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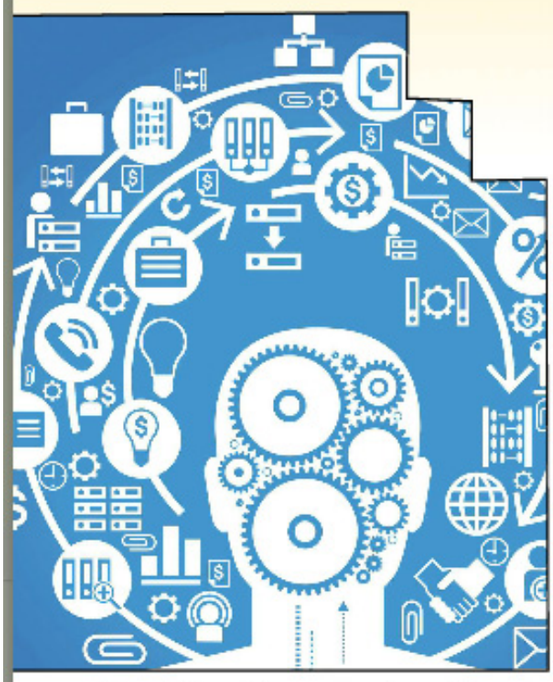

Expert Insight On Selecting A CRO

By Rob Wright

What was once referred to as outsourcing is now commonly called strategic partnering when discussing the business of drug development. In order to successfully strengthen drug pipelines, bio and pharma companies have been increasingly turning to CROs for help. By developing strategic partnerships with CROs, large and midsize companies have been able to capitalize on a reallocation of financial resources, moving from the fixed-cost internal R&D model to one which is more variable and external to the organization.

One of the biggest examples of the implementation of this new model was demonstrated last year by Pfizer, which announced the closing of its Sandwich, UK, R&D facility and the subsequent strategic partnership with two CROs — ICON and PAREXEL. For small and virtual bio/pharma companies, outsourcing of clinical trials has always been part of the business model. For sponsors, the challenge remains how to best qualify, select, and partner with a CRO. But the selection process is not a one-way dialogue. During recent discussions with CROs, most have expressed an interest in being more selective when developing strategic partnerships with sponsors. The goal is to not only match up with expectations and deliverables, but also to align synergistically in the area of corporate culture so the strategic partnership has long-term sustainability.

In an effort to help you gain a greater understanding of the CRO selection process, *Life Science Leader* reached out to seven experts. The resulting roundtable provides insights from highly experienced executives and consultants who can give perspectives from a small biotech startup to a Big Pharma company. The panel includes Peter Carberry, M.D., SVP global development operations, Astellas Pharma US; Peter DiBiaso, head clinical business and development operations, Vertex Pharmaceuticals; Maxine Gowen, Ph.D., president and CEO, Trevena; Jonathan Kfoury, VP, L.E.K. Consulting; Coreen Oei, SVP of clinical operations and project management, BeiGene; Marc Tolkars, senior director clinical operations, Luitpold Pharmaceuticals; and Santosh Vetticaden, president, Global Drug Development Consulting.

WHAT ROLE DOES COST PLAY IN THE CRO SELECTION PROCESS?

Peter DiBiaso, Vertex Pharmaceuticals: While cost efficiency is a key selection consideration and a desired benefit of a CRO partnership, it is not typically a leading criterion. Of greater focus is the evaluation of quality and service expertise (i.e. fit for purpose) for the proposed scope of work. Cost might also play a greater or lesser role according to the type of project being supported. In a more transactional buy — i.e. single study, low study complexity — cost might have a greater influence, whereas in a more strategically driven selection process, other factors will weigh more heavily.

Marc Tokars, Luitpold Pharmaceuticals: For smaller companies, the unfortunate truth is that cost is a major consideration when selecting a CRO. Contracted tasks such as site selection, contracting, monitoring, site payments, and data review are usually not the sole responsibility of either the CRO or sponsor and can often be shared. This provides a cost savings, as the sharing of tasks reduces the CRO's workload while providing sponsors a greater understanding of challenges posed by a trial and faster input toward problem resolution. Some CROs seem reluctant to fully enter into this type of relationship or fail to pass on the savings to sponsors.

