GOING GLOBAL

The Contract Research Organization (CRO) market is growing exponentially and serves an important role in taking on the outsourced responsibilities of major pharmaceutical companies. Their roles can include: product development and formulation, clinical trial management, central laboratory services for processing samples and data management for NDAs. Below, three of the industry's leaders discuss the benefits of engaging – and challenges facing – the CRO industry.

John Hudak is President and Founder (in 1991) of Criterium Inc., a full-service small, global CRO providing customized clinical development, data management and interactive voice technology services to pharmaceutical manufacturing, biotechnology and medical devices companies. Criterium is headquartered in New York, with offices in California, Florida, South Africa, The Netherlands and India. John has over 35 years of progressively responsible research and business development experience in both the corporate pharmaceutical and contract clinical services sectors.

Agnes Pinnel is Managing Director and Co-Founder of Argint International, a regional CRO providing study management, regulatory and monitoring services throughout Central and South Eastern Europe. In her current role Agnes oversees the operations of the company while continuing to actively engage in projects, applying her extensive international experience to the implementation of studies in CEE and SEE. Agnes has the necessary local knowledge to successfully guide clients through the clinical trial process in this region. Prior to founding Argint International Agnes spent 10 years working for a top-five CRO, managing many large multi-national trials and later establishing and leading the regional office for CEE.

Ben Jackson is Co-founder of Quartesian LLC and is responsible for defining and developing Quartesian's competitive strengths and providing strategic direction of the firm. He led the effort to create a secure, low-cost, scalable global IT network from ground up. Ben has over 20 years experience in biostatistics programming, database design and programming for the pharmaceutical industry. Ben has held management positions at a number of major pharmaceutical companies including SmithKline Beecham, Johnson & Johnson, Pfizer and Forest Laboratories

What are the main obstacles which delay clinical trials ultimately resulting in a loss of revenue? How can your organization ensure higher success rates?

BJ: I would say recruiting the desired patient population is the greatest obstacle that delays clinical trials. Especially in the developed world where patients receive the best medical treatment and there is not a strong desire to participate in a clinical trial unless one feels it is the only means of getting the best medical treatment for a particular illness. Even with government websites that list potential and ongoing clinical trials and the many different channels of advertising to recruit patients, it appears that the demand for patients exceeds the supply.

Turnaround time of case report forms (CRF), query resolution and data cleaning, reconciling data from different sources (e.g. paper CRF data and electronic data from a central laboratory) and the increasing complexity of the trials and the data being collected are other main obstacles that delay clinical trials. As medical knowledge and technology advances and with more biological and chemical entities in the formulary, the questions that study protocols attempt to answer have become inherently more complex. Another level of complexity has been added with the multitude of data collection methodologies, such as electronic patient reported outcomes (ePRO) and interactive voice response (IVR). These technologies have been adopted by the industry to increase efficiency, as they have done so, but they also require a new set of working practices and knowledge base for conducting clinical trials.

Our organization strives to ensure success in completing clinical trials without costly delays through a two-pronged approach: strategic patient recruitment and proactive risk assessment. Generally speaking, success in any undertaking is most often obtained through long-term cooperative agreements. With regards to recruiting appropriate patients for a given indication and treatment, we believe it is preferable to discuss the long term goals with a client in terms of what kind of studies they want to conduct as opposed to just finding the required number of patients for a particular study at hand. For example, we could target certain practices or geographic regions that may prove to yield success in recruiting the needed patients over the course of a given phase of a program. We want to facilitate arrangements between sponsors, sites and ourselves such that each feels they have a vested interest in the successful and timely completion of a given clinical trial as well as an entire drug program. Another principle in planning for the successful undertaking of complex tasks like clinical trials is accounting for "what if" scenarios.

That is, if the players involved – sponsor, site and CRO – acknowledge the level of risk at certain junctures of a clinical trial that might lead to failure or delay and agree to minimize such risk through shared responsibility and ownership of critical and fault-prone points in the clinical trial process.

