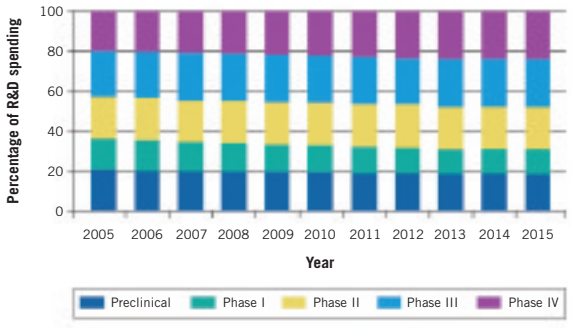
Secrets to a Good Relationship

Brendan Ellis at InCROM Europe examines the importance of facilitating partnerships between CROs and patient recruitment sites

Years ago, the lines between phases were clearly defined, and the phases themselves were always performed in a consecutive manner. It was almost unheard of to run a Phase I study in parallel with a Phase II study, let alone with a Phase III study. However, given the recent clinical development environment and the impending blockbuster patent expirations, the industry is being forced more and more to question conventional ideas in an attempt to shorten development times to get their products onto the market.

However, the responsibility for creating innovative solutions to reduce clinical development time should not lie solely with pharma and biotech companies trying to get their products onto the market. With the predicted decrease in Phase I and II spending shown in Figure 1, it is imperative for CROs to start addressing how they too can support the needs of their customers in their innovative endeavours proactively. This has been seen through expansion into niche markets, increased use of information technology for electronic regulatory submissions and electronic data capture (EDC) and the more recent trend of offering a larger array of biomarker assays, which has all helped in getting to the pivotal go/no go decision earlier on in development. Another of the these trends is performing patient pharmacokinetic (PK) studies at a much earlier point in the development of the compound, but the problem posed here is whether the patient recruitment sites are able to provide overnight facilities to do this or, alternatively, whether CROs with overnight facilities can perform the patient recruitment needed to necessitate this. Often the answer in both cases is that they can't. In the same way that there is a growing trend for pharma companies to collaborate on certain projects, so too is it vital that sites with complementary services look to collaborate with one another to help meet the demands of the industry. This article will look at one such collaboration and the pitfalls to avoid when setting up a patient PK study.

Figure 1: Which phase gets the most dollars?



Pharmaceutical and biotechnology market: percentage of R&D spending by phase (US), 2005-2015

Source: Frost & Sullivan, 2008

AVOIDING THE PITFALLS

It is essential to hold the kick-off meeting between the collaborating partners (and sponsor if relevant) as soon as the study has been awarded, in order to discuss all of the logistical issues that can, and will, undoubtedly arise during the course of the study. The more prepared both parties are, the more likely the study is to succeed and the partnership to flourish. Ideally, to get the most from the kick off meeting, it is best if the principal investigators, project managers and business development teams from both sites attend. An agenda for the kick off meeting, along with the current version of the protocol, should also be sent out in advance for all parties to consider before sitting down at the meeting to discuss it. The most crucial points to agree upon during this meeting are:

Regulatory Submissions

When discussing regulatory submissions it is critical to determine:

- Who will be preparing and submitting the CTA/EC/SSA/R&D submission?
- What are the timelines for the submission dates and expected approvals?
- Can these be done in parallel to reduce time taken to first patient first visit?

Contractual Set Up

There are several issues to take into consideration before starting to put contracts together.

How will the contract be set up? Would the sponsor prefer a tripartite contract or be happier contracting the study to one party leaving them to subcontract the other party? In the UK, the ABPI has produced both a bi-partite and tri-partite contract template for collaborations with an NHS Trust. By looking to

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create an agreed template upon entering into the collaboration, contract set-up time for individual studies is reduced markedly, which in turn helps to reduce the overall time to get to FPFV.

