An integrated approach to the clinical supply chain: - how we must master the links between IVRS systems and trial supplies.

Most readers are well aware of the challenges associated with set-up and management of the clinical supply chain: the push for small, generic packaging, limited bulk availability, the financial pressures on each trial and the reduced timeframes in order to reach 'first patient in' targets. Adding multiple vendors into this pressurized mix results in most trials requiring significant amounts of time and resources to maintain the supply chain and keep the patients on track. From a vendor's perspective, similar issues and pitfalls reoccur between many sponsor companies and their partners within the supply chain.

The success and smooth running of clinical trials (in the context of trial supplies and patient randomization) is influenced by decisions taken upfront in both construction of the IVRS and in relation to the packaging and labelling of the clinical supplies. As both of these activities are driven by the study protocol, it is critical to have input and agreement from the clinical team, supply team, IVRS and packaging vendors before documents are set in stone and timelines confirmed. We have identified several key interface areas that we believe, if managed correctly can vastly improve the overall management of the supply chain and hence the delivery of medication to the patients.

PHANTOM CASE STUDY

To illustrate the points raised, we shall consider a phantom study – clinical trial 1234. The key variables of this trial are as follows:

- Three groups – active (drug x), comparator y, placebo (1:1:1 ratio)
- Total of 500 patients over 50 sites
- Each kit = Run in carton, visit one carton, visit two carton and visit three.
- Run in = one weekly wallet card – all placebo
- Visit 1,2,3 = five weekly wallet cards each
- Treatment = three months
- Countries involved = Russia, UK, Spain, Germany, Italy, Sweden, Brazil, Mexico, USA, Denmark and the Netherlands.

PACKAGING AND LABELLING OF THE SUPPLIES

The importance of packaging design and strategy to the smooth operation of the supply chain is often overlooked.

Ideally, patient kits should be:

- Generic – not assigned to a specific patient or country.
- As 'small' as possible in terms of drug content multiples - in order to minimise waste of expensive drugs
- Stored in a way that that permits easy retrieval for shipping.
- Readily available from the master depot

So, even in the decisions made between the clinical supplies vendor and the sponsor's clinical supplies team we see bigger implications for the trial. For example:

Bulk Drug Availability

Bulk drug availability may not all be delivered in one neat batch. More often than not, we require several manufacturing and packaging runs to fulfil the complete trial requirements and these need to be factored into the overall timelines.

Label Text and Total Quantity of 'Kit Types'
As is the nature of patient kits, they come in all sizes and component contents; the challenge is to fit all the label text onto one booklet and onto each individual component in the kit. The label language groups may have to be split for instance this will double or triple the quantity of kit types that need to be monitored in the supply chain. Occasionally, the blister card itself may become a multiple if dimensions mean that all doses cannot fit onto one card. Frequently, the immediate container is so small as to be prohibitive for full multilingual labels – UK teams can consult Annex 13 for guidance on minimal text requirements.

Numbered and Stored Kits
The teams should examine how the kits will be numbered and stored – as dictated by the randomization. What variables and fields will the IVR use to identify each kit? Will this be a number on the outer carton or on each individual wallet? It must be exact in nature- the list may be used for label set generation, loading of available kits into the IVR and ordering of medication. Leading 0s and changed formats due to system compatibility can create many problems.

Deviation of Dosing
Definition of the duration of dosing available in each kit being shipped – it is surprising how the stakeholders within the supply chain can interpret this differently. If this is incorrect, the whole supply strategy for a program can be jeopardized. For instance, study 1234, the minimum shipping unit is a run-in or visit kit, not an individual wallet.

Storage
The supplies may be organised and stored in bulk by kit type or may require specific compilation into an ascending order, as dictated by the protocol randomization requirements. Through experience we find that on some occasions supplies are not compiled into the correct order and there is a incompatibility between how the IVRS is set up to order stock versus the picking process at the distribution facility. Also at times kits are ordered using an identifier that is not visible on the kit bulk outer or where a scrambled number is used without a sequence locator – we have to locate a specific pack from hundreds of kits – not very compatible with shipping turnaround times.