AP: The main cause of delays to clinical trials is inadequate patient recruitment due to poor or "conservative" site selection, such as not placing studies in emerging markets or involving too few countries/sites in the program from day one.

Clinical studies can also be delayed due to issues with regulatory and EC approval caused by: poor study design or protocols which do not take account local clinical practice, a lack of knowledge of local regulatory/EC requirements, not adapting documents to local requirements or poor translation of documents

Other causes can be de-motivation of investigators due to lack of support from Sponsor/CRO, inadequate study budgets or late payment of investigator fees.

We know our markets and are familiar with the capabilities of the investigators. Our site selection is extremely thorough – we only recommend sites that have adequate staff, facilities and patient pools to successfully implement the study and meet recruitment targets. Our reputation is based on delivering patients and high quality data and under no circumstances will we commit to unrealistic targets or timelines. Our clients appreciate our reliability. We work in countries that have large pools of trial-naïve patients treated in centralized hospitals. Recruitment rates invariably exceed those of sites in Western Europe and the U.S.

We have internal clinical regulatory experts that have excellent relations with local regulatory agencies/ECs and who continually update their knowledge as local laws and requirements change. All submission packages are thoroughly reviewed to ensure documentation meets the quality standards and expectations of the regulatory agencies/ECs. We therefore guarantee that the submissions we make to regulatory agencies/ECs contain all the necessary items to prevent delays in approval of studies.

Finally, we have the necessary experience to guide sponsors through the logistical aspects of conducting studies in our countries of operation, including import of clinical trial materials and compatibility of technology to be used in the study with local systems.

JH: There are four or five obstacles. The first is coming up with a protocol that the regulatory agencies in each country you work in are going to approve. So there could be regulatory approval delays in some countries – there are countries that take four months and there are countries that take ten months to approve a protocol. Secondly, there are sometimes delays caused by sponsors, things like drugs that don't get delivered. But I think one of the more prevalent obstacles occurs after you set your study up and you get all your regulatory approvals but then you have low patient enrollment. There just aren't enough patients that meet the criteria in your study to fill it very quickly. So you have to perform aerial hoops to get those patients into the study and increase the number of sites. A fourth obstacle is slow data acquisition. Even with the implementation of electronic data capture and some other methods of collecting the data, unless your workflow reflects a real attention to managing data in real time, accessing the data can slow down your study. The fifth obstacle would be study failure – you don't recruit, you recruit the wrong kinds of patients, your drug doesn't work – any of these factors can result in slower development and losses of incremental revenue.

We ensure success by presenting ourselves as agile: so we can show clients our capabilities to go to where the patients are. There are pools of patients in the United States for many studies, but those pools of patients are dwindling because more and more therapies have become available, and investigative sites are less likely to take a patient off medication that's working for them in order to put them in the study. Obviously, patients aren't willing to do that either. So we'll go where the patients are and that means either to pockets in the United States or outside of the U.S. The other component of this is the way we collect data – in real time – and how we apply the same standards to patient recruitment, monitoring and data collection anywhere in the world. This way, when we target a study to occur in, say, South Africa, we would first find a better pool of patients because there aren't as many therapies available and patients don't have as much money or insurances for treatment – making them more likely to participate in a clinical trial. When they do participate in a clinical trial, our monitoring procedures are the same in South Africa as anywhere in the world, excepting some variations required by local regulations. But the key standard procedure that ensures a higher success rate is that real-time data collection occurs in our hub in New York, where, we monitor the data centrally first and then get the data back out to the sites and our monitors to make sure that it is done in a consistent way. We also have local personnel who are experienced in submitting for regulatory approvals in a given country. At the end of the study when we're closing a database, it goes rapidly because we've done it in real time all along.

U.S. pharmaceutical and biotech companies are beginning to gain interest in conducting clinical trials outside the U.S. How do you see this positively impacting the conduct of clinical trials in terms of efficiency and cost savings? Furthermore, what challenges do they face in conducting international trials?

