Selection of CROs

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This article summarizes important topics and criteria one should pay attention to, when selecting Contract Research Organizations ("CROs"). Having worked on both sides, sponsor and CRO (and as development adviser), the author tries to focus on the needs and objectives relevant of both sides. This article will discuss the importance of timing, contract, pricing, size of the partners and personnel.

Introduction

CROs are service companies to the pharmaceutical industry. As such they should be considered as process specialists, i.e. their expertise is usually defined by the offered type of service. Because of this, CROs acquire a certain routine in the performance of these tasks. This is the reason, why during the last decades companies increasingly outsourced many tasks to CROs, as CROs often have a cost advantage compared to hiring and keeping new staff, to perform these tasks. As CROs are highly specialized in their processes, they are mostly more cost efficient than in house personnel.

CROs might be distinguished from Contract Manufacturing Organizations ("CMO"), the latter performing production or production development tasks. As certain principals apply to both, e.g. adherence to international guidelines and associated laws, CMOs are discussed in this article as well, in spite of the fact, that CMO selection might include many more technical criteria in the selection process than for CROs.

No matter if one selects a CRO for GMP manufacturing, toxicology and/or safety testing or a clinical research organization, there are principal requirements that are common to all tasks. Needless to say, that the strict observance of GXP (GMP, GLP or GCP) is key as quality is the most critical factor [1, 2]. Certificates like ISO certification or FDA inspection approval letters may give the sponsor a better feeling, but certainly do not replace the usual quality measures and audits of the sponsor.

Choosing a CRO is a hard decision, because there is a huge and still growing number of CROs in the market, offering their services. Generally speaking there are two categories of CROs: broad generalist (one-stop-shopping) organizations like Covance, who are in business already for decades that offer a full range of services from preclinical up to clinical services and companies specializing in only one or two specific technologies. Therefore the question can arise, whether it is worthwhile, to split tasks among different CROs, e.g. the clinical operation and the report writing of a clinical study. In case of a split, it should be taken into account, that the specialist and/or price advantage can diminish just through the coordination tasks between several parties that have to be managed by the sponsor. In addition, responsibilities in the splitting scenario have to be clearly defined for each of the parties involved. This is especially true, if one decides to split tasks in a clinical study e.g. monitoring & project management from biostatistics and report writing. Often it is not a good idea, to rely on one of the providers of services for coordination, when it was decided by the sponsor, to split one project over more than one service company.

There is an increasing trend, to outsource at least in part tasks e.g. stability-testing or microbiology-testing. According to a survey by Thomson CenterWatch in the USA, 72 % of CROs think they work effectively with the sponsor, but only 55 % of the sponsors rate an effective coworking [3]. As the response rate in this survey was 6 % only, the results might not be very representative.

Timing

Timing is of crucial importance in the selection process. Especially comparatively new and inexperienced companies tend to underestimate the necessary time to be dedicated for a CRO, to set up a study. In this respect there are no differences for a GMP manufacturer

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is a graduated chemist (Dipl.-Chemiker), who also studied pharmacology and toxicology during his thesis. Before starting OPTIPHARM on January 1st 2004, he gained a solid experience of 23 years working in the pharmaceutical and biotech industry, including 3 years in a CRO. He worked in staff and line management functions in mid-size and blue-chip pharmaceutical companies on both sides of the Atlantic (Bristol-Myers-Squibb, Degussa Pharma/ASTA Medica, Novartis, ICON, Boehringer-Ingelheim, november AG). He is deputy chairman of the SANOCHEMIA supervisory board in Vienna (Austria). His special expertise includes general management and operations, R&D, project management and project controlling, business development, diverse indications with particular experience in oncology. He works mainly as an interim manager.

Table 1

Tracking of clinical CRO offers (source: all tables made by the author).

company	A	B	C	D	E	F	G	H	I	K
contacted	16.07.2012	16.07.2012	18.07.2012	16.07.2012	17.07.2012	17.07.2012	16.07.2012		16.07.2012	16.07.2012
CDA signed	16.07.2012	18.07.2012	23.07.2012	20.07.2012		23.07.2012	17.07.2012		19.07.2012	17.07.2012
study proposal	17.07.2012	18.07.2012	23.07.2012	20.07.2012		23.07.2012	18.07.2012		19.07.2012	18.07.2012
question contact	26.07.2012	19.07.2012				24.07.2012	19.07.2012		31.08.2012	
cost proposal	06.08.2012	08.08.2012	10.08.2012	15.08.2012		14.08.2012	10.08.2012	23.02.2012		
			14.08.2012							
		14.08.2012								
turned down	21.08.2012	25.08.2012	25.08.2012	20.08.2012		21.08.2012	21.08.2012			
task										
protocol	31.300		29.578	24.382		21.456	43.641			
submission	33.500	11.000	4.000	8.611		14.356	33.920	13.079		
PJM	84.450	50.000	10.000	88.958		62.208	46.110	28.117		
volunteer recuitment	16.200		35.520	4.357		37.150		17.405		
study conduct	51.850		11.500	23.472		99.764		256.163		
Medical oversight				9.965		4.620				
clinical Lab		117.000	125.280	36.000		114.016	177.700	845.862		
Susar-Prozessing	0	28.000	800	10.894		11.477	1.980	0		
Clin Trial supply/medication	150			415				5.566		
Site monitoring		22.000	18.000			24.112	31.875	0		
bioanalyt								57.490		
clin data management	43.330	69.000	19.800	57.313		21.997	53.420	35.000		
biostatistics/data analysis	35.000	72.000	8.000	38.007		19.583	52.000	34.001		
archiving of trial doc.	21.770						6.100	2.400		
clin. Trial report	23.500	20.000	18.400			13.842		3.960		
QA	40.486		1.400	1.281		3.200		3.600		
other costs				29.000		1.800		0		
pass through costs	76.470	41.000	141.717	308.000		16.080	283.949	147.660		
optional		37.000								
total	458.006	350.000	298.715	604.655		351.645	552.995	604.441		
total plus lab		467.000	423.995	640.655		465.661	730.695	1.450.303		
						in Poland				
comments		incl. safty data db		understood ?		583.800 in D				