Study Medication Requirements
Should the kits contain the complete study medication requirements for the study or just the kits needed for each visit? Do we need actual visit cartons – and if so how are these being assigned at the site? Studies fit into both camps here. The sample study 1234 lasts for three months – there will be a trade off between shipping complete kits or visit kits. The full kits (containing all the visit kits) to the site will have subsequent storage issues and waste, and the smaller 'by visit' shipments results in almost trebling the amount of shipments required therefore transferring the strain to the shipping process or expensive drug (not to mention the associated cost). However, for a longer trial the answer becomes more clear-cut.

Dose Titrations
For studies involving dose titrations, the traditional approach would be to produce all dose types for all patients, leading to huge wastage of study drug. Based on previous study data or escalation prediction, the clinical and supplies teams can make a proportion of the drug required for each dose level. Also, the IVRS can optimise the amount of inventory for each dose type to be made available at the sites. This leads to savings in terms of bulk, cost and production time.

KIT LIST AND MANIPULATION
Incompatibility frequently occurs in the process of generation of the kit list and / or randomisation list, labelling of supplies, storage and the fields used by the IVRS to order each shipping unit. Often for double blind IVRS-based studies, the clinical supply kits will be

numbered using a scrambled ID number and a sequence identifier (in order to locate the kits for shipping).

The kit list (as opposed to a randomisation list) is generated upfront and supplied to the packaging vendor to control the label order and format of the completed clinical supply kits. This list may be manipulated to suit the internal systems at the packaging site.
Similarly, the client presents the list to the IVR vendor; again this may be adjusted to suit the particular system in use at the IVR site. An integrated approach to kit list management involves agreement between the IVR and clinical supply functions in terms of formatting and co-sign off.

SITE SUPPLY STRATEGY
As discussed briefly above, these variables are generally agreed between the IVR vendor and the client clinical group independently of the packaging vendor. It is useful for the packaging vendor to be aware of these variables for instance, if the kits will be supplied using a just-in-time method for a particular patient visit window (central randomization and / or sparse drug supply) or if the site will hold a suitable stock level with resupply triggers that can be adjusted as the study and recruitment progresses (stratified randomisation by site and / or plentiful supply of study kits).

Why should these be of interest to the packaging/ distribution vendor?
From these variables we can produce a reasonable set of assumptions for the volume of shipments required for the study. Besides providing a better grasp of the cost implications, this also provides a window on the volume of shipments linked to a study and helps resource planning.

As the drug supply strategy is central to the IVRS set up, any discrepancy between the expected and actual availability of patient kits may drastically alter the supply strategy. For instance, it may be readily assumed that all the kits for Study 1234 will be available immediately, and will include a reasonable proportion of spares to allow for waste at the end of the study. The IVR team may have decided that a site stock strategy of say five kits each of A, B and C is appropriate for all sites – how then can this be fulfilled initially if only 25 per cent of the supplies have been produced? Communication of inventory levels and supply strategies ensures that this process is managed effectively.

If lead times were prohibitive (from whatever source), would it be an option to produce the supplies in two campaigns? For example all the runs-ins and visit one kits up front, with the remainder of Visit two and Visit three following up two weeks later? There is always a risk involved in these decisions, but by looking at the whole picture the teams can balance operational delivery with the real need for the study- a fact especially true for those trials of a longer duration – for instance one year – Do you really need all the kits available at once?

Why have kits expiring on shelves when they are not needed for a considerable time- certain countries such as China have very long lead times for regulatory approval. Again there is a trade off between phased delivery and the risk of interrupted supply. Interrupted supply, which is a disaster for all involved, can arise from a myriad of factors. Just a single item becoming unavailable can derail the best-laid plans.