AP: Completing a clinical study on time can save millions of dollars in patent-protected sales revenue. The clinical research markets of countries historically considered to be "core" countries for conducting clinical trials is saturated. Pharmaceutical and biotech companies will benefit enormously if they place clinical trials in non-core countries. There are two main components to this cost saving. Firstly, increased patient recruitment rates will reduce the cost of clinical trials by reducing project timelines. Secondly, investigator/hospital fees and the clinical management and monitoring costs of regional CROs in these countries are lower than those found in Western Europe and the U.S. Sponsors should consider involving these countries/sites in clinical trials from the start rather than using them as rescue countries when other countries fail to deliver. Sponsors should not shy away from making the initial investment required to involve these sites from day one as this will produce efficiencies in patient recruitment and significant cost savings overall.

The perception that conducting clinical research in these countries is complicated or logistically difficult is unfounded providing sponsors enter into partnership with local experts who can guide them through the clinical trial process in these countries. Ideally, sponsors should involve local experts as early as possible in a development program, ensuring protocols are designed with global as well as U.S. requirements in mind. Sponsors need to approach global studies with a flexible

attitude. Documents prepared for use in one country may not be appropriate for use in another. Changes to templates will need to be made to take account of local requirements and cultural expectations.

If sponsors approach global trials with the understanding that occasionally they will need to adapt their way of working to fit in with local environments then they will find the experience to be very rewarding. Having managed trials internationally, I can honestly say that on average the efficiency of regulatory agencies and ethics committees and the dedication of investigators in Eastern Europe surpasses that found in Western Europe.

JH: The impact on efficiency is that oftentimes you have an easier time recruiting patients – there are more patients available to go on to a clinical study because a given region in the world may not have all of the drugs that are available for treatment and patients may not be as affluent and be able to afford the medicine. By the same token, if we're increasing patient recruitment, we can also reduce the number of sites that are recruiting and doing studies. That's another cost-driver: how often you have to go to the sites and how often you have to monitor them. As an example, if the basic costs in Russia are 20 percent or 30 percent less and you can do it with 20 percent or 30 percent fewer sites – instead of needing 50 sites to do a study, you can do it with 35 – then overall savings for the same timeframe may be almost half. That would be an ideal case. In general, what we quote is that those efficiencies are probably 10 percent to 20 percent savings by conducting studies in Eastern Europe and South Africa, 30 percent savings by conducting work in India and China and it will actually cost 10 percent or 20 percent more by doing work in Western Europe, where there may be a whole other set of problems because you have so many regulatory agencies to deal with.

With the FDA, if you're confident in your protocol, you can submit it to the FDA and if they don't express any concerns in 30 days, then you can go ahead and do the study – it's kind of a passive approval. In other parts of the world, the regulatory agencies are more active and they have active approvals of protocols that are going to be done on their soil. So that can slow things down. A country like South Africa has only six submission dates per year going to the regulatory agency and then about a 3-month turnaround time to approve new protocols. So you can always count on at least three months, and because you have to prepare the package when you are working on these things, more likely at least four months for an approval in South Africa. The same holds for India, it takes about four months, and in China, it can actually be as much as 10 months. You have to really plan ahead.

The one area that is not the challenge you might think is language. Most sites that we deal with worldwide are fluent in English, and even where that's not the case translations of documents and the like into a local language are relatively simple for us to do.

Then there are other issues like importing drugs into the country that can cause some delays, but that, by comparison, is minor. The key is getting the regulatory approval: once you have that, it's fairly easy to get drugs into the country for a clinical trial.

BJ: There is no doubt that conducting trials outside the U.S. is a cost savings. With the current information technology, geography is no longer a barrier. General communication and knowledge transfer across physical boundaries is much less expensive and more commonplace. People in different parts of the world have become more familiar with communicating with each other on a regular basis. Terminology and practices are starting to converge across local boundaries. Thus, some of the rudimentary issues that were formerly obstacles to efficiently conducting clinical trials outside of the U.S have been removed.

Again, patient recruitment and the cost per patient are the key drivers here. Patients are more willing to enter a clinical study in other countries as it is most often the best way they can receive quality medical care. For example, in some countries the prescribed medication for a particular illness may not be affordable to most of the population. Patient compensation and the overall cost per patient are lower. Here is the efficiency, rapid recruitment and cost savings.