[2] which has to have the certified equipment available, a toxicological CRO, which has to have the right animals available at the right animal age or a clinical CRO, which for instance has to identify centers, set up sites and comply with all regulatory paper work requirements. In addition, it takes time, to agree on a contract, which is acceptable to both sides.

The upfront selection process absorbs quite some time, since generally not all contacted CROs will reply within a similar time window. Selecting a clinical CRO would take a little more time than selecting a GMP manufacturer or a toxicological CRO. This is partly due to the fact that one has a bigger choice selecting good clinical CROs and that clinical studies tend to be more complicated and expensive. A simple excel sheet does help, keeping track of CRO activities and offers. Table 1 gives a simple example of tracking and cost comparison as a selection-help for a clinical CRO: In fact it is mandatory to make a task-list before any CRO is contacted, to gain clarification within the sponsor about what will be outsourced. This also supports the challenging process of comparing the offers of the CROs, as they tend to bundle tasks differently, thereby making a direct comparison difficult.

Once CROs have delivered a cost proposal to a sponsor, they are kept waiting for an extended period of time, which can become very annoying as often they were pressed in the first place, to deliver the proposal in a short time period. The sponsor should keep in mind that the CRO often puts quite some know-how into the offer in order to show competency and secure, to achieve the contract in the end.

It sometimes happens that a sponsor takes costs as the only criterion, to make his decision and gives the study to the cheapest CRO, which often is not admitted. They may fail and during the study the CRO has then to be changed and the study repositioned. Of course this consumes unnecessary efforts, time and money.

The contract

52 % of the CROs and sponsors asked in a survey [3] mentioned above, rated contract and budget negotiation & approval as the highest factors causing study delays.

Open and *transparent communication* is the key. If a company has the feeling, that communication does not take place on the same wavelength, taking a different – even a more expensive – CRO should be seriously considered. The communication process with the CRO should be well established from the early beginning on. Generally there will be dedicated persons (*project managers*) on both sides assuring new information is passed in the respective organization

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to the relevant people at the right time and monitoring the progress during the course of the study. Ideally these persons should be identified early during the bidding process.

As always, the underlying contract between the parties should reflect all necessary scenarios like in a license contract [4]. The core parts of the contract are obviously the financial terms and conditions. Especially less experienced companies should make sure, that they avoid change orders. At any rate, change orders – resulting often enough from misunderstanding and different interpretations – can literally poison the working atmosphere between the parties. In order to diminish misunderstanding and different interpretations, a task/to do list should clarify in detail and in-depth all important responsibilities and establish an atmosphere of fair-play and trust.

Early on one should keep in mind already potential delays in the study e.g. because the study medication is not available at the desired time and how to compensate the CRO for keeping the necessary, experienced resources available. A good contract should create a win-win situation and will facilitate working together smoothly. It has to be agreed upon as well, which SOPs ("Standard Operating Procedure") are going to be used during the study.

Pricing

Cost pressure on the sponsor side and likewise also on the CRO side seem to be the norm. This is due to the fact that sponsors have to decrease the time to market and there is increasing competition on the CRO side. If a CRO is newly set up, they might try to go with dumping prices into the market even below their own costs, just to obtain part of the "big cake". Later on it will be difficult for them to increase prices and become profitable. For the sponsor the question arises, if this CRO has included all costs and how often they can practice this, to remain a player in the competitive market. As a consequence, sponsors should be skeptical about unnaturally low prices, not to mention doubts in quality. Unfortunately, cost bits for a project can easily vary by more than 100 %. Only

Table 2

Extract from a task/to do list for selecting a clinical CRO.

