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PSI, INC, Chiltern take top site ratings

CROs gaining more ground in ability to support and manage investigative site relationships

By Karyn Korieth and Annick Anderson

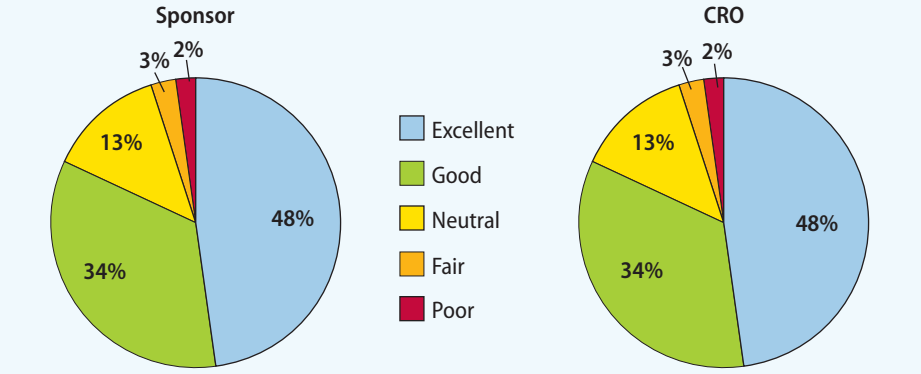
Investigators report their working relationships with CROs have become more effective during the past two years, according to a new CenterWatch survey, and nearly half said overall CRO performance, for the first time, matches that of sponsor companies.

As sponsors increasingly implement integrated and strategic partnerships that give CROs more autonomy in managing trials, the survey found that the average CRO has improved its ability to oversee sites and support study conduct in each of the six project categories measured. In addition, performance gaps have narrowed, compared to 2013, across attributes investigators consider most important for study success.

In the 2017 CenterWatch Global Investigative Site Survey, five CROs came out on top: PSI CRO, INC Research, Chiltern, QuintilesIMS and Parexel. Two additional CROs—Icon and PPD—also received high marks from investigative sites for overall relationship quality. PSI CRO, INC Research and Chiltern were also the top-three ranking organizations in the 2015 survey.

Sites now rate sponsors and CROs identically

Average aggregate site ratings for all attributes in 2017



Source: CenterWatch 2017; n=1,376 global investigative sites

The latest survey results reflect how CROs have adopted a more strategic view of site relationships in recent years and invested resources in a wide range of initiatives designed to ease site burdens, support study conduct and improve the efficiency of clinical development processes. Significantly, the proportion of sites giving the average CRO an "excellent" rating has increased by 15 percentage points during the past decade, from 33% in 2007 to 48% this year.

"The fact that we have stronger strategic relationships in the industry between CROs and sponsors enables us to have much stronger relationships with sites," said Clare Grace, Ph.D., vice president, Site & Patient Access, INC Research. "That is coupled with a much bigger understanding and recognition across the industry that the site relationship is absolutely critical to the success of a study. People are now striving to make those relationships and working practices much more harmonious and streamlined."

Despite the improvements, investigators report, both in survey results and through interviews, that CROs fall short of performance expectations in several areas critical for study success, including providing professional contract research associates (CRAs), being organized and prepared and having easily accessible staff.

"CROs have truly come a long way. They have made significant improvements," said Jon Ward, chief executive officer of Aspen Clinical Research, a phase I-IV research center located in Oren, Utah. "We have not, however, seen an improvement with the quality of monitoring support. If the communication-breakdown elements can be corrected and there was lower turnover of CRAs, sites would be very productive and pleasant machines where very little frustration would occur."

Methodology

The 2017 CenterWatch Global Investigative Site Survey, conducted online from October 2016 through January 2017, asked principal investigators and study coordinators to rate the CROs they worked with during the past two years on 37 project attri-

butes in six categories: overall project support, study monitoring support, protocol/study design and planning, contracts and budgets, site management and workstyle. Key changes this year included a new question about the effectiveness of risk-based monitoring processes. In addition, sites provided feedback on the importance of these attributes to their success in conducting clinical trials.

Clinical research professionals representing 1,376 sites across 15 countries completed the survey. The highest concentration of respondents was from Europe (49%), followed by North America (35%), South America (9%) Asia Pacific (6%) and Africa (1%).

A total of 12 CROs with sufficient sample size were included in the analysis, compared to 11 in the 2015 survey. CRO rankings were determined by overall relationship quality ratings based on the percentage of "excellent" scores from sites. Throughout the survey, when comparing importance/excellent gap changes and aggregated CRO ratings from 2015 to 2017, an approximate two percentage point difference between values was statistically significant.

Since it launched in 1997, the biannual CenterWatch survey has become an important tool with which CROs evaluate the quality of their site relationships and identify systems or processes for improvement.

