

## Transforming clinical trials through CRO-ePRO partnerships

Gregg Jewett explains why recent trends in the biopharmaceutical market make a CRO-ePRO alliance so valuable to industry.

Clinical research professionals have been well aware of the strengths and capabilities of contract research organisations since their emergence over 20 years ago. In contrast, the global electronic patient-reported outcomes or “ePRO” organisation has emerged as an important player in only the past five to seven years, and some decision makers in the clinical trial sector have become knowledgeable of the strengths and potential of this service provider to the drug development scene. What may have eluded many industry professionals at present, in 2011, is the absolute, strategic value of CRO-ePRO partnerships.

In the discussion of how these two important players converge for the ultimate benefit of the clinical trial, it is important to review the state of the clinical trial industry over the past several years and its subsequent impact on both CROs and ePRO providers, as well as the impact that these services have had on the industry in return.

### The last decade for CROs

Throughout the bulk of the 2000s, revenues of biopharmaceutical companies grew at high rates, with dozens of “blockbuster”-status drugs in the marketplace. As a consequence, clinical trials were increasing in number, growing in size (number of countries, sites, subjects) and becoming more complex. Small biotechs and virtual companies started to appear in great numbers with major funding from venture capitalists and well-heeled scientists. The “Big Pharma” companies were getting even bigger and the small- to mid-sized companies were growing in kind. More money was pooled into pharmaceutical R&D than ever before, with every organisation searching

for that next blockbuster or at least looking to increase their slice of this growing pie. Even in the early 2000s, CROs were often regarded as the only way to help pharmaceutical companies run these larger, now worldwide, complex trials.

Smaller companies were looking to CROs for operational support and insights to clinical research. Big companies were working with CROs for their global footprint, therapeutic expertise and speed. These needs translated into outsourcing to CROs at an impressive, steady rate, growing in double-digit percentages for most of the decade. In fact, from 2002 to 2008, the spend in the total R&D CRO market (which includes pre-clinical, Phase I studies and central & specialty laboratories) almost doubled from \$10.8 billion to \$20.6 billion. More specifically, the core clinical CRO market (direct support of Phase II-IV studies) also nearly doubled from \$6.1 billion in 2002 to \$11.3 billion over the same time period<sup>1</sup>.

As we moved through the 2000s, however, a slow, intense storm was also brewing in the biopharmaceutical industry, on multiple fronts. From a lower number of new drug application approvals, to pricing pressures from governments and healthcare networks (particularly in the US), to the looming sight of generic competition, sponsors saw some difficult days ahead. Many biopharmaceutical companies, especially the largest ones, were starting to forecast their sales and pipelines out into the two thousand-and-teen years and they all saw strikingly similar trends – the end of patent life of many of their top-selling drugs, and tougher chances at success and approvals for new drugs.

Added to these pressures was an overall US economy sliding into a recession and a stunted global economy, which made 2007 the start of a few extremely difficult years for the biopharmaceutical industry, as well as for many companies that support the clinical trials that they order. This impacted not just the major pharmaceutical companies; by 2008, even the small pharma and biotech companies, many of which had started to push their projects into clinical phases, had not only lost revenues but their funding sources had all but dried up. Acting in survival mode, the larger players in the industry did their best to survive and compete, and that mostly meant to acquire or be acquired.

Over this time frame, one could see the tangible effect of the challenges of the entire

biopharmaceutical industry upon the CRO community. Not only did CRO spending growth decline substantially from 17.2% in 2007 to 7.9% in 2008<sup>2</sup>, but it actually fell to 0.0% in 2009, according to Jeffries & Company. Zero growth when it was averaging nearly 15% for several years prior.

According to *clinicaltrials.gov*, the number of Phase II-III trials (the heart of the clinical trial world and the core of a pharmaceutical company product’s submission data) actually decreased in both 2008 and 2009, completely unprecedented for this industry. Even the US Pharmaceutical and Research Manufacturers Association itself stated that its member companies spent 1.1% and 3.4% **less** on global R&D in 2008 and 2009, respectively. PhRMA has been providing reports since 1970 and had never previously reported two consecutive years of reduced spending.

All of the major corporate mergers and acquisitions came and they came at a hefty price, as publicly traded companies with investors quite used to steady growth and high margins, had to cut costs immediately and significantly. This was to be accomplished one of three ways: 1) pipeline rationalisation; 2) the elimination of jobs and/or locations; and 3) efficiency in procurement and sourcing. All three of these cost-cutting measures had a direct and dramatic effect on the CRO industry.

