

## Clinical Trial Supply Fundamentals

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Manufacturing and distributing clinical supplies can account for 20% or more of the cost of a clinical trial.<sup>1</sup> A single pill of no obvious distinction can cost hundreds of dollars. In an era when every dollar is important, an efficient supply management plan is thus essential.

The cost of clinical supplies is not just the manufacturing cost of the medications. It also includes supply chain planning, management, procurement, packaging, shipping and destruction costs.

### One Size Does Not Fit All

Every clinical trial is different. The optimal supply management plan strikes a balance between seven key factors to deliver clinical supplies when and where needed at minimum cost:

- **Therapeutic Area Trends** address questions like disease prevalence; enrollment, adherence, retention, mortality and replacement rates; and the appeal of the study to investigators and subjects in relation to standard of care and competing trials. These issues influence initial, resupply and replacement stocking.
- **Regional Demographics**, i.e., the characteristics of the places where the trial will be conducted, influence external packaging, shipment sizes, in-transit timelines, depot locations, shipping vendors, import/export brokers, licenses and tariffs.
- **Supply Cost** is the cost of the investigational product plus any placebos, comparators and concomitant medications. Wastage of expensive drugs can be minimized with small shipments at the latest possible date.
- **Supply Availability** specifies how much investigational product is available when and where. If supply is barely adequate, parceling it out dose by dose (dosing unit) for enrolled subjects may be optimal. With sufficient supply, it can be shipped per subject, per group of subjects (a "bolus" shipment), or all at once.
- **Shelf Life** is the length of time investigational product will be viable after dispensing. If shelf life is six months and repackaging and distribution requires two months, shelf life will only be four months (three if policy prohibits dispensing to subjects less than 30 days prior to expiration). Shorter shelf lives require faster, more frequent, and smaller shipments to minimize wastage and protocol violations.
- **In-Use Time** is the period of time from one supply dispensing visit to the next, allowing for the maximum visit window. For example, if a trial calls for subjects to visit the clinic every two weeks with a window of  $\pm 2$  days, the in-use time is 14 days plus two days (in case the visit is early) and two more days (in case the next visit is late), for a total of 18 days. If the dosing regimen is one pill per day, the dispensing unit (e.g., bottle) should include 18 pills. Since actual visit windows may vary, 18 pills per bottle guarantees each subject will have enough drug to follow the protocol. However, the average subject will waste some pills, for example, if their actual visit schedule is more frequent than every 18 days. Therefore, planning to supply exactly enough to cover the average or nominal treatment schedule is insufficient. If the trial calls for dynamic titration, this method is still applicable, but additional calculations are needed.

- **Technology** directly affects the cost and efficiency of clinical supply for all but very small studies. At the basic level, an interactive response technology (IRT) system transmits real-time demand from sites to a central supply depot, where clerks order shipments. More sophisticated systems automatically ship and restock products based on sophisticated algorithms. Good IRT systems are easy to use and offer powerful forecasting, reporting and management tools.

## **What's in a Supply Plan?**

Most supply plans include three major components: packaging, distribution and shipping:

### **Packaging**

There are two types of packaging. Internal packaging consists of the dispensing unit(s), i.e., the package(s) dispensed to the subjects (or site pharmacy for intravenous administration). External packaging consists of the boxes and packing materials that contain the internal packaging.

The primary consideration for internal packaging is the quantity per package, which is driven by enrollment expectations, supply availability, in-use time, and shelf life. If quantities cannot be customized for the study, the supply manager and protocol author should discuss an appropriate dispensing schedule that limits the number of wasted dosing units.

The primary consideration for external packaging is ensuring that the contents arrive safely and legally at their destination. Multiple layers of packaging, temperature control agents, and special containers may be required. Different countries have different packaging requirements.

### **Distribution**

The primary consideration for distribution is the number and location of supply depots. A central depot may be adequate for a study. However, global studies may require regional or even national depots, depending on logistical factors such as transportation and customs and health department rules and processes. Relatively centralized structures generally minimize inventories and simplify management but increase the cost of individual shipments.

Pooling supplies across multiple studies can reduce costs, even if each study needs its own dosing unit. The IRT system must be able to handle the complexities of multiple studies.

### **Shipping**

The primary consideration for shipping is the movement of supplies from a depot to a site. The distribution strategy dictates the mode of transportation, so the key shipping parameters are the size and timing of the initial shipment, upper and lower buffer limits, and resupply quantities. (When site inventory hits the lower buffer limit, it triggers a new shipment. No shipment should cause site inventory to exceed the upper buffer limit without a manual override.) A typical conservative initial shipment consists of just enough clinical supply to enroll one subject to any treatment arm. Any shipment creates the possibility of waste because investigational products generally cannot be returned to the depot or transferred to another site without increasing the chance of damaging or losing accountability of the material. The IRT system then triggers subsequent shipments.