Performance gap closed

CRO performance remained the same or showed modest improvements, compared to both 2013 and 2015, for each of the individual relationship attributes measures. Overall, CROs received an average "excellent" rating of 48% across the 37 attributes, which represents a three percentage point increase from 2015 and compares to an average rating of 42% in 2013. Moreover, gaps between the importance of project attributes to study success and the ability of CROs to deliver them either narrowed or stayed the same between 2015 and 2017 for seven of the nine "most important" attributes.

Top ranked CROs in 2017 on attributes rated the most important

Attribute	Top CROs receiving highest percent of sites rating 'Excellent'
Has professional, knowledgeable & well-trained monitors/CRAs	**INC Research**, Parexel, PSI CRO
Is organized and prepared	**INC Research**, inVentiv, PSI CRO, PPD, Quintiles
Staff is easily accessible for escalation of issues and provides timely & appropriate resolution	**INC Research**, PSI CRO, Quintiles
Maintains open communication	Chiltern, **INC Research**, PSI CRO
CRO ensures timely drug availability	Chiltern, **INC Research**, PSI CRO

Source: CenterWatch 2017; n=1,376 global investigative sites

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—Clare Grace, Ph.D., vice president, Site & Patient Access, INC Research

Companies that made the largest improvements from 2015 to 2017 included PSI CRO (21.2%), inVentiv (10.7%), Parexel (6.7%) and Icon (5.6%). QuintilesIMS, PRA Health Sciences and INC Research also showed strong improvements in overall "excellent" ratings. PSI CRO and INC Research both ranked among the top three CROs for each of the 37 relationship attributes measured.

The results underscore how CROs, under increasing pressure from sponsors to achieve high levels of performance and efficiency, have focused efforts on strengthening the quality of their relationships with sites in recent years to improve clinical operations.

"By having a strong relationship with a site, you begin to develop efficiencies that in turn lead to success for both the site and the project. While there are benefits all along the project timelines, we see the greatest benefits during the startup phase of a project," said Jim Esinhart, Ph.D, chief executive officer, Chiltern. "It allows you to look at what worked well and at the hiccups so that you can make adjustments for future work."

Significantly, as the role of CROs has evolved and sponsors have rapidly transferred site management responsibilities to their CRO partners, the overall performance gap between sponsors and CROs has closed for the first time in the sur-

vey's 20-year history. The average CRO "excellent" rating of 48% reached the same level given to sponsors this year; the CRO-sponsor performance gap has steadily narrowed since 2001, when CRO ratings across all aspects of study conduct support, compared to sponsors, were nearly 25 percentage points lower.

"The 'build and break' mentality that the industry has grown up with has made it quite difficult for site relationships to get the focus that they deserve. That is now changing," said Paul Evans, head of Global Site Solutions at Parexel. "These results show that relationships are important, just like they are in any business. We need long-term relationships that are not just for the life of the study, but go beyond an individual study. The improved performance comes from those improved, longer-term relationships. That is the key to what we are trying to build with our site strategy."

The survey results also suggests that CROs have increasingly recognized the critical importance of building strong relationships with experienced, high-performing investigators as the site landscape has become more competitive in recent years.

"CROs can either be site friendly or not in business," said David Scott, president and CEO of Palm Beach Research Center, who has been involved in clinical research since 1996. "There are CROs that sites will not work with unless the study is special and the reimbursement matches the expected aggravation."

CROs out-performed sponsor companies by three percentage points in four individual attributes measured: efficiently handling study queries, providing protocols that require minimum amendments, supporting initiatives to help sites build stronger relationships with study volunteers and using technology to make processes more efficient. Sponsors, however, continue to edge-out CRO performance by five percentage points for having professional CRAs, which investigators raked as the most important element for a conducting a successful study.

"In large part, [closing the gap] has to do with the CRO's ability to get a study started quickly with more amenable terms and communication than we have ever seen previously, except when we dealt with the sponsors directly," said Aspen Clinical Research's Ward.

CRO performance also notably improved for having professional medical staff in clinical operations, which was ranked among the top 10 most important attributes. The widest variability between sponsors and CROs in 2015 was for this project attribute. Investigators have long maintained they prefer working directly with sponsors, in part, because sponsor project teams typically have greater medical expertise and knowledge about the protocol. Yet CRO "excellent" ratings increased from 49% in 2015 to 54% in 2017 for the quality of its medical staff members, making it one of the top areas of improvement during the past two years. The performance gap between sponsors and CROs for this attribute narrowed three percentage points.

"Because protocols are becoming so much more complex, it is important [for investigators] to be able to access a knowledgeable physician quickly to have that physician-to-physician discussion, which is often about very small nuances in a patient profile or what is happening in the study," said INC Research's Grace. "More and more, sites value that access to medically trained support and informed physicians who can really support the protocol."