WHAT QUALITY METRICS DO YOU UTILIZE WHEN BUILDING COLLABORATIONS WITH CROs?

Jonathan Kfoury, L.E.K. Consulting: Developing an agreed upon issue esca-


Peter Corberry, M.D., SVP global development operations, Astellas Pharma US


Peter DiBiaso, head clinical business and development operations, Vertex Pharmaceuticals


Maxine Gowen, Ph.D., president and CEO, Trevena


Jonathan Khoury, VP, L.E.K. Consulting


Coreen Oei, SVP of clinical operations and project management, BeiGene


Marc Tekas, senior director clinical operations, Luitpold Pharmaceuticals


Santosh Vetticaden, president, Global Drug Development Consulting

lation/resolution plan is key to ensuring that the CRO middle and senior management is fully engaged in the study's progress. Sponsors should routinely review reports on what issues were raised and how they were resolved, especially early in the trial when the learning curve is steepest. It is also important to establish a dashboard with the CRO that details leading indicators for the trial each week, i.e. projected completion of enrollment based on active sites and patients enrolled to date, across sites and geographies. This ensures alignment on progress and identifies potential bottlenecks.

Santosh Vetticaden,Global Drug Development Consulting: In general it is recommended that both sponsor and CRO develop a quality plan which addresses the needs of each organization. In addition, it is extremely useful to review the CRO's internal quality plans which often go beyond those areas emphasized by the sponsor. The metrics for quality are too varied to cover in detail, but a few examples include qualifications and training of staff, trial metrics such as enrollment, evaluable patients, reporting time for various activities in data management, and safety reporting.

WHAT NEW TRENDS DO YOU SEE TAKING PLACE WITH CROs?

Maxine Gowen, Trevena: Some CROs are becoming more flexible in taking responsibility for their promises and often refer to this as *risk-sharing*, although I tend to think of it more as *delivering*. The traditional model does not appropriately align incentives, i.e. the longer a trial takes to complete, the more a CRO is paid. This is not sustainable, particularly for loss-making companies with restricted cash availability. CROs will ultimately destroy their customer base if they do not look at their business as relationship-based vs. contract-driven.

Coreen Oei, BeiGene: There has been an increase in pharma-CRO strategic partnerships, especially among the larger pharmaceutical companies and global CROs. These have changed the relationships between CROs and sponsors from tactical/transactional models to those resembling an alliance or partnership. While Big Pharma companies benefit from strategic partnerships, small to midsize biopharma companies may be overlooked. Smaller clients may not view these CROs as having enough capacity to provide the necessary attention in light of demands from larger companies. To guarantee attention from big CROs, smaller biopharma companies need a sizable pipeline of work.

HOW DO YOU GO ABOUT ASSESSING RELIABILITY FOR A CRO?

DiBiaso: As with most business relationships, reliability and trust are dependent on the outcome of your last project. However, there are strategies to encourage greater success. One such approach is establishing mutual collaboration for developing and agreeing to the overall project plans. While in many cases CROs have been selected for particular expertise, this shouldn't discourage the sponsor from contributing to or requiring transparency in the early planning process. This type of input fosters joint ownership of plans and subsequent outcomes. Defining leading key performance indicators that enable teams to make required course corrections or deploy contingent strategies is also essential.

Vetticaden: Because no two clinical programs or trials are exactly the same, it is challenging to define reliability, which may vary depending upon the areas being assessed. In general, it is important to assess the prior reputation, experience, and track record of the CRO being evaluated. Most CROs maintain metrics in areas such as trial completion on schedule and on budget which may provide useful data. Diligence of the CRO's prior experience, competence of key study personnel, organizational structure, plan to deliver, plan for contingencies, and margin of error in their estimates, often provide useful insights for assessing CRO reliability.

HOW WOULD YOU DEFINE ACCESSIBILITY AND WHAT CAN CROs DO TO DEMONSTRATE ACCESSIBILITY AND EXECUTE ON BEING ACCESSIBLE?