When conducting an international trial, one must have a certain level of competence and presence in the country where a trial or any part of a trial is being conducted. The challenge is to build expertise in a number of countries. We would never go into a country where we did not have any regulatory expertise, knowledge of how to import drugs into the country or understanding of local medical practices.

When embarking on an international clinical trial, what are some of the most common requirements and concerns that you are receiving from clients, and how do you overcome these?

JH: I don't know about requirements, but I would say the expectations that some sponsors and clients have are that once they have a final protocol that they can just submit it and start a month later, like in the United States with the FDA. I think the regulatory leg really is an eye-opener to clients who aren't aware that you have to give yourself more lead time in order to conduct these studies in other parts of the world. Some typical concerns our clients have expressed are: What kind of patients are we dealing with? Are they going to be a homogenous group of patients that the FDA may or may not accept? What's their practice of medicine, is it similar to the medicine in the United States? We've even had clients say to us erroneously, "Isn't everyone in South Africa HIV-positive?" But the ultimate concern is that if they're going to go out and do the study outside the U.S.; they want to feel assured that they are dealing with an experienced contract research organization that will enroll patients and staff efficiently, get the study done less expensively and, at the end of the day, get the patient data to be accepted by the FDA.

BJ: Clients want to be assured that any data collected in any country would be valid for submission to a regulatory authority. If the data collected from outside the U.S. will be submitted as part of a U.S. NDA, for example, then a client wants to be assured that all the GCP guidelines and federal regulations are adhered to and that all the necessary regulatory filings and documentation are completed. They want the trial conducted at sites that have run GCP compliant trials. They require qualified investigators, research coordinators and monitors. Essentially, they want the trial conducted to the same level of competence and compliance as it would be conducted in the U.S. Needless to say, they want to be assured that all the local regulations are adhered to.

A client would have a particular strategy in mind for conducting an international clinical trial. It may be the need to recruit

patients, as is often the case, or it may be to get the drug approved in a number of different countries. In both instances, patient safety and regulatory compliance are of paramount importance, followed by the concern that the scientific questions raised in the protocol can be answered.

If a sponsor is interested in having a drug approved in a particular country or has a long-term strategy in mind then this changes the outlook. It is no longer a one-off situation. The view is beyond a single trial. In this instance, time to IRB or regulatory approval, understanding local medical practices and logistics become long-term commitments. Establishing experience and a presence in a country or seeking a partner with such experience is the only way to overcome country-specific concerns in these areas.

AP: Sponsor concerns include uncertainty about the regulatory and ethics approval process. They need to be reassured that countries have well-established laws and regulations protecting human research subjects that are similar to those in the United States. This is very much the case: Most countries in Central and South Eastern Europe (CEE/SEE) have either fully adopted the European Union (EU) Clinical Trials Directive due to EU membership or have brought their regulatory and ethics review process in line with the Directive as part of their preparation for EU membership. Sponsors also want to be reassured that their studies will be conducted to ICH GCP standards and that investigators are suitably qualified and trained to perform study assessments. Investigators in CEE and SEE are fully aware of their responsibilities under ICH GCP and take them very seriously. Most have had formal ICH GCP training and can provide certificates upon request. Other sponsor concerns relate to logistics and these are easily overcome if the sponsor chooses to partner a local CRO with experienced people who can guide them through local processes and suggest best practice. Sponsors are concerned about cultural and language barriers. However, there are more cultural similarities than differences between CEE and SEE countries and the U.S./ Western Europe and a high percentage of the population can also speak/understand English as this is studied at school.

How has the adoption of e-clinical technologies evolved and impacted the overall clinical trial process? What effect has this had on the management of data and what role does this play in an international trial?