2017 CRO rankings

Overall Ranking	CRO	Sample Size	Average percent rating 'Excellent' across attributes
1	PSI CRO	54	76.1%
2	INC Research	464	51.1%
3	Chiltern	78	49.1%
4	QuintilesIMS	671	48.6%
5	Parexel	455	47.9%
6	Icon	375	47.3%
7	PPD	413	47.0%
8	PRA Health Sciences	141	45.0%
9	inVentiv	222	44.8%
10	Covance	372	44.8%
11	Bioclinica	80	42.0%
12	Medpace	82	40.6%

Source: CenterWatch 2017; n=1,376 global investigative sites

Grant payment processes improved

Survey results suggest that CROs have recognized the importance of understanding study challenges from a site perspective and have begun to incorporate investigator feedback into improving clinical development processes.

In one notable improvement, CRO performance increased by five percentage points between 2015 and 2017 for budget negotiation and grant payment processes, the project category that each year receives some of the lowest scores in the survey. Investigators have expressed ongoing frustration about lengthy negotiation processes, particularly when a CRO is involved, and a lack of transparency in how budgets are determined. The Society for Clinical Research Sites (SCRS), a trade organization that represents the voice of investigators, also began an initiative to call attention to the financial hardships causes by grant payment delays.

CRO performance for the ability to offer realistic grant payment schedules increased from 39% in 2015 to 44% in 2017 as top-rank-

ing companies have established new processes that allow for faster grant payments to sites. INC Research began a new business unit dedicated to investigator payments, linked operational and payment systems and revised processes to take into account the complex financial needs and workflows that vary between countries. The initiative has resulted in a 30-day average for payments in the U.S. and 48 days outside of the U.S. QuintilesIMS pays sites monthly on all new projects, unless the site or sponsor requests quarterly payments, and has introduced new tools to simplify administrative requirements for sites when submitting invoices.

"Listening to sites and really understanding their needs is an important part of site relationships," said Kimberly Ray, vice president, Site & Patient Networks at QuintilesIMS. "What we heard from sites over and over was that investigator payments are a huge pain point, so we have addressed processes to help speed those payments. We still have more work to do and will continue to refine the processes in 2017."

CRO performance in the contracts and budgets category also has improved as organizations have established site partnerships and preferred provider networks, which typically include master service agreements, and have improved systems to streamline budget and contract negotiations. QuintilesIMS, through its Precision Enrollment program, has built a network of oncology sites that can be activated within 21 days once a patient has been identified. In another example, Parexel, which has dedicated site relationship teams, has begun a Straight to Startup program that expedites contract negotiations for its Site Alliance Network members. In addition, the company has implemented a new contract life cycle management system that compiles contracts from across the organization and allows teams to accelerate contract discussions for new studies by reviewing language negotiated in previous agreements with a site.

"We don't start negotiating every contract from scratch. We can short-circuit some of the discussions around the fine details of individual clauses from previous contracts with a site in a much more systematic way," said Parexel's Evans. "Because we work with different sponsors, there is a danger for CROs to treat every interaction with a site as a new one. Things like Straight to Startup and the contract life cycle management system allow us to maintain a history of what works with individual sites so that we aren't always re-setting the clock to zero every time we work with them."

The ability for CROs to hold informative investigator meetings also showed one of the largest improvements in this year's survey. The average "excellent" rating increased from 47% in 2015 to 52% in 2017. INC Research, QuintilesIMS and Parexel are among the companies that have internal groups, rather than third-party event partners, to handle investigator meetings. Top-ranking companies design meetings that limit redundant information and use technology to share data in a more informative manner. INC Research, for example, has adopted a task-based training approach, as opposed to role-based training, that trains site staff only on tasks that they have been designated by the investigator. Organizations also establish methods that allow research staff to complete required training, such as good clinical practice (GCP) certification, online rather than during meetings.

"Wherever you are in the world, the demand on clinicians, investigators and coordinators is increasing. Sites appreciate that we are time efficient in what we do," said Evans.

Highest rated CRO attributes

Attribute	2013 Percent of sites rating 'Excellent'	2015 Percent of sites rating 'Excellent'	2017 Percent of sites rating 'Excellent'
Ensures timely drug availability	49%	52%	54%
Effectively uses communication technologies (e.g. web portals, IVRS)	48%	51%	54%
Has professional medical staff in clinical operations	46%	49%	54%
Understands local regulatory/ethics issues	47%	50%	53%
Maintains open communication	47%	49%	53%
Holds informative investigator meetings	44%	47%	52%

Source: CenterWatch 2017

Adopted initiatives

The three highest-ranking CROs, which were the top three companies in the 2015 survey as well, have each adopted strategies and implemented programs to ensure CRAs are well-trained and have expertise both in the study protocol and therapeutic area. Leading companies also focus on improving communications with investigative sites, ensure study teams understand site concerns and incorporate investigator feedback into better supporting site operations.