Oei: A key requirement during the request for proposal (RFP) process is having the sponsor's questions addressed in a comprehensive and timely manner. I consider accessibility as my company

having visibility with the CRO, as well as the ability to interact with the CRO's senior management. I like to determine if there is transparency and trust in the potential partnership, as I am entrusting the execution of my company's clinical assets to the CRO. Engagement by the CRO's senior management team helps to ensure that my company is getting the right attention and service.

Tokars: In my mind, accessibility is not simply ensuring that the CRO staff assigned to your project is available for a teleconference or meetings to present suggested solutions to project challenges, but instead, to be a true partner, CROs need to allow sponsors transparency into their thought processes and internal deliberations. Talking through the challenges, the history, and potential future remedies with high-level experts, often not intimately involved in the day-to-day operations of the trial, provides a 360-degree review of the problem and often results in discovering the best solution.

WHAT METRIC DO YOU USE TO ASSESS PRODUCTIVITY AND HOW DO YOU WEIGHT THIS WHEN COMPARING DIFFERENT SIZES OF CROs?

DiBiaso: While productivity and overall efficiency are critical components, the high rate of variability across sponsors and CROs in terms of their respective development and operations models makes true industrywide comparisons difficult. Fixed-unit prices, as part of the bidding and contract process, provide some comparative assessments. Functional metrics, such as workload monitoring of average-site-visits-per-monitor, active protocols, and active sites are but a few of the useful metrics when evaluating a CRO by service offerings. It is essential to understand your own resource utilization and effectiveness measures so you have a basis of comparison when CROs cite their own productivity metrics.

Gowen: During the CRO selection process, we evaluate their standards for timelines, turnover rates, meeting usage, i.e. updates vs. real work. An evolving approach during the execution of the study is using earned value (EV) analysis to assess productivity at a high level. Calculating EV creates a relationship between tasks, project costs, and schedule. This provides one objective way of evaluating project health.

WHAT IS YOUR APPROACH TO EVALUATING CROs FOR REGULATORY COMPLIANCE?

Gowen: We solicit the CRO's prior audit and inspection history and the outcomes of those audits/inspections. The CRO's SOPs may also be requested and reviewed to ensure they have adequate processes and standards in place so that, when properly executed, their team adheres to the usual and customary practices. A post-selection CRO audit may identify areas of increased risk for regulatory compliance. In early phase studies, audits can more easily be performed prior to, or as part of, CRO selection.

Vetticaden: Prior to selecting a CRO, evaluate its overall experience, track record, depth of knowledge, qualifications, and experience of regulatory personnel. Supplement this with a review of

prior regulatory inspections, recently completed NDA (new drug application) or other submissions, whereby the CRO had primary responsibility for executing a pivotal Phase 3 trial. Conduct a tailored audit to address sponsor learnings from the review. Once an ongoing relationship with a CRO is established, a phased-in/phased-out approach should be employed. For example, the sponsor should initially review CRO regulatory packages prior to submission. This may lead to iterative interactions, which can eventually be phased out as sponsor and CRO achieve alignment.

WHAT TRICKS OR RESOURCES HAVE YOU FOUND TO BE HIGHLY USEFUL IN THE CRO SELECTION PROCESS?

Peter Carberry, Astellas Pharma US: We have a two-step process that enables us to first identify an initial set of competent vendors through a request for information (RFI) process and then proceed to final selection through the RFP. Blinded to the vendors, we score the RFP responses against a comprehensive set of criteria that can be measured, at least semiquantitatively, and then weight appropriately. The scores are combined to give us a final result. The top candidate(s) are then invited to defend their proposals before we make a final decision.

DiBiaso: Regrettably, there are no tricks to alleviate the time and commitment required for a successful selection. The best approach is investing time to educate the team so they understand their overall role and primary goals. Functional representation needs to be supported by their respective line leadership. This often requires significant alignment and input outside of the regular selection meetings. Executive leadership needs to provide clear and objective guidance to the team. In some cases this can serve as an adjudicator for issues of disagreement, as well as to help the team when there is a challenge in reaching consensus.

WHAT ADVICE WOULD YOU GIVE TO THOSE INVOLVED IN THE CRO SELECTION PROCESS?

