All Sites Summary Report

Country Name: England
Site Number: 1000-1
Principal Investigator: Demo Site

Subject Screening Number	Subject Randomization Number	Dispensing Unit Assigned	Bottle Number Dispensed	Date Assigned	Date Returned (Local)	Quantity of Capsules Returned
9001	1016	98765	12345	1-Mar-2006	8-Mar-2006	0
9001	1016	98765	12346	1-Mar-2006	15-Mar-2006	0
9001	1016	98765	12347	1-Mar-2006	22-Mar-2006	10
9001	1016	98765	12348	1-Mar-2006	22-Mar-2006	20
9001	1016	98765	12349	1-Mar-2006	22-Mar-2006	20
9002	1019	97531	23455	2-Mar-2006	9-Mar-2006	0
9002	1019	97531	23456	2-Mar-2006	16-Mar-2006	0
9002	1019	97531	23457	2-Mar-2006	23-Mar-2006	0
9002	1019	97531	23458	2-Mar-2006	30-Mar-2006	6
9002	1019	97531	23459	2-Mar-2006	7-Apr-2006	20

Issued by: **Covance Interactive Voice Response Services**
210 Carnegie Center, Princeton, New Jersey 08540
Issue Date and Time: **01-Jun-2006 02:45:50 pm Eastern Time**

Figure 2. A sample report detailing returns to an investigator site, providing consolidated subject information, drug assignments and return information.