Pipeline rationalisation, which is essentially the full and complete review of a newly merged company’s entire portfolio, from pre-clinical testing all the way to marketing-related support, had the most immediate impact on CROs. This tact is fully justifiable knowing that companies and their clinical research programmes that were once competing, were now coming together and had to be shown as not impeding their new sibling’s growth and potential. In fact, sometimes only one sibling programme would survive this review and course of action. Two things made this a dangerous and difficult time for CROs. Firstly, the rationalisation process is a slow and tedious one, and can easily take up to a year or longer, which translates into significant delays for any projects that may have been planned and sourced (and perhaps even contracted) but not yet launched; and secondly, as the prioritisation of some programmes appeared, the ensuing de-prioritisation of other programmes occurred as well. These had often been projects that had been planned and sourced

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(and perhaps even contracted) and were hence delayed or cancelled. The entire service provider community saw this first-hand, as practically all of the CROs took the hits – and the public ones often had to refine revenue estimates downward, as much as 20% from 2009 through 2010. A few leaders in the space even showed some net losses in those years.

The next fallout area of this biopharmaceutical M&A activity may be the only one that seems to have had a direct, positive effect on the CRO world: redundancies. The unfortunate reality is that when these behemoth companies come together, there will be the streamlining of operations, the reduction of positions and the elimination of jobs. Although the majority of these layoffs have come (and will continue to come) from manufacturing and sales, it is a fair estimate that 20-30% of the cuts will be from clinical research. Even some site location decisions have been made, again mostly with plant operations, but also where both legacy companies had major clinical operations offices in London or Paris or northern New Jersey in the US. We have all seen or heard the numbers. When those massive deals closed, Pfizer/Wyeth announced 20,000 layoffs over five years, Merck/Schering Plough announced 16,000 over three years and Abbott/Solvay announced 3,000 cuts over two. Abbott has further announced another 2,000 jobs to be removed just this year. Additionally, the economic downturn had impacted the entire industry, not only those companies who were part of an acquisition. For example in 2011, just to trim their spending, Astra Zeneca announced some 8,000 job cuts and Eisai noted that it would slash almost 1,000 jobs over the next few years. All of those job losses simply meant that the biopharmaceutical companies themselves now had fewer project managers, clinical research associates and data managers to internally run and manage their studies. Sponsors had to increasingly look to CROs for the resources.

CROs had been gaining more trust and taking on more responsibility from pharmaceutical companies over the past decade though. Most CROs improved and further developed their own capabilities, with nearly all of the major players now encompassing the full range of clinical trial support activities, from clinical operations to project management, to data management and statistical analysis to pharmacovigilance. A number of CROs even built up standalone functional outsourcing groups to further support sponsors effectively. Working alongside their CROs now, sponsors began to think of them not merely as a commodity (or a collection of nameless people with tasks thrown over a fence to them), but as integral members of their clinical team and as partners

of the sponsor organisation. As part of many biopharma initiatives, discussions and strategies emerged as to how to elevate their key CROs up the scale from tactical to preferred to strategic partner with optimal usage and best practices. As a result, a huge number of pharma-CRO partnerships arose. Numerous positions were created on both the pharma and CRO sides with partnership or alliance in their title to help foster and manage these growing relationships.

According to the Jeffries & Co. analysts, the clinical CRO market growth rose only 1.8% in 2009, it is further estimated that there was a 5.2% rebound growth in 2010, and the projected growth target for 2011 is even higher at 7.4%. These clinical growth rates are higher than the growth rates expected for the broader CRO market (including pre-clinical) or the entirety of global pharma R&D. This means that although the entire biopharmaceutical R&D sector is projected to pick up and increase once again, albeit marginally (about 3% per year), the clinical CRO market is projected to double that<sup>3</sup>.

The third output of this perfect storm for the pharma world was to be dropped into the laps of purchasing and sourcing teams within the sponsor companies. For as soon as the mergers or acquisitions and their price tags were announced, also came the announcements of potential cost "synergies", often in the billions of dollars. Immense pressure was put upon the procurement departments to guarantee these savings with all of their vendors and service providers, immediately and for the future. Though they were in the middle of pipeline rationalisation with few-to-zero new studies starting up, evaluations and negotiations with CROs caught fire. As the biopharma industry ramped back up with more spend and greater buying power, only the best CROs would win the preferred or partnered relationships to source the products and services that were necessary to keep this newly formed sponsor company running at anticipated high levels. It was almost a "rationalisation" for the outside service providers as well, as this process eliminated some vendors from the new sponsor's mix, and squeezed the revenues and margins of the CROs that were selected.