PSI CRO, which received the highest excellent score on each of the 37 attributes measured, employs medical doctors or related professionals as CRAs and two years ago added communication modules to compulsory CRA training that focus on relationship building, clarity of communication and being helpful when working with sites. In early 2016, PSI CRO built a group of start-up specialists that focus on identifying the most problematic areas of startup around the world and addressing them through training—both internal and external—and more concentrated site work.

"With study protocols becoming more complex and looking at much narrower pa-

tient populations, investigators are experiencing more difficulties these days estimating their enrollment potential, enrolling patients to fit more restrictive eligibility criteria and keeping up with growing case report form [CRF] sizes," said Olga Alfonsova, global head of development at PSI CRO. "All of this means more attention, hand-holding and engagement from their CRO. While many technical checks can be done online, the time on-site remains invaluable for working through areas of concern, strengthening areas of success and otherwise building relationships with site staff."

INC Research, which ranked among the top three companies for each project attribute, views its therapeutically aligned delivery model, which extends to the CRA and project-specialist level, as key to its strong performance in CenterWatch site relationship surveys. Investigators have access to medical staff and CRAs with experience in the study's indication who can speak in an informed manner about challenges presented by the protocol and offer advice. As CRAs grow and develop, they typically advance to become project managers and group leaders, bringing first-hand knowledge about site relationships to management roles.

"It makes a huge difference to sites to have that body of expertise that goes right the way through," said INC Research's Grace. "It gives that level of experience that is absolutely necessary, particularly as study protocols have become so much more complex."

Chiltern trains its CRAs not only during study startup, but throughout the trial to ensure monitors are prepared to support sites as procedural changes occur or new data impacting the study becomes available. Chiltern has begun programs to better understand site needs and how CRO project teams can facilitate study success. In one example, employees were sent to visit sites and shadow study coordinators to experience their day-to-day activities and struggles first-hand.

Lowest rated CRO attributes

Attribute	2013 Percent of sites rating 'Excellent'	2015 Percent of sites rating 'Excellent'	2017 Percent of sites rating 'Excellent'
Provides protocols that require minimal amendments	35%	38%	41%
Is flexible—willing to modify protocols/budgets	34%	39%	41%
Has low monitor turnover	34%	40%	42%
Provides prompt payment of grants	36%	39%	43%

Source: CenterWatch 2017

"We view our sites as an integral partner. Without them, neither we nor our clients will be successful," said Chiltern's Esinhart. "With that as our foundation, we are interested in how sites view us when working together. Do we make it easy for an already busy site to work with us? Do we communicate effectively? Do we make unreasonable requests? Do we ask them to have five different login credentials to use our technology? We work hard to try to design our processes around the needs of the site."

Top-ranking CROs also have implemented programs that can improve trial timelines and, ultimately, site performance. QuintilesIMS, which was among the three highest-scoring companies for providing patient recruitment planning and implementation assistance, has started focus groups with sites to determine how the CRO's access to large databases of healthcare information, which were acquired through its merger last year with IMS Health, can be used to support sites. Anonymous patient density data, for example, could help identify geographic areas with patients that would fit inclusion/exclusion criteria for a study and inform a customized strategy to contact nearby physicians who could potentially refer patients to a participating site.

"There has been focus on how CROs can work with the sites better because, in the end, recruitment and gaining of quality data all starts at the site. We need to work closely and well together," said QuintilesIMS' Ray.

Wide gaps remain

Despite the improvements, investigators have raised expectations for both sponsor and CRO performance in providing better study management and support across all the project attributes considered "most important" to running a successful study.

"Besides having to deal with CROs, which usually have layers and layers of bureaucracy, the protocols have become more and more complex. As a result, patient recruitment is much more difficult. When you throw into the mix competitive enrollment, which is now the norm, sites are really challenged. The environment has gotten worse since 2013. Sponsors and CROs should be doing more to support sites in these key areas," said Phillip D. Toth, M.D., medical director and president of Midwest Institute for Clinical Research in Indianapolis, Indiana, whose site has participated in more than 500 clinical trials since 1988.

The widest performance gaps—ranging from 18 to 25 percentage points—identified by previous CenterWatch surveys as the biggest challenges to the quality of CRO-site relationships remain critical. These areas include providing knowledgeable, well-trained CRAs; being organized and prepared; and having easily accessible staff.

"Overall, I have not found there to be an improvement," said Jennifer Selk, co-owner of Florida-based Suncoast Clinical Research. "Monitoring has been continually declining.

