Supply chain logistics can make or break a clinical trial. In many cases, failure to provide and manage trial supplies on time has resulted in costly delays. So how does a CRO partner work with a Sponsor to ensure supplies are properly managed?
Get ready, we’re chatting through The Seven Deadly Sins of Trial Supply Management, brought to you by PSI expert and supply chain aficionado, Alan Morton.

Our first warning sign? Lust. Being seduced into using an inappropriate vendor. Vendors will claim to be able to complete all services better than all the rest.

Being tied to a particular vendor limits the ability to objectively choose the best one for the job. Ensuring that the selection is made on quantitative and unbiased data will help – we’ve all heard horror stories about ‘This packaging vendor doing...’ or ‘That IWRS system is rubbish – don’t use them’.

A couple of recent studies chose a well-known IXRS provider. The reasons for the choice are clear – they are a big, well-known company; they were doing the eCOA, so they had an easy integration; their sales pitch was very slick, and they were promising cheaper and quicker set-ups than the others that could have been used. The studies were reasonably complicated – one was a triple blind study using a biosimilar product and the other was a double-blind double-dummy study using a combination of IV and tablets, both with matching placebo and dispensed at different times throughout the patient’s treatment schedule.

Because of these complications, the automatic shipment generator did not work properly, meaning that PSI had to provide and fund an additional resource to manually trigger each shipment from within the system. As well as the resource issues, there was also the added risk that the person triggering the shipment could make a mistake, leading to an increased chance that a patient could be left without treatment.

Make the Right Choice the First Time. It is very difficult to change vendors mid-way through a study, so assessing the ability of a vendor and being critical of their abilities is vital to ensuring that the best and most appropriate decision is made. How do you fancy having to tell your senior management that the vendor that you suggested is not able to deliver and we need to pay to change to another one?

Having proper oversight and working from solid metrics and KPIs helps ensure that a decision to use a particular vendor is not made on reputation or hearsay. Water-cooler stories about vendors making mistakes can tarnish their reputations unfairly, so while the selected vendor may not be suitable for complicated studies, their quick setup times still make them a good choice for more straightforward ones.

PSI doesn’t have preferred suppliers. We have a number of approved vendors that we have carefully selected and audited prior to using them in our studies. We work in partnership with them and see their performance as an extension of our own, so just as we pick Project Managers according to their strength and knowledge of an indication, we ensure that the vendor that we recommend for a study is able to cope with the work that we are allocating to them.

Chasing after one vendor with the expectation that they will serve every project, in the same manner, is the first in our series of deadly sins in trial management. Don’t fall into lusting over a certain vendor, but rather ensure that every vendor is the right match for the specific study.
Our second sin: Over-production. All studies need a certain amount of overage, but kits left over at the end of a study are often seen as wasted money. There’s more to the story than that, however. When supplies are both available and priced low, it often costs less to produce more supplies and send one large quantity shipment to the sites than it would cost to ship smaller quantities in multiple batches.

However, this logic is reversed when the drugs are either expensive, hard to obtain, or both.

Let’s look at one example together. An 800 patient study getting ready to launch requires 3-4 vials per patient to be dispensed every 3 weeks for over a year. Each vial can cost upwards of £677 for the drug alone. And if we do the math, it adds up quickly: the drug cost is over £10m! Not including other aspects of the trial, or any other necessary supplies, we can easily see that even little overages in shipping and production can quickly impact the cost of the trial.

Making the Right Calculation. The correct amount of overage is never an easy calculation. In order to define our overage parameters, we need to understand the risks involved in the study and ensure that we have overage to cover those risks. Damaged shipments, temperature excursions at the site, broken vials, missing kits, environmental damage to a depot, and so many other factors are all considered as risks throughout the trial supply process. And while not every risk will actually hit on every single study, suppliers and CROs need to ensure that they both understand the exact factors and that they have a continuity of supplies to treat current and future patients.

With the right overage calculation, a study would never see delays from drug shortages, nor would they see outrageous costs from excessive supplies. Having a higher buffer at the start of a study provides flexibility. Once patients are recruited and we understand locations, visit schedules and dosing information, we can tailor shipments to meet the site/patient requirements and optimize on-site supply stock accordingly.