### Future outlook for CROs

Though the new pharma company pipelines are restarting and smaller biotechs are re-emerging and the amount of new trials is increasing once again, there are still pressures from all sides of the industry. Competitiveness is higher than it had been, and it seems that "efficiency" is the buzzword – how to do more with less. Sponsors clearly have to

increase their chances of moving successful molecules through clinical trials and to market, and to do so with fewer resources to run and manage the studies, along with tighter purse strings. Small companies are back and producing but are staying quite small. The big companies have stabilised but are significantly leaner than they once were. Many CROs have the therapeutic experience, the global footprint (and local knowledge) along with the bandwidth to both launch and manage clinical trials effectively, if given the opportunity to do so. The only remaining question is speed. Business Insights recently said that studies are being completed 30% faster using CROs than those run by the pharma companies themselves. The good thing is that because of the challenges that have affected the industry over the past decade, there has been a concerted and necessary move towards increased outsourcing to CROs.

There is certainly no guarantee for the success of drug approvals by utilising CROs of course, but CROs are, and have been for some years now, the best way for biopharmaceutical companies to be efficient in running successful clinical programmes. It's simple: CROs are the answer for clinical trials.

### The last decade for ePRO providers

It is obviously spelled ePRO, but amusingly enough, ePRO actually starts with the "PRO", not with the "e". You don't have ePRO without the need to gather information directly from the patients. The PROs, Patient Reported Outcomes, have been used in clinical trials for dozens of years, obviously and originally on paper. The instrument, or questionnaire, was developed on paper. The responses and answers were recorded on paper, and the analysis or transmission of the data early on, was purely on paper.

No question, it is a great concept: data directly from the patient. The ability to gather information throughout the patients' daily life and not simply waiting until they come back into the doctor's office for their regular visit is nothing less than groundbreaking. The rationale is even stronger if the patients are taking the investigational drug while at home, which is often the case. It is even stronger if there is a need to see the incidence or recurrence of symptoms regularly, which is typically the case. Furthermore, the rationale is even stronger if a patient's quality of life is an important consideration, and globally, quality of life is increasingly becoming a highly valued measure for the industry. With the increased complexity of trials currently and need for additional data, that original concept of self-reported patient outcomes is more significant than ever before and its core benefits are undeniable. Bringing

the patient and the patient experience closer to the centre of the research with PROs will undoubtedly give sponsors better data and more accurate results. Treatment efficacy and safety will be more thorough and can only strengthen the regulatory submission package towards approval. These PROs will also help to compare competitive products in a world of post-approval marketing and comparative effectiveness requirements.

Unfortunately there had not been a major focus or consistent measure of ePRO trends throughout the decade. With tools like *clinicaltrials.gov*, we can gain some better insights though. In early 2000s, the US Food and Drug Administration indicated that only 30% of trials had PROs as primary or secondary endpoints. It has been more recently noted, in 2009, that CenterWatch listed that around 75% had some PRO component. Additionally, there has been a considerable increase in PROs as the primary endpoints, particularly in indications that are well-suited for patient self-reporting such as pain, overactive bladder, some inflammatory diseases (eg asthma), and even some CNS (eg depression) indications. Representatives from the FDA stated that of the all new molecular entities evaluated in the 2003-2008 period (n=141), one-third of the submissions had a PRO instrument and its data<sup>4</sup>.

Regulatory agencies themselves saw the growing importance of PROs, such that they thoroughly studied and evaluated it, and provided some distinct guidance to the industry on their findings. In 2005-2006, both the FDA and the European Medicines Agency issued documents that supported the usage of PROs with the benefits to be realised as well as the means to test and validate those claims. They both identified the facts that:

- some treatment effects are known **only** to the patients;
- patient perspective is different from safety and core efficacy data yet **augments** the entirety of the labeling claim; and
- capture of a PRO is a **formal** assessment and must be validated.

The FDA further released its Final Guidance on Patient-Reported Outcome Measures in December 2009<sup>5</sup>, solidifying the agency's earlier stance in support of PRO collection and moreover, ePRO collection, provided that electronic record keeping guidelines are adhered to and that data can be accessed by only the right individuals when necessary. ePRO clearly meets the FDA's ALCOA standards for collecting patient data in labelling claims (Attributable, Legible, Contemporaneous, Original and Accurate). In perhaps the most telling statement, the agency states explicitly that "If a patient diary or some other form of

unsupervised data entry is used, the FDA plans to review the protocol to determine what measures are taken to ensure that patients make entries according to the study design and not, for example, just before a clinic visit...". This means that if there is patient reported data, the sponsor will need to prove its compliance to the protocol. All in all, those issuances provided additional visibility to the positive effects of capturing PRO data.