Another important consideration when setting up the contract is the provision of insurance and indemnification. This is not normally an issue when the sponsor enters into a tripartite agreement with the two collaborators, but it becomes more of an issue if one of the collaborators is required to subcontract the other. A way of overcoming this issue is to stipulate in the main contract with the sponsor that the sponsor agrees to indemnify the party collaborating with the sponsor and its agents. Agents can therefore be defined in the contract as any subcontracted party including, but not limited to, the collaborative partner.

Another point of consideration when setting up contracts is making sure the necessary GMP requirements have been thought about and whether there is any need for a Technical Agreement to be put in place between any of the parties. If the unit does not have a GMP-certified pharmacy, there may be a need to alter the way the contract is set up. It is vital to confirm whether there are any GMP considerations as soon as possible and this should really be one of the first points of discussion when looking to put contracts in place.

Table 1: Logistical and practical issues for study conduct

Study procedures
• Screening
• Outpatient visits
• Follow up
Labs
• Safety labs
• Bioanalytical labs
• Courier
• Supplies
Equipment
• Does any equipment need to be arranged or hired?
Pharmacy
• Manufacture or labelling needed?
• QP?
Regulatory reporting
• AEs
• SAEs
• GCP/protocol deviations
Archiving

Table 2: Roles and responsibilities

Eight-page document covering
• Project management
• Trial set up
• Study initiation
• Study treatment period
• Trial close down
• Data transfer
• Archiving

Study Logistics

This is the most crucial point to discuss: not only is it the most detailed, but it can also affect the cost of the study. It is a good idea to have a copy of the latest protocol to hand for decisions to be made as to which party will be responsible for which activity. A list of the main points for discussion can be seen in Table 1, although this is by no means exhaustive. The objectives of this discussion are to determine which party will be responsible for any given activity or procedure. The results of the discussion are documented and then represented in a Roles and Responsibility or Scope of Work document. Once this is finalised, it is then added as an Appendix to the contract. While many Roles and Responsibility documents cover only very top levels points, to ensure all parties to the collaboration are clear on each activity throughout the study the template for this type of collaboration should cover the study in a great deal more detail and should fall under the seven main topics detailed in Table 2. It is essential that a sufficient amount of time be invested in the set-up of the study to ensure the success of the project. Failure to plan adequately dooms a study from the beginning.

EXAMPLES OF THE COLLABORATION AT WORK

The following case studies demonstrate how flexible the partnership can be while still successfully meeting the objectives of the study.

Sponsor A

Sponsor A was looking to perform a patient PK/pharmacodynamic (PD) study in Hepatitis C (HCV) patients. The design of the study consisted of five nights of hospitalisation followed by two outpatient visits (OPVs) then the follow-up visit (FUV). Sponsor A contacted a London NHS Trust to enquire about the feasibility of recruiting HCV patients, but while the recruitment for the study was feasible, the NHS site lacked the facilities to house patients overnight. The NHS Trust then suggested to Sponsor A that one particular CRO had a clinical facility that was within 10 minutes walk from the recruitment centre that did possess overnight capabilities. Upon discussion with the clinical facility, the study was awarded as a joint collaboration between Sponsor A, the NHS Trust and the CRO.

During the kick off meeting it was decided that Sponsor A would be responsible for the CTA submission, the CRO would be responsible for the EC submission and the NHS Trust would perform the R&D submission. As for the conduct of the study, because the NHS Trust was responsible for patient recruitment, it was agreed that screening, OPVs and FUV would occur at the NHS Trust site and that the CRO would be responsible for patients while they were hospitalised. For this to be successful, it was determined that a patient handover between the NHS Trust and the CRO should be performed upon admission to the unit and then again upon discharge, and that during hospitalisation, the principal investigator from the NHS Trust would be able to offer medical input and support at the CRO site. To ensure a smooth transition between sites, close lines of communication would need to be established which would be documented in the Roles and Responsibilities table.