Carberry: It is really helpful for sponsors to spend time defining and incorporating business requirements and quantitative expectations in the RFI documents prior to engaging in the

process. Do not preselect in, or out, any vendors, but agree up front on the competencies, capabilities, and performance clinical teams can expect, and allow the RFI process to assist in the selection process. The selection process by itself will not nurture the relationship with the vendor selected. Effective and collaborative governance using measures incorporated in the RFI and RFP process is more likely to result in a successful, productive relationship with quality output.

Gowen: If something does not go well when negotiating the contract, it will probably get worse once the contract is signed. Be methodical and have internal agreement on the necessary scope of work for each CRO and stick to it throughout the RFP process, bid defense, and final selection. When scope definition changes, communicate it clearly and consistently to all involved. Include in the contract, limits for deviation from the plan and give a clear process on what will then happen and who will bear responsibility. Ensure that you have clear instructions regarding change orders, a well-known device for dramatically increasing the cost of your trial. Be clear that you will not pay change orders unless the work has been previously approved.

WHAT ARE SOME OF THE FRUSTRATIONS YOU HAVE HAD IN GOING THROUGH THE CRO SELECTION PROCESS?

Kfoury: Some larger CROs have highlighted their strong experience in a therapeutic area (TA) of focus, but then assigned a team that did not have depth in the field. Ultimately, the CRO project team is critical to a successful trial. A CRO's corporate experience in a given TA doesn't necessarily translate to on-the-ground team member judgment and decision-making ability. Turnover at CROs can be high. It is key to really vet the proposed project team for experience, skills, and most importantly, fit.

Tokars: The greatest frustration we often encounter during the CRO selection period centers around inflexibility. Comparing different CROs for a single project can prove difficult, especially when requesting costs for services in specific formats and breakdowns. Business development groups, almost stubbornly, try to fit their cost algorithms into our preferred formats and often fail miserably, adding error into the estimates. Inflexibility in what services CROs may not want to share with the team also adds a great deal of complexity to the process, as realistically estimating the costs for the shared task proves difficult.

WHAT COULD CROs DO TO MAKE THIS PROCESS EASIER ON YOU?

Kfoury: CROs should work to provide more transparency up front on their proposed team's specific experience within the TA and geographies in question, as well as detail how their projections for cost and timing in similar engagements have mapped (or not) compared to actuality. These simple steps can quickly build comfort with sponsors around a CRO's credibility and capabilities in specific TAs of focus.

Oei: It is always helpful when the CROs provide a proposal that is as comprehensive as possible. The proposal review process is often highly interactive. The CROs should be prepared to turn around queries on the proposal sponsor in a reasonable amount of time.

Vetticaden: CROs need to ensure their RFP submissions include an executive summary highlighting their strategy, key differentiators, costs, timelines, key challenges, and mitigation strategies. It is useful to include options for consideration by the sponsor since it provides insights into the CRO's thought process and abilities. It is also helpful to identify up-front counterparts to the sponsor's relevant team, such as the core study team, so as to rapidly build confidence with the sponsor regarding the CRO's depth and breadth of expertise.

"AS A CRO, IF YOU WANT MY BUSINESS YOU NEED TO...

"...show an acceptable level of expertise (both theoretical and technical competency) about the model/study, have a good system for communication, and be competitively priced."

Tess Pulido-Rios, Research Scientist, Dept. of Pharmacology, Theravance

"...earn my trust and confidence through sustained, timely delivery of accurate results at reasonable cost and contact my team lead directly when you anticipate issues delivering on any of these promises, i.e. speed, cost, and accuracy."

Ralph Lambalot, Ph.D.; Divisional VP, Biologics Dev. & Manufacturing Launch; Abbott Bioresearch Center

"...take ownership in the project, stop nickel and diming us on every clincial study, fully understand the best methods for analysis before initiating the study and providing final project estimates, and most importantly, clearly communicate the progress of the study as milestone payments are made."

Chris Fields, VP Scientific Affairs, Applied Food Sciences Inc.

"...give me a realistic bid and contract (not necessarily the cheapest bid) and keep to the cost and timelines promised."

Kent Allenby, MD, FACP; VP, Drug Development, Proprietary Products; Dr. Reddy's Laboratories, Inc.