AP: In recent years, the technology available to EDC vendors has advanced considerably, enabling systems to be developed that can collect and analyze the large amounts of data generated in clinical trial programs. Additionally, the telecommunications infrastructure has developed to the point where mobile phone technology and internet access is widely available and it is now possible for sites in most countries around the world to utilize EDC systems. The advantages gained by implementing EDC technologies include real-time availability of data, real-time data validation checks, reduction of paperwork and the reduction of storage space at sites. Most importantly, the location of sites becomes irrelevant – collection of data from sites located in the same state as the sponsor takes the same time as collection of data from sites located on the other side of the globe. This ongoing query generation and resolution decreases the timelines for database lock and this in turn cuts

costs and maximizes patent-protected sales revenues. The costs of developing such systems will continue to decrease and further significant savings will be made when compared to the cost of shipping paper CRFs and DCFs around the world.

JH: From our perspective, it's a good thing. E-clinical trials can reduce the time it takes to receive data, but it also is a tool that can be misused. The whole idea that EDC is going to speed up your collection of data is only true if everyone in the game of generating and documenting the data is committed. For instance, we've been involved with studies where the client says, "I want to use EDC and I want to use it at all the sites." So, that indicates that you must select sites based on their ability to enter data into the computer. But a more controlling concern is: Can we get the patients in?

Patients are king. You need to get patients into the study. So you select sites that are going to produce for you. They aren't always the sites that can enter data into the EDC very efficiently. We've been involved in situations where – and it doesn't go country by country, although the infrastructure of the internet in different countries really does have an effect on that – some sites are just slow, some sites have a hard time getting the data into an e-clinical system. So, unless you're very careful about how you select your sites, EDC can actually slow the process. Obviously, with any e-clinical technology, the simpler it is to use, the more likely it's going to be used in the way that you mean it to be used and adhere to the schedule you need. Sometimes e-clinical technologies can just add cost where it reduces your efficiency at the site because you have this additional cost of e-clinical technology when another form of data collection is already in place and more suitable for a given site.

The specific impact on management of data is that when you do e-clinical, data management may be taken out of the hands of your traditional biometrics group, so you really have to have systems in place that break down those silos, those different departments doing different things to the data as it comes in. If you're going to go to an EDC system or an Interactive Voice Response (IVR) system or any e-clinical, real-time system, you really have to rethink your SOPs and break down those silos because then what you will have is the ability, with the proper workflow, to have clinical people reviewing data almost as it's being generated and then getting those queries back to the sites – so that what traditionally would have taken six to 12 weeks could take six days to complete and clean a patient visit. When applied to an international trial, it gives you the ability to manage from a distance, and it makes the world flatter because you're able to see everyday what's going on at a site in Mumbai, India or St. Petersburg, Russia. Because those data are coming directly to a central facility, it gets reviewed and queried in a matter of a day or two.

BJ: I think e-clinical technologies will create a revolution in the overall clinical trial process. The information revolution has changed the world landscape entirely and that means our business as well. I have one little anecdote here. I was sitting in my office one afternoon and received an internet call from our office in Ukraine. They were working very late to meet a deadline. We shared a desktop and discussed an issue with a CRF design and the recording of dose limiting toxicities. I think this little story says a lot. I'm not even talking about IVR, EDC or adopting XML for data interchange. Such are the things that people have in mind when they talk about e-clinical. I think this simple example of a general technology that allowed us to resolve an issue in real time over a distance of thousand of miles says a lot.

There is no doubt in my mind e-clinical has made international trials less risky and more within the grasp of smaller companies. Conducting clinical trials globally has become a much less daunting undertaking. I think it has really leveled the playing field.

Access to clinical data has become more readily available through standard desktop software. Decisions can be made more rapidly. I think, as is often the case with any technology, we can expect to see the management of clinical data becoming less expensive while ever decreasing the gap between the end of the study and a locked database.

Companies can go anywhere in the world to find skilled data management professionals for the most competitive price. What is today specialized technology will soon be viewed as a commodity.

What data collection tools and data management techniques will be utilized to a greater extent in this decade?