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In regards to study procedures, it was decided that safety samples would be performed at the NHS Trust for their parts of the study and that the CRO would use a local laboratory. Sponsor A had already selected a bioanalytical lab and courier and so these service providers were used. Initially, Sponsor A had requested for the contract to be set up between themselves and the CRO, with the CRO then subcontracting the NHS Trust. Just before signing the contract but after all contract negotiations had been completed, it was discovered that the CRO did not meet the GMP requirements for the protocol and, as such, there needed to be a direct contract in place between Sponsor A and the NHS Trust so that a Technical Agreement could be put in place. To do this, the decision was made to set up a tripartite agreement. While this resulted in more contract negotiation, there were fortunately no delays to the start of the study because of this oversight and it became an important point of consideration for future study set ups.

Sponsor B

Sponsor B was looking to perform a patient PK/PD study in rheumatoid arthritis patients. The design of the study consisted of three periods of one night stays followed by five OPVs ending with the FUV. Sponsor B contacted the NHS Trust directly and was only interested in establishing a contract with them, meaning that the CRO had to be subcontracted by the NHS Trust. To cover any indemnification issues, the CRO was defined as an agent of the NHS Trust in the contract between the Trust and Sponsor B. The definitions, indemnity/insurance clauses and signature page of the contract between the NHS Trust and Sponsor B were then added as an extra appendix to the subcontract between the NHS Trust and the CRO. As there were no GMP requirements for the study, no Technical Agreement was needed. For regulatory submissions, Sponsor B was responsible for the CTA submission, the CRO performed the EC submission, and the NHS Trust was responsible for the R&D submission. To ensure this was done in the timeliest manner, EC and CTA submissions were performed in parallel and the R&D submission was prepared so that it could be submitted the moment approval for both CTA and EC had been received. While patient recruitment was performed at the NHS Trust, for the sake of consistency, the PIs of both sites agreed that all study procedures and visits (including consent and screening) should be performed at the CRO with the exception of biopsy procedures. The biopsies were conducted at the NHS Trust facilities and subjects were then escorted to the CRO (a five-minute walk) by clinical staff to complete any further visit procedures. As a result of this decision, all safety samples were analysed by the CRO's local lab. Sponsor B contracted a bioanalytical lab and courier independently for sample shipment and analysis. As the CRO was responsible for all overnight and outpatient visits, project management was performed by the CRO and the CRO Project Manager was in close communication with the NHS Trust clinical team which in turn reported back to Sponsor B.

CONCLUSION

With the increasing demands on the industry to get compounds into patients at earlier stages of development, CROs and patient recruitment sites, and indeed even competing CROs, will need to look at how their services complement one another to help further address the needs of pharmaceutical and biotechnology companies.

However, for a project that is shared between several parties, the level of planning has a direct correlation with the outcome of the study. It therefore goes without saying that the more preparation spent at the beginning of a project, the more successful the outcome will be. This positive outcome not only benefits the collaboration and the needs of the industry, but also plays a role in getting new medicines onto the market and to those that need them.

About the author

Brendan Ellis joined InCROM Europe in January 2008. Before this he was a part of InCROM's Japanese operations, having joined the Tokyo office in June 2006 as Global Liaison Officer, and was involved in maintaining customer relations around the globe. Upon a six-month secondment in InCROM Europe in 2007, Brendan was transferred to his current position of Business Development Manager in London and now manages all business development for InCROM Europe's Phase I unit based in East London. Brendan graduated with a BSc in Pharmacology from The University of Melbourne in 1998. After graduating, he worked within the Department of Pharmacology, researching mRNA expression in Parkinson's Disease modelled rats.
Email: brendan.ellis@incrom.com

Note

The author would like to thank Dr Paul Astin of the Barts and the London NHS Trust for his input into this article.

Reference

1. **www.abpi.org.uk/publications/pdfs/MCTA-ENGLAND-FINAL-OCT06.pdf (bipartite contract template), www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_079884.pdf (tripartite contract template)**