The Right Tools, the Appropriate Resources. The use of IXRS systems helps consolidate shipments for multiple patients and treatment visits, and the lookout windows can be altered to provide the ideal frequency of re-supply shipments. And other tools, resources, and algorithms can come into play to fine-tune the supply process to eliminate excess overages.

Every excess cost is a bill passed on to another business owner in the clinical trial partnership. When overages aren’t calculated properly, trials could either be delayed, over budget, or both. Mitigate that risk by fully understanding risks in trial supplies, and investing in the appropriate tools and resources to make the right overage calculations and judgments. Don’t fall into the sin of gluttony in drug supplies: 50% overage without a proper calculation? It’s time to evaluate.
Sin number 3: Greed & Penny Pinching (I'm Not Paying For That!)

Penny-pinching on overage and costs of shippers. Temperature monitors are around $50 each and temperature controlled shippers vary from $60-80 to over $500 per shipment for passive units and substantially more for active ones. Using temperature-controlled shippers can increase the weight of a consignment considerably, increasing courier costs significantly. Because of that, courier and shipper fees are often targeted as an area in which to save money.

We are regularly asked if it would be acceptable to ship supplies without using temperature-controlled shippers or monitors. The way to answer this is another question: Would you take medication that you could not guarantee had been stored appropriately? Most likely, the answer is no.

The reason for the question is simple; it costs approximately 3 times more in courier fees to send an insulated shipper vs a cardboard one. Over the course of a medium-sized study, this would amount to perhaps $30,000-$40,000. And while it sounds a lot, it's a very small percentage of the overall study cost.

It is incumbent on the company providing the medication to prove the medicine has been stored correctly at all stages in the production process. From the manufacture of the drug substance to the final patient dose, supporting data has to be provided to ensure proper storage. This data comes from the building management systems in the production processes and warehouses that store the medication, and from the temperature monitors that record the actual shipment temperatures in transit.

Failing to use a temperature monitor or a temperature controlled shipper means that there is no proof that an excursion didn't take place, so the integrity of the supplies cannot be confirmed – a very easy observation for an auditor and potentially deadly to a patient.

Duty Fees, Taxes, And Cutting Costs. Duty fees are also seen as an area to try to cut costs. No-one likes to pay tax, and import taxes and VAT in some countries can be exorbitant! For the example that we just discussed, around 1000 vials of the drug will be sent to India over the course of the study - total drug purchase cost = £677,000. To pay tax at the purchase price would mean paying 16% of the landed cost in customs duty - £108,000, plus VAT on the duty paid cost – another £85,000. Local taxes and education levies add another 6% (£46,426) – a total tax bill for import into India of nearly £240,000!

Putting a small nominal value against the drug cost is often seen as an easy way to reduce that cost. But when challenged, it can cause long delays and possibly lead to temperature excursions and useless supplies. It can also tar the reputation of the shipping company, meaning more scrutiny of every shipment from them. Some countries also restrict the sale price of the drug after commercialization to the value declared during the trials - can a sponsor really make a profit when selling a biosimilar for $5.00 a vial?

Is It Worth It? With so many moving parts in a clinical study, it's imperative to do things the right way, every single time. Cutting costs on shipping and/or overages could be a potential risk to the success of the study. And when you get too greedy, or pinch-pennies too tightly, you're committing a deadly sin of trial supply management and putting a study at risk.
Sloth (Failing to plan adequately or on time)
People tend to stick to their area of expertise and focus their attention on making the arrangements for what they understand. This often means that areas such as IMPD collation, Protocol Writing, CTA Submissions and Site Selection area all arranged in good time and the drug purchase and distribution arrangements can be left until later. Unfortunately, it can take over 6 months to arrange for the purchase and packaging of the supplies, arrange the distribution aspects and Import License applications, and then ship to a country. This means that although a study is otherwise ready to go, the drug supplies are not ready, so start-up is delayed until these aspects are taken care of.

Failure To Plan? Planning To Fail.
In-depth planning is vital to make sure that the strategies for production and distribution of the supplies are robust and appropriate to the type of drug that is being provided. Knowing the lead-times for each of the component parts and re-supply timelines when the study is in progress is vital to allow scheduling of additional packaging campaigns to be done at the right time.