AP: EDC systems are becoming the standard and I anticipate that technologies will further develop enabling full integration with other clinical trial data sources and data capture technology. Use of systems capable of "plug and play" or wireless communication with data capture systems will result in more source data being captured directly into clinical trial database. I also see clinical trial designs being adapted based on analysis of real-time data captured within such systems. For example, amendments may be issued to change study endpoints or allow the inclusion of additional assessments if the collected data indicates this is necessary. Also mobile phone technology will continue to advance and the uptake of this technology throughout the population, even in so-called "third world" countries, will enable utilization of these "standard" systems for the collection of clinical trial data.

JH: No one data collection tool is going to be used all the time. The key is how you mix the use of data collection tools. Like in transportation, where in order to go from New York to Los Angeles you'll need to walk, drive, take trains or buses and/or fly; different data capture tools will enable you to accomplish different things. An IVR system is certainly an easy tool to deploy in the field because everyone has touchtone telephones – and, in particular, if you want to collect data directly from patients. The EDC is certainly a useful tool in given situations. Paper will always have a role in this business. Until that point at which everything can go in a box at one end and be transmitted directly to the box at the other end, you're always going to have a need for these different data collection tools. Our philosophy is that if you can collect the data in real time, you can do something with it in real time. If you collect data in such a way that it gets batched, then you're only going to be able to deal with the data when you have access to it, not all the time. So, as a general answer to your question: We'll learn to apply tools better in real time from these studies.

BJ: I would say ePRO, IVR, EDC and XML. Again, the argument is that every other aspect of conducting business has greatly changed due to e-commerce and we are no different. Handheld devices are doing the work that desktop and laptop devices did before. Voice recognition and internet transactions are common everywhere. XML has already been widely adopted by regulatory bodies such as the FDA for data exchange. All these tools and

techniques are in use today and as the decade progresses I would expect they would become more commoditized and less expensive. User acceptance of these technologies would be more widespread as well.

In large part the allure of working internationally is due to larger patient population pools. What countries should Pharmaceutical and Biotech companies consider conducting trials in, to ensure successful patient recruitment? What countries are high targets for conducting successful patient recruitment?

JH: It's different in different parts of the world. Let's start with the United States or Europe. In order to get a study filled in the United States, you may have to produce ads on TV to recruit because you must increase the geographical area in which you're going to recruit patients. This is because there are generally fewer patients in any given area of the U.S. or EU available for clinical trials, particularly if they're being adequately treated with available medication. On the flip side, if you go to Russia or to South Africa and India, the need to budget for advertising is greatly reduced or eliminated because it won't add to the recruitment rate. There are more patients than we need for many studies because there aren't adequate treatments in these countries.

As far as which countries are high targets for conducting successful patient recruitment, it's going to depend on the indication. Some indications are more appropriate in developed nations, but the countries where you're more likely to have higher recruitment are more the emerging or developing countries – South Africa, India, Russia, China, a lot of the Eastern European countries. Again, they don't have the paid healthcare net that we have in more developed countries – Japan, the United States and the EU.

BJ: I would say India, central and eastern Europe and China. In the case of India and China, there are very large patient populations. All of the regions have a significant population naïve to standard western medications. India is especially attractive in that the level of proficiency in English is very high. There are also many skilled physicians. The experience base in conducting GCP trials in all three is increasing. Eastern Europe has a very good record of recruiting patients given the nature of medical practice there. Many researchers are also practicing physicians. The cost of recruiting patients can be greatly reduced as there is not much of a need for expensive advertising.

AP: The centralized healthcare system in Central/South Eastern Europe means that sponsors can benefit from efficiencies by increasing recruitment rates per center. In most CEE/SEE countries patients visit large hospitals for treatment rather than being treated by community physicians and GPs. This enables Argint to access larger pools of patients, including trial naïve patients, at each site than can be found in most Western European countries or the U.S. Additionally, limited access to newer therapies results in patients being more prepared to consider participation in clinical studies.