Paper collection is still a widely used modality to capture such data, even with the limitations per the regulatory guidance and standards. For many sponsors, however, once ePRO is understood and utilised, there is very little question that the best way to employ collection of PROs is via ePRO. It becomes clearly evident that, as compared to paper, ePRO brings the following enhancements to your PRO data:

- reduces errors;
- eliminates need for double-data entry;
- provides exact time and date-stamps;
- generates greater portability and convenience;
- prevents loss of data;
- provides real-time access to data;
- improves data accuracy;
- privately and confidentially entering data;
- eliminates illegible, conflicting or superfluous data; and
- empowers patient compliance.

Not only can ePRO improve patient retention, it also lessens the burden on sites. It makes monitors and data managers much more efficient. It provides quality and integrity to the data, and it has the potential to transform clinical trials. This transformative power of ePRO is evident since electronic capture has been shown to minimise error-filled, missing and incomplete data when compared to paper PRO. The reduction in data variance increases the study's statistical power, which allows sponsors to lower the sample size of patients in subsequent trials. This remarkable tool can be implemented when ePRO is used in Phase II of a programme and then continued into Phase III. As the statistician evaluates the completeness of data from the earlier study, the transformative impact of ePRO can project out lower numbers of Phase III screened, enrolled and completed subjects and/or shorten the timelines to get to those necessary levels of subjects. There is no question that Phase III studies are the largest, longest and most expensive part of the entire clinical trial process already, so making this more efficient would be transformative.

The agency support and increasing proof of the overwhelming benefits of utilising ePRO has allowed the ePRO industry to grow in the past several years, and grow at a fevered pace.

The high-pressure storm that hit pharma companies in 2007-2009, and subsequently the CROs, was the same storm that hit ePRO providers. But the results were not quite the same. There were still significant delays and study cancellations for the ePRO industry. In a flat and shrinking clinical trial world, however, the ePRO market experienced growth through this time period.

Industry leaders identified ePRO adoption and utilisation at approximately 20% of the PRO space in 2008, which meant that only one of every five clinical studies with a PRO instrument, captured that data electronically. But since it is showing a continued 25-30% annual growth, estimates hover around 30% utilisation in 2010 and target 47-51% adoption by 2012. This adoption jump from one-in-five PRO studies to one-in-two in four years undoubtedly makes ePRO the fastest growing segment of our entire industry. The gain for ePRO adoption and utilisation is encouraged by the regulatory visibility, the necessity of higher competitiveness and differentiation of products, the potential to transform clinical trials statistically, and the absolute need for efficiency.

There is certainly no guarantee for success and drug approvals by utilising ePRO of course, but ePROs are, and have been for a few years now, the best way for biopharmaceutical companies to be efficient in running successful clinical programmes. It's simple: ePRO is the answer for clinical trials.

## Convergence of CRO and ePRO

There are clear reasons why usage of CROs and utilisation of ePROs would be valuable for biopharmaceutical sponsors independently. But there are also a few trends that seem to pull CROs and ePRO providers together. The top three are described below.

### "Full" outsourcing

At an increasing rate, and one that likely dovetails with the fewer numbers of resources within biopharmaceutical companies to run them, these clinical trials are being fully outsourced to CROs. This can mean a variety of things but typically is comprised of the CRO taking on all, or nearly all, of the operations of a clinical trial, across all functions (including data management, which we will get to later). Full outsourcing can also mean that the CRO must now advise upon, select, contract with and/or manage all other third-party vendors, including expert services like ePRO providers.

In doing this, the CRO is often brought in very early as a trusted party, and may even be involved in the protocol design, the identification of countries and the finalisation of timelines, which is the perfect point for ePRO providers to be identified and brought

to the table as well. A few of the top ePRO organisations can provide some ePRO consulting to the trial leadership, for both the CRO and the sponsor. And not only should the ePRO provider be able to give their experience in that therapeutic area, with that specific indication and in those countries, but they should also be able to identify the occurrence and options of PRO instruments and hopefully even compliance rates among the potential patient population and in the selected countries.