As an example – if a patient is on treatment for 1 year and visits the hospital every 3 months to collect medication, we need to have new supplies on the shelf at the hospital that have an expiry date of at least 3 months after their visit to allow the patient to be dispensed their treatment. Add to this the lead time to get the supplies to a local depot (planning timelines always works on the longest lead time – for the Philippines it can take 90+ days to arrange the shipment) then add on the production time, which can take another 3 months, and you may need to start planning re-supply campaigns a year or more prior to the expiry date of the supplies!

This is made more complicated when supplies have a short shelf-life, or when countries, such as India or China insist upon a set amount of residual shelf-life available when they are imported.

Planning - Put Patients First. So what does all of this mean? When planning a trial, you cannot just “chill out”. There’s no time to fall into the deadly sin of being a sloth because it’s quite possible that something will go wrong if you let time pass without planning appropriately.

Be sure to calculate your timelines accordingly, and work together with sponsors and vendors to ensure a smooth process for drug supply and drug management. After all, the patient is counting on your ability to manage these logistics, and all others, without any error.

Wrath (That timeline is not acceptable! Put your CEO on the phone and he’ll make things happen faster!). Ruining partnerships over unreasonable timelines? We can fix that.

Vendors are generally open and honest about what they can achieve. In fact, we can most often trust their transparency, responsiveness, and availability. It’s a partnership, a team effort.

But when all the slack - all of the reasonable timelines and grace periods - is taken out of a project plan before it has really begun, vendors aren’t able to work through a contingency plan or catch up if there are problems in the project. If there are any errors, delays become eminent...

Can Delays Be Managed? Delays can arise from a multitude of areas and aren’t limited to just a few ordeals.
Bulk drug orders can be delivered to the packaging facility late, label text can take longer than expected to be finalized, typhoons and volcanoes can disrupt shipping lanes, customs can open supplies to inspect the contents, and the list goes on and on. And while some of these issues can be anticipated and planned for, many are unforeseeable.

**Set Your Partners Up For Success.** Allowing the vendor time to manage production and distribution directly correlates to the amount of time a vendor has to correctly assess and mitigate against risks. As such, vendors have a greater chance of getting the supplies where they need to be on time. With a properly built timeline, that means that sites and patients are able to receive their supplies by the actual time those supplies are needed. Setting appropriate timelines and properly assessing risks is a huge factor in eliminating any potential “wrathful” behavior. Because every aspect of trial supply management involves multiple teams, we always need to remember the keyword: team. Because as we mentioned before, it’s a partnership. It’s a team effort.

**The Final Key: Realistic Timelines.** Wrath on either side of the vendor partnership is a deadly sin to fall into, and one that could ruin both the current study and potential studies. When we’re close to strict deadlines, it’s easy to overreact, demand a phone call with a boss or two, and get stuck in a wrathful mindset. But by creating realistic timelines, this behavior is immediately mitigated. Timelines are ensured, and the sites and patients – again, as noted before – are able to rely on the true timelines.

We might not be able to predict a typhoon, late deliveries, or volcanic lava sweeping through a shipping lane. But we can build a few extra days into our own project schedule on the backend, to ensure supplies are delivered by the agreed upon date from the outset. Whether it’s a CRO, sponsor, or additional vendor, the deadly sin of wrath, can indeed, become extinct.

**Pride (I know what I’m doing – how dare you question me)**

It’s easy for us to fall into the same habits and trust our own expertise. But often times, our pride in knowledge and experience gets in the way of innovation, improvement, or, for better terms, lack of thinking. Let’s look at an example.

In the post-study review of an antibiotics trial, data showed that 82% of the kits produced during the study were never used. Some expired, some were damaged, some had temperature excursions, and some were never sent from the central depot to the sites. The majority of the unused kits sat on the shelves at the sites at the end of the study because the number of reserves held at each site to support recruitment was too high. The clinical team insisted on having enough of the blinded drug on site to treat 3 patients concurrently. A review towards the end of recruitment of this study, however, showed that the average site only managed to recruit 1 patient every 3-4 months. Of the 900+ patients recruited, less than 30 were in treatment at the same site, at the same time, as another patient.

