GCP: It’s Never Too Early to Start

Start-up biotech companies face a range of GCP-related decisions when entering clinical research, including whether to outsource key activities and who to approach for advice. **Vernon Harten-Ash** and **Val Lyness** offer start-ups tips to achieving trial success in addition to maintaining GCP compliance

KEYWORDS: GCP; Start-up companies; Outsourcing; In-house resources; Seeking advice

Moving into the clinical phase of product development is a major step for any start-up biotech firm, involving a huge range of decisions, many of which have GCP implications. A start-up company will need some fundamental quality systems in place, even if some tasks and processes are to be contracted out. It makes for increased efficiency and GCP compliance. But what areas should this include? Before arriving at a definitive list it is essential to consider which services and functions will be carried out in-house and which will be outsourced.

Outsourcing solutions

Outsourcing has a number of benefits for a start-up company, which will often not have the resources for full-service projects including data management, biostatistics and pharmacovigilance. There are specific knowledge and skill gaps to be filled and outsourcing can seem a practical and cost-effective solution - the faster a trial is completed, the quicker a product can move market.

Equally, a start-up company will not have legal entities in all countries where the trial will take place, which can make it difficult to hire monitoring staff directly, whether contract or permanent. In addition, legal representation for key activities is sometimes required, for example, insurance may need to be issued by a legal entity in a particular country.

Using a CRO on an interim basis may seem the answer. They are experienced, and with multiple function expertise can hit the ground running and move the project along. Isn’t it better to get things underway and look at the wider requirement for in-house clinical research processes and standard operating procedures (SOPs) later on?

If the in-house/outsourcing decision seems an obvious one, there are some notes of caution. CROs can be expensive so before entering into an agreement it is important to establish budgetary guidelines and ways to keep costs firmly under control. Start-up companies may lurch from funding bid to funding bid, therefore it is important to

monitor the interim budget closely in regular monthly project review meetings with vendors. Unit-based budgets work best for start-ups but not necessarily for CROs. Fixed-price costs are easier to control and invoice due dates can be anticipated in advance, making it easier manage the cash flow. Ideally only pay for complete units.

It may be very tempting when working with a CRO to start with a letter-of-intent and not a full contract as they can take some time to agree, especially when the start-up has venture capitalists and investors who are keen for the study to start immediately. Ideally sort out the contract and the budget as soon as possible as it will save hassle later on and reduce any future misunderstandings. Ensure a contract is in place with all vendors, establish vendor management, SOPs and processes, and budget for an audit of all vendors.

It is crucial that a CRO has the resources and experience at bid-defence. It is important they understand the nuances of the project and have done their homework. They should be asked to present a plan outlining how they plan to run the study, and it is important to know whether they can work in all countries, have global SOP's, a process and communication structure and specialist understandings, for example, in genetics, biotechnology or devices. Companies must ask questions, such as, 'have they done a risk management assessment?' 'Do they have contingencies to cover such eventualities as poor patient recruitment or staff handover?' And, 'do they have the necessary regulatory expertise in the right countries for the right product type?' Audit the CRO's SOPs to ensure that their processes are clear, GCP compliant and up to date.

Finally, use a CRO with good project management processes, a clear project plan, budget and timelines, quality metrics, a visual/graphical representation, risk and contingency processes and a regular project review at the project leader and management level – both with and without the sponsor.

In-house resources

In addition to outsourcing, it is important to consider recruiting some in-house resources, even if only on a contract basis - for example, an experienced clinical project manager or clinical director who understands CRO issues and realistic costs. Ideally this person will be someone with CRO and pharmaceutical experience, who can drive the CRO and recognise challenging but realistic timelines – as some start-ups have inexperienced senior management, who are highly versed with the 'R' of R&D (perhaps gained from an academic research background) but less experienced with the 'D' and must trust the advice provided by established clinical research professionals. This person can also establish a working partnership with the CRO and help train staff on study logistics and the nuances of a product or therapeutic area.

An understanding of, and commitment to, GCP is also essential. The expert hired to provide expertise must be pragmatic, have commonsense and a firm approach so corners are not cut. Some start-ups push to begin trials without full GCP, perhaps

because they think they are exempt due to their size or sometimes because their senior management or board of advisors do not understand clinical research. A strong-minded clinical director is needed to persuade them otherwise.

However, strong-minded managers do not necessarily make good line managers, so it is important to consider using contractors/freelancers/interims. Recruit wisely and ask the right questions – do they have the experience, skills and competencies for the role?

Other elements to consider before making decisions on in-house versus outsourcing include the time it takes to carry out tasks. Some activities are quicker to do in-house, such as protocol writing – or at least the synopsis – especially if the CRO does not have the expertise in the product type or therapeutic area. It may be more time-effective to write a skeleton and hand it over to a CRO medical writer to format and polish. The final study report may be better written – or at least co-written – by someone in the sponsor company who has probably been more involved in the study from the outset.