Just as sponsor companies have looked to “partner” with CROs in order to facilitate and optimise the interaction between the two, ePRO providers need to do the same. Operational standards and best practices need to be developed and employed by the CRO and the ePRO provider jointly, and built up as early as possible, in order to set the stage for smooth operations within the clinical trial. This is particularly important since the most critical juncture for both CROs and ePRO providers are the eight weeks prior to the first patient in, where both organizations are scrambling to meet their deadlines. When CROs and ePRO providers have built best ways of working together, there is great opportunity for that efficiency, previously mentioned, to be fully realised.

### e-Clinical efforts

e-Clinical and paperless clinical trials are (conceptually) extremely popular to sponsors. With electronic clinical trial management systems (CTMS), interactive voice response (IVR) systems, electronic data capture (EDC) and ePRO tools used regularly, it seems we are closer than ever to such a reality. We have seen and heard the potential benefits to them and we know that all this beneficial data leads to clearer results and quicker decision-making, but by far the biggest hurdle to these very important systems, though, is their interaction with each other. Anyone knows that just because there are two electronic systems, it in no way automatically guarantees that they will play nicely with each other. CTMS are already fairly cumbersome and full of information. Standard IVR systems are best when tied into drug supply systems. ePRO and EDC are perfect together. It would be impossible to discuss CROs and ePRO for too much longer without talking about EDC. As stated earlier, CROs are being asked at a greater rate to manage all parts of the trial, including data management activities. Many CROs started out building their own EDC packages, but have quickly learned to pick up the knowledge and experience (as well as contracts and licences) with many of the top applications. This may be one area that the sponsor still dictates to the

CRO their preference, as they will likely need to merge that study's data with data from other studies and would want to minimise any risk of technical miscommunication when they pull it all together for submission to the authorities.

ePRO data is akin to EDC data in quite a few ways, including its collection of site and patient information, as well as the storage of and availability for data analysis throughout the trial. There are various levels of integration, and some ePRO providers are better than others when exporting or extracting data from the ePRO system and depositing it to another, like EDC. But this is all patient data, complementary patient data, and if these data are easily integrated, there is a greater opportunity for that efficiency to be fully realised.

### The need for efficiency

Efficiency is defined by Merriam-Webster as “the quality or degree of being efficient”; and efficient is defined as “productive of desired effects; especially productive without waste.”

CROs and ePRO providers working together in partnership will produce those desired clinical trial effects, with minimal waste. When CROs and ePRO providers are working together in partnership, they can provide the most up-to-date report to the sponsor clinical team as to how the clinical trial is progressing. Among CRAs, EDC data and ePRO data, you have a near real-time, all-inclusive view to your study. Depending on the protocol, it may just complement the standard safety and efficacy data, or the PRO may also be the primary endpoint for your study and your submission claim. Either way, it can be argued that ePRO simply has the best possible data sponsors can get, since it comes directly from the patient. However, the one element that cannot be questioned is the speed of the data. With a few ePRO providers that are working wirelessly and globally, sponsors can see their data much faster than ever before. When PROs are required for a study, only ePRO will provide better data, quicker.

Unless implemented, these are merely concepts and ideas. Improved outcomes, enhanced development of clinical research and efficiency can really only take place when there is partnering between the organisations involved. The interplay is not simply necessary of the data systems themselves, but of the people that are building, monitoring and managing these critical systems as well.

A recent survey by CRF Health showed that although an overwhelming majority – over 80% – of sponsors believed it to be important that their ePRO provider strategically partner with their CRO, yet less than 20% identified that their ePRO provider actually did partner

with their CRO. There is clearly a wide divide here that some CROs and ePRO providers can look to bridge. Sponsors that were surveyed also indicated increasing usage of both CROs and ePRO providers at high levels over the next few years, so these outsourcing and data collection trends discussed earlier will only continue to bring these two services together.

Although it will be challenging for most in these fields, true CRO-ePRO partnership can be produced. To date, it has been largely in name only, with perhaps a press release and loose business development affiliation. Many in the ePRO business know that to ultimately benefit sponsors and their clinical programmes, CRO-ePRO partnership must involve broad and deep connections in both organizations, and include operational delivery and best practices. Then will CROs and ePRO providers truly help to make this research world as efficient as it can be, and that very well may be the answer for clinical trials.

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### French tread carefully through a regulatory minefield

France is in the midst of a three-month consultation process that it hopes will help lay to rest the spectre of Mediator, the Servier drug that has thrown the French drug regulatory system into chaos. The aim of the initiative, according to the health ministry, is to produce a “national strategic vision” for the regulation of medicines and other health products, and to restore public confidence in the system. But already questions are being asked about the consultation process. *Ian Schofield reports.*

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