**Letting Pride Get In The Way? Consider Your Risks.** Setting a study up without considering potential disruptions or complications is folly. What was once appropriate for the start of a study may not actually be appropriate as it progresses, and we have to keep that note in the forefront. Re-visiting and updating the plan with actual information is vital to ensure that the right decisions are made at the appropriate time. This could mean varying the timing or quantity of re-supply campaigns, changing the courier type, or even deciding that an in-country depot would be more appropriate than direct to site shipments. In the previous example specifically, it means altering the buffer stock appropriately throughout all phases of the project. Unfortunately, the stock status and levels of excess were discovered too late to reduce the site supplies to a level where it could be used by the patients remaining to be recruited. The stocking decision was based on previous experiences with other studies, rather than weighing the considerations of the current study.

And to save a lengthy explanation, it was due to the fact that pride got in the way. We all know what we’re doing, all the time, right? We’re experts. We have years of experience and have worked on dozens of studies in the same indication, right? That doesn’t mean we can fall into the habits of setting up studies the same way every single time.

**Innovate, Improve, Learn.** As a CRO, it’s our job to tailor every study around every aspect of the project, rather than using some sort of template to run a program. We have to ensure that we’re digging in, learning new aspects, innovating, and improving at every stage of every study. And when we’re managing trial supplies specifically, this has to be a key focus.

What’s the answer here? Don’t let the pride of experience outweigh the benefit of consulting, learning, and improving. It’s never too late to innovate.

**Envy (They’re getting the job done quicker than us, how can we stop them from making us look bad?)** For a number of reasons, there will occasionally be more than one CRO working on a study at the same time. This can sometimes cause problems behind the scenes.

PSI was recently brought on to a study to boost recruitment that was way behind schedule. However, the incumbent CRO remained in control of the drug supplies. Shortly after we got going, we were able to recruit patients far faster than the other CRO, but soon found that the drug supplies needed to treat the patients were subject to delays and stock-outs. Though this was an issue that affected the entire study, it was also a positive learning outcome for risks associated with splitting the study across two organizations.

**Don’t Let The Rush Overcome The Supply.** It takes significant resources – time and money – to identify a patient, screen, enroll and start treatment. It is unforgivable (as well as unethical) to allow this to happen, and then not have the supplies available to treat them when they arrive at the site.
In order to prevent this, we need to be clear with the sponsor about our expected recruitment forecasts and discuss variations – especially when recruitment is faster than expected. This will then show how much supply we will need at each point. If it becomes clear that the supplies will not be available, then we should slow recruitment rather than risk running out of drugs for ongoing patients.

**Moving Ahead: Mitigation and Planning.** Now that we understand the major pitfalls that can cause problems during the course of a study (remember the other 6 sins we previously discussed?), we need to understand what we can do to avoid them. Setting milestones or checkpoints along the course of a study will help ensure that reviews are carried out in good time. Think about it: how often do even the best of the best project managers need to rely on the goodwill of others to help avoid a crisis by prioritizing work when slightly better planning and more timely decision making could have avoided the issue altogether?

The pointers below are a cyclical process, which has been used in a number of forms and is a key part of all good project management toolkits.

- **Plan** Focus on the end goal and identify what we need to do to achieve that goal.
- **Assess the risks** Weigh the options and review the cost/benefit analysis, and mitigate against risks that can’t be avoided.
- **Develop a strategy** Break the plan up into milestones and work out the timelines.
- **Execute** Use the plan as a guide. Focus on timelines and deliverables. Be aware of risks happening and take action when they do.
- **Evaluate progress** Compare real-life with the forecast. It is a lot easier to get a plan back on track if action is taken early.
- **Re-plan** When life happens, update the plan with the new information.
- **Communicate** Make sure that when the plan changes, the relevant people know, and most importantly, know what they now need to do.

**We know that mistakes are all too common in trials.** And when a trial is split between two CROs, the risk of these mistakes can be even larger. It’s more important now than ever to ensure solid planning, analytical strategies, and appropriate mitigation options. Don’t let envy, and the feeling of “competing” against the other organization, ruin a well-designed study strategy.

And remember, your supplies and logistical aspects matter. As we mentioned before, running out of supplies is both unforgivable and unethical.

The seven deadly sins of trial supply management: envy, pride, wrath, laziness, failure to plan, greed, and lust - are the key habits to avoid in order to ensure a trial is set up for success. Before diving into a trial, be sure to review these weak points, and implement the advised mitigation plans to overcome potential downfalls.

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**About the author:**

Alan has been working in the logistics and supply chain arena for almost 30 years and has spent the last 7 working for market-leading drug supply and packaging vendors supporting studies all over the world.