## **Other Considerations**

### **Resupply Algorithm**

Resupply consists of two levels: trigger-based and predictive resupply. Trigger-based methods ship material to sites when their on-hand inventories fall below a “floor” and are then returned to a “ceiling” — these inventory levels are the “triggers.” The triggers are used to resupply sites during enrollment and should be discontinued or significantly decreased when site supply availability meets the demand for remaining subjects yet to be randomized. Waiting until enrollment is complete to discontinue trigger shipments can result in a surplus at sites because the ceiling setting in the inventory system may exceed remaining dose requirements. An advanced IRT system will allow individual site resupply levels for high, medium and low enrolling sites and provide the ability to discontinue resupply for an individual site. The same principles used for determining initial supply can be applied to resupply shipments.

Predictive resupply strategies rely on more sophisticated calculations than simple inventory floors and ceilings. With a predictive strategy, enrollment forecasts are entered into the IRT system, and the algorithm combines dosing requirements for known (enrolled) subjects and expected enrollments into total demand for an investigator site. This method more accurately predicts actual usage, provided the enrollment assumptions are correct. The advantage is that as a trial becomes fully enrolled, all future doses are known at a site and the buffer inventory intended to be used for randomly arriving new subjects can be eliminated. Often, IRT supply strategies consist of a combination of predictive and triggered limits, which stock sites with a minimum floor of inventory to provide a buffer against mishaps but use the predictive algorithm to determine when and how much to resupply.

### **Buffer**

The minimum inventory carried by a site, controlled by the floor in a triggered supply strategy, should be sufficient to cover the lead time required to replenish inventory at that site. For example, a routine shipment could take two weeks to travel from a regional depot through customs to an investigator site. Additionally, these shipments typically have temperature deviations requiring two days to reconcile. In this example, the minimum site inventory should be set to cover at least 16 days of demand at that site so supply interruptions can be accommodated without interrupting patient dosings. This buffer concept should apply at every node in the supply chain, with depots and manufacturing plants carrying enough inventory to balance (buffer) against the possibility of production or shipment mishaps.

### **Minimizing Site Inventory**

If supplies are expensive, scarce or have a short shelf life, shipments can be limited and delayed to minimize site inventories.

S. Hamilton and K. Fai describe using forced randomization as a means to institute a dynamic approach to the shipping algorithm by fully utilizing the IRT system.<sup>2</sup> They state, “A dynamic approach to distribution strategy is to initiate each site with enough supplies to cover the first n number of subjects, regardless of the number of treatment arms or stratum.” Using this method, the randomization list is generated in blocks of  $x/n$ , allowing for more evenly distributed subject population, as well as significantly reducing waste. Using this method permitted the sponsor to reduce waste by approximately 25 percent.

Another solution is to delay shipping a seed supply (the initial shipment) until a subject is screened at the site. This approach is practical only if the supplies reach the site before the screening/dosing window closes and study subjects are willing to return for a second visit. Expedited shipping processes and costs will be required.

### **Minimizing Shipping Costs**

If supplies are inexpensive, the trial is very short, or enrollment is highly predictable, shipping costs can be minimized by shipping large quantities of supplies to reliable sites. Large shipments require adequate storage facilities at the sites.

### **Destruction**

Unused clinical supplies are not just wasted, they also incur destruction costs. Destruction costs include accounting for them at the clinical sites, shipping them back to the sponsor, and physically destroying them, typically by incineration.

### **Forecasting and Adjusting**

Once the supply plan parameters are in place, they can be used in a model to forecast demand and supply. Few studies proceed exactly according to plan, so close monitoring and rapid adjustments to the plan are essential. Actual results can be compared to the forecast to find faulty assumptions and adjust the forecasting model.

Supply forecasts are generally constructed in spreadsheets, but the complexity of global studies and adaptive randomization schemes are beyond the capabilities of spreadsheets, so the use of more advanced forecasting tools — in conjunction with sophisticated IRT systems — is advisable.

### **Conclusion**

Unless clinical supplies are trivial, wastage and unnecessary shipments can comprise a major part of the entire cost of the study. Carefully planning, forecasting and managing clinical supplies can significantly reduce these costs, while ensuring that supplies arrive at the research sites when needed.

### **References**

1. A. Fleischhacker, Y. Zhao, "Planning for Demand Failure: A Dynamic Lot Size Model for Clinical Trial Supply Chains" 2008
2. S. Hamilton, K. Ho "Efficient Supply Algorithms for Stratified Clinical Trials.", Applied Clinical Trials, February 1, 2004

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