Seeking advice

Finding the right people to advise on decisions is crucial. In-house expertise is essential to manage CROs and other vendors, to ensure quality and efficiency, and maintain adherence to budgets and timelines. One way is to have in-house therapeutic advice, or at least make it available through an advisory board of key opinion leaders (KOLs). If affordable, it is also worth having other experts available on a consultancy basis, such as a statistician to review a CRO statistician's input. Such people could be used on an *ad hoc* basis to check that costings make sense. An experienced clinical project manager, for example, may be able to review a data management plan or statistical analysis play up to a point but do they have the expertise to understand the methodology and budgetary units?

In a small company there can be no weak link. Recruit in-house staff very carefully and consider using contractors, perhaps with short-term contracts that might lead to permanent placements, which gives both parties the time to test the water. But it is essential to recruit one or two people who can drive CROs and other vendors – hard but fairly.

Sponsors must have regular contact with investigational sites and co-monitor with the CRO. This is important for a number of reasons. Firstly, start-up companies are unlikely to be known to the investigator, so it provides reassurance that the company holds quality and patient safety as high priorities. It also helps overcome any potential issues with the CRO by bringing knowledge in-house, helping develop relationships with KOLs and ensuring the monitoring is consistent. However, those conducting global trials should not just seek advice from US KOLs (or vice versa) as the approach in the EU is often very different.

Quality systems

Having put in place some in-house expertise, even on a contract basis, to manage the project, it is time to put some quality systems in place. Look particularly at vendor management, finances, employee policies covering such areas as contracts and travel and documentation and approval processes. Ensure there are secure and transparent filing systems in place with both electronic and hard copies. Don't duplicate everything the CRO does, but do file what they do not and ensure that there are clear processes for filing (including e-mails).

Other areas that need systems include:

- Risk management and disaster recovery
- The process of obtaining legal advice quickly so that contracts can be approved by a sponsor
- Identifying high priority SOPs to cover any immediate in-house activities, such as protocol writing and product distribution
- The management of multiple vendors, including manufacturing, packaging and distribution, IVRS/IWRS suppliers, data management and pharmacovigilance.

When it comes to serious adverse event reporting, it is essential to have a process to handle these, even if the CRO is responsible for pharmacovigilance in case a site calls the sponsor first. Start with 'must have' processes and SOPs, such as vendor management, if you are contracting out and then add on lower priority procedures as activities come in-house but ensure vendors comply in terms of activities contracted to them.

When it comes to regulations, if in doubt, go with the toughest. For example, in the UK, statutory instrument states that the investigators' brochure must be updated annually. This is not stipulated in the EU Clinical Trials Directive but applies if you are using UK sites. Valuable time can be lost thinking regulations can be bypassed. If the Polish authorities want the protocol to be translated into Polish, just do it! If you send it in English and hope for the best, it will be returned.

A commonsense approach to GCP

The best way to ensure GCP compliance is to start out with a firm foundation. Remember GCP is commonsense, so don't over complicate issues or add unnecessary bureaucracy. Establish clear review processes and ask, what will the CRO need the sponsor to review and approve - and when? It is important to know who can sign what in the company and make sure this person is readily available. It is best to avoid situations where, for example, a contract clinical project director might sign off an essential document plan for the CRO but cannot sign legal or financial documents, such as contracts on behalf of the sponsor if they are not an employee.

So, what causes some people not to commit to GCP? It could be that the investors, senior management or board, and sometimes departments within the company, might not understand the trial processes or feel that GCP compliance may cause delays. On occasion they might try to encourage the clinical department to by-pass

standards and this must be resisted. Driving the project forward will require strong-minded and committed expertise. Senior management's support for quality is critical to a study's success. In established companies who are new to clinical research, some might be stuck in their ways, making it hard to shift the dynamics and encourage a regulated environment.

It is important that the sponsor is always ethical in their approach – the patient's safety comes first – and expertise is always on hand to interpret specific regulations such as the EU Medical Devices Directive or genetic or advanced therapies regulations.

Above all it is imperative that the start-up company does not grow too large before in-house processes are in place. This can easily happen when the focus is on getting a trial up and running and everyone is busy. But remember GCP is not retrospective and can't be retrofitted. It's never too early to start and don't forget - small companies are inspected too.

Vernon Harten-Ash
Managing Director
Harten Group
Cambridge, UK
Tel: +44 (0)1223 233777
Fax: +44 (0)1223 235777
E-mail: vha@harten group.co.uk

Val Lyness
Consultant
Hedsor Clinical Development Services
Bourne End, UK
Tel: +44 (0)1628 527290
E-mail: vlyness@yahoo.co.uk