Lead times need to be considered in terms of how realistic it is for sites to receive initial and resupply quantities. Also, the release process for the supplies must be factored into any metrics – a timeframe is required for review and release of any GMP documentation. These critical variables are discussed in the drug shipping procedures listed below.
Expiry dates should be monitored using a combined approach to reporting that allows key data to be centralised and a single vendor contact to co-ordinate expiration date monitoring. This is effective when IVRS order numbers and shipping references can be combined.

The ability to make rapid adjustments to supply strategy in the middle of a trial is critical to the success of an increasing number of studies. This remains relevant whether a trial is expanding into new regions to meet patient enrolment targets, or the sample size for a given treatment arm is being adjusted in response to an adaptive design. In order to successfully navigate these dynamic periods, the complete 'ripple effect' of study changes must be fully understood. For instance, when recruitment is behind and new territories and sites are considered, the implications for additional labelling and packaging runs must be clearly defined for the study team and lead times at each level of the supply chain including country specific distribution to sites considered.

Drug shipping procedures and distribution metrics

For sample study 1234, two sets of instructions are generated that reference the actual shipping instructions for clinical supplies – IVR drug shipment details and distribution instructions from the shipping vendor – both documents relate directly to the shipping procedures used on the vendor floor.

As many of the variables and procedures are duplicate, one approach would be to integrate these documents or at least allow co-sign off. Often, the variables related to the IVR portion are agreed without sign off from the distribution vendor, leading to requests that cannot be processed on time or in the correct format.

- Agreed drug order form – this can be drafted jointly and reused as a template for multiple protocols. This removes any surprises for the sites and keeps the kit types, quantities and ordering requirements constant.

- Ordering process- clearly defined email addresses and escalation routes. Central contact mailboxes are most frequently used alongside a backup fax number.

- Depot definitions - a clear statement of all the depots involved, including the master depot where the bulk of inventory is held and clear definitions of the ordering process.

- Lead-time considerations and variables must be agreed for each direct to site, depot to depot and depot to site shipment for all countries involved. These metrics must include time taken for release of supplies, import licence applications, any inspections required and proforma invoices. Also, the date needed at site used by the IVRS should reflect the actual date required by the patient if possible – many studies have shipments that are flagged as being late on the system when in fact the window is several weeks in advance of the patient visit.

- An approximation of the shipping volume is useful, again for resource planning. A useful picture can be built to estimate the number of shipments a study is *likely* to require. Using the study supply strategy, variables such as the number of sites, patients per site and minimum shipping units can be used for resource planning for a protocol.

Management of depots and ancillary items

In regional depots may be required for certain countries, thus prohibiting a direct to site approach from the master depot. These may be needed to fulfil regulatory / legal requirements or to fulfil a primarily logistical function. Temperature sensitivity for example, makes it easier to distribute from an in-country depot. The IVRS will be need to be configured to monitor stock levels within these depots as it would in the master depot (for instance packaging/distribution site) but consideration needs to be given to the following: -

Bulk Ordering Process
Understanding hoe the bulk ordering process is defined is key. It would be best practice to have this incorporated into the IVR design. This allows for the larger amounts of kits to fulfil the quantity estimated for a particular country to be managed and tracked properly. For study 1234, it is important to document how the supplies will be "segregated" in terms of quantity for the depots (Brazil, Russia and Mexico). Also – consider how an order will be raised to ship the bulk kits to a particular depot and the kit list uploaded into the IVR. Incompatibility in this process can lead to sites being given the green light to proceed resulting in supply orders being generated, where the kits still reside at the master depot. Again it is vital that all lead time considerations are accounted for: that is the release of supplies, application for any importation licences and the transit time after approval. This can result in orders not being fulfilled and patients being dropped out of the study. Failure to consider these requirements will result in the supply chain breaking down.

Direct to Site Ordering
Management of the direct to site ordering process within a depot country should be included. The process to be followed by the global distribution vendor must allow a central tracking and tracing of all in-country shipments using depots.