Task	Sponsor	CRO	Lab
Site selection with final decision (visit of facilities, MRI, confirmation of information provided in questionnaire)		×	
Study set-up		×	
Investigation and establishing of general logistics (custom, couriers, storage, etc.)		×	
Preparation of work specific instructions and forms (safety plan)		×	
Supply of additional equipment if required (like refrigerators, deep-freezers etc.)		×	
Site set up and dummy run		×	
Pharmacy dummy run		×	
Laboratory Manual			×
Development for the safety lab			×
Lab manual development			×
Monitoring Manual			×
Investigator Meeting	×		×
Pharmacy training		×	
General GCP and study specific procedure training		×	
Investigators / Institutional grant negotiation		×	
Preparation of master Investigators and institutional contracts	×		
Translation of contracts into local languages		×	
Investigators / Institutional grant administration		×	
Study Initiation		×	
Provision of Study drug	×		
Provision of CRFs		×	
Provision of study documents		×	
Provision of laboratory kits			×
Provision of AB-kits			×
Site initiation visit		×	
Interim Monitoring visits		×	
Tracking list maintenance		×	
Study site compliance management (regular phone contacts with study sites and other functional management units)		×	
Study Documentation management according to Sponsor SOPs		×	
Site file		×	
In house monitoring files		×	
Trial Master file	×		
Study closure activities		×	
Study closure visit		×	
Return / destruction of used and unused study medication		×	
Return / destruction of other study supplies		×	
Local archiving at the study sites		×	
Archiving of TMF	tbd		
Study supply logistics		×	

a thorough task analysis reveals, whether these differences results from misunderstanding of the required services, unreasonable pricing, or truly reflects actual prices. The overhead of global services providers impact the costs for small projects significantly.

Quality management systems fulfilling international guidelines and standards are not cheap. Therefore this topic should be considered from the start of the bidding process, as some parties might have different opinions about quality and this will ultimately have a bearing on different prices.

Especially smaller companies developing (biological) products should try to have no unrealistic approach considering time and to assess the funds required [1]. The selection of CROs is a difficult task, for which large companies have appointed people with experience not only on the technical-scientific side, but also with regard to commercial and legal aspects. If such a person is not available within a smaller company, as is most often the case, they are better advised, to spent money for an external consultant, than to take the risk of change orders or delays in timelines due to a bad selection process of the CRO. Additionally companies should make sure, that they have the right development persons in the supervisory/scientific development advisory board [1].

The price a CRO quotes in a cost proposal is a prime selection criterion. Sponsors often try to press the CRO, to still reduce an already competitive price. It should be kept in mind though, that once the project has started, the service provider can usually not be exchanged. An initially attractive price may then result in an expensive outcome, possibly even significantly higher price, due to frictions such a situation will cause. The more transparent the proposal is, the better for both parties and this way change orders might be avoided.

Size of a CRO and of the sponsor

The size of a CRO should not be neglected. The size of a selected CRO might differ in each stage of development. E.g. if a company is just starting clinical phase I, it might work with a smaller (local) clinical CRO and later change to a bigger (international) CRO, in order to obtain the necessary patient population in the desired timeframe. The same is true for a GMP manufacturer, as one might not need the costly "Mercedes", if there is no prove of concept yet and a less costly "Toyota" might do the job. The GMP gradient should always be on the increase.

Sticking to the same CRO has the advantage that one knows one another already, trust is established and the workflow is facilitated, but the sponsor surely will spend more money, selecting a bigger CRO right from the start. For bigger companies preferred providers should be considered.

According to the author's experience smaller companies are usually better off, considering smaller CROs. Generally speaking these would be a little cheaper for the same amount of work as they do not have to finance a big overhead. In addition there would be a better fit. On the other side a bigger CRO would give one more security that their likelihood to "survive" is higher.

Personnel

Ethical problems on the CRO side, which has to keep a certain amount of personnel and maybe lay off some personnel on short notice will not be discussed here.

The personnel one meets during the selection process might not be the one, running the study. Make sure e. g. put it into the contract, that people on the study have the adequate knowledge and experience. It seems obvious, but confirm, the CRO has the necessary capabilities, to run your study. If a CRO intends to subcontract part of the study, this should be mentioned in the contract. Sometimes a CRO claims, to have special experience in a certain indication, however not all people having this experience are still with this CRO or gained experience only from bids for similar projects. One should try as well, to have constant personnel during the course of the study; this might be difficult especially in a clinical study, as clinical CROs tend to have a rather high rate of fluctuation. Project turn over might generate inefficiency and additional expenses. The personal relationship is vital for the success of the study. This topic is rated higher on the sponsor side than on the CRO side.

It is of additional value, to find out the track record of the CRO with respect to client satisfaction, budget and schedule. Some CROs maintain (and share) metrics regarding client satisfaction.

Summary

In the selection process the size of the company and the CRO should be considered. Of course quality topics have to be taken into account. Even, if not in particular, the selection of services for small-to-midsize projects requires experienced personnel or a professional advisor. This can speed up the selection process, facilitates the communication between sponsor and CRO and ultimately may result in a smoother project performance. The cost savings by means of that should be apparent. Finally a good contract that considers all scenarios from the outset should be established, to create a win-win situation and will ultimately facilitate working together smoothly and in a productive manner.

LITERATURE

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