Hungary, Poland and Czech Republic were the first wave of CEE countries discovered by sponsor companies and they continue to be excellent places to conduct clinical research. Currently there is justifiable interest in placing studies in Romania, Serbia,

Slovenia, Croatia, Slovakia and Bulgaria. These countries have enormous potential and I have had great success conducting trials in these territories in recent years. There is a desire by all people involved in the clinical research industry in these countries, from regulators to investigators, to perform research to the highest standards and build their reputation internationally. Recruitment rates are consistently significantly higher than rates at U.S. or Western European sites. In the future, Argint will be targeting Bosnia, Moldova, Macedonia, Montenegro and a number of other countries, all of which are developing or have developed their clinical trial infrastructure.

What is the "silo mentality'" as related to contract research and how do we overcome it? Why is it important to do so?

BJ: I think the big thing with silo mentality is that "between" sponsor and CRO. Many CROs have become large organizations and have layers of internal management. There is often a disconnection as this kind of organization interacts with another organization of substantial size, e.g. the sponsor. This is the "between" silo mentality. The "within" silo mentality also exists in larger organizations. That is why I think sponsors and CROs should work to form study teams around projects and function as a joint venture on the project at hand.

AP: This is the lack of communication and cooperation between departments or between stakeholders in a project resulting in unwillingness to accept change or strive for more efficient or effective ways of working, resistance to new strategies, such as placing trials in emerging markets or failing to embrace new clinical trial technologies. The end result is stagnation within an organization and a lack of competitiveness.

It is critical that senior management put structures in place that encourage and facilitate cross-departmental communication, collaboration and creative thinking. In my opinion, project managers should be empowered within the project setting and should be able to demand support from other departments. Projects often fail due to poor support from internal suppliers. The delivery of departmental services to projects should be monitored by senior management and steps should be taken to restructure departments whose working practices are impeding the success of a project or the company as a whole.

JH: The silo mentality in any corporation relates to different departments, and it's the same thing in contract research – having the data that you're generating go from the investigator through the monitor to data and then to the statistical group. Also, you could look at another silo mentality by looking at each country as a separate silo. It is important to realize that this is a continuous stream of effort to get data from the patient evaluation to final database and that it involves all those departments working together all the time so that this flow of data, instead of stopping at each department before it gets to the next, really does flow through the process with less friction. So, how do we overcome it? By using tools that are friendly and easy to use, and cross-training clinical people and data people, having a statistician as part of the project team from start to finish, throughout the process. So, the silo mentality is best broken down by forming real working teams that are multi-functional.

Obviously, technology plays a key role in clinical trials. What is the importance of integration?

AP: It is vital to evaluate existing systems and where necessary update them to enable them to interact with any new technology, or select technology that facilitates easy integration into existing workflow. Otherwise the benefits of the new technology cannot be fully realized. Systems do exist that have built-in flexibility to enable handling and processing of both paper and electronic data. These systems are highly attractive as they permit integration with current systems and ongoing projects while allowing for a full transition to the EDC technology over a period of time.

JH: Here's how I would qualify that – it's about the integration and the workflow. When you break down the silos, de facto, you're integrating the processes because your team is a multi-functional team. When you use various data collection tools, you want to be able to integrate the data that you get directly from a patient, from the lab, from the site and from electronic sensing devices, like a blood pressure monitor. We're used to having our blood pressure taken and somebody writes that blood pressure down. But the simple example is that if a blood pressure monitor were connected to some device that collected that information directly, then you're really dealing with one of the largest cost factors in conducting clinical trials –our quest to correct transcription error.

In terms of integrating, it's integrating all the processes and all the different methods of data collection so that they talk to each other. We use integrated applications, for instance, when a patient calls an adverse experience into the IVR system. This automatically generates a fax to the site requesting follow up with the patient. Once the site responds to the adverse experience in a standardized fashion and puts it into the EDC system, the EDC system populates the database and the IVR system would know that there is no need to send out a second request to the site. These are the kinds of things our systems are doing now as a routine matter.

BJ: I cannot overemphasize the importance of integration. Some disciplines have a function of system integration. Just as the disconnection between organizations leads to failure, the disconnection between technologies leads to failure as well. This is a potential problem that is easier to identify and fix than the organizational problem. Removing the human factor and focusing on the finite functions and requirements of systems and how they integrate is a very tractable problem to solve.