Deport Blinding
Needs to be established as to define the exact status of the in country depots. Kit type descriptions may be present on the outer bulk containers – for instance for study 1234 all the kits are packed into bulk by their particular kit type and not mixed/compiled together. Each individual lot will have scrambled Med ID's on each kit/card and the associated sequence numbers for picking and packing. These labels that identify each type may need to be re-approved or removed in order not to unblind the depot.
Ancillary Management

Generally, a fixed text quantity suffices for ordering initial supplies of ancillary items, but it can lead to problems when resupplies are required. For certain study types with large patient populations (and hence large volumes of product), this process should be tied into the IVR set up and managed accordingly using trigger and resupply levels. Relying on a manual approach can lead to supplies running out at site as no-one has realised the lead times, subsequently creating a large volume of urgent resupply orders for non-clinical (and still critical) materials.

Management of drug lows
An often neglected area of the supply chain; as study 1234 progresses, kits will be use at various rates dependant on recruitment. The IVRS will have drug low assignments to alert the team when stocks of particular kit types begin to dwindle. The management of this process needs definition upfront from all parties. Why? – in the heat of trial maintenance, visit dates, and day to day issues, information from the IVRS alone sometimes may not be enough. Careful definition of study thresholds with accompanying alerts may be the key to averting shortage of drug supply and potential crisis; it must be defined upfront as to whom the responsibility of monitoring and management of this belongs.

Who exactly will monitor the drug lows for study 1234, linking back the supply chain to total inventory at the master depot / If no inventory is available, who will plan the subsequent resupplies? Has the lead time for this and / or purchases been taken into account? This process shows itself on a routine basis – then the production operations are put under considerable strain in order to avoid patient loss by lack of available medication.

An alternative approach to this is to allow the packaging and distribution vendor to assume responsibility for the clinical supply management. This proves especially effective for those companies that do not have a dedicated resource for clinical trial supplies.

Project Management

A number of options are available once the contracts are signed and the study team can commence work. These can be decided upon given the study organisation, client operating history and preference, or the timeframes involved with the trial.

A novel approach would be to use a lead point of contact between the IVRS and distribution vendor to manage the supply chain. This would only be possible if both services are located in the one organisation.

It is recognized that it is very difficult to have expertise in both packaging/ distribution and provision of a software based supply chain management service. The lead point of contact concept streamlines the joint experience from the vendors but also allows the client to leverage the expertise of both closely related niche areas.

A lead point-of-contact model allows a streamlining of the communication channels involved in the study and development of a master project plan that covers both supplies and the IVRS. Some companies outsource day-to-day management of both activities to a CRO, adding another layer of complexity to the process. Decisions after all, still need to be made by the owners of the IMP- the pharma company.

Otherwise the IVR vendor, client and distribution vendor must meet upfront and define roles and responsibilities for the successful management of the supply chain.

Often, a three way document that examines and covers the issues mentioned within this article helps clearly establish roles and responsibilities. There are specific references to the clinical supplies made in most IVR URS documents, and it may be appropriate to allow exchange of this section to allow screening by the supply/distribution team members. Also, an exchange of high level packaging and distribution documentation may allow the IVR team to identify any misunderstandings or incorrect assumptions used within IVR set up.

Too often the IVRS and trial supplies team members only meet after the key decisions have been made.

Conclusion

There are multiple tasks and decisions that affect the smooth running of the clinical trial supply chain. Identification of the overlapping areas between the IVRS and provision of the clinical trial supplies for each protocol will greatly aid the provision of medication to patients. These areas must be shared upfront by all parties and agreed at a minimum, however best practice dictates that merging of the appropriate documentation and consideration of a lead point of contact may be the best approach of tackling the IVR and clinical supply interface. Also, consideration should be given to working from a 'Master Plan' that details in a high level key dates from both sets of activities.

For more information contact:
integrated@almacgroup.com
EU T: +44(0)28 3833 2200
US T: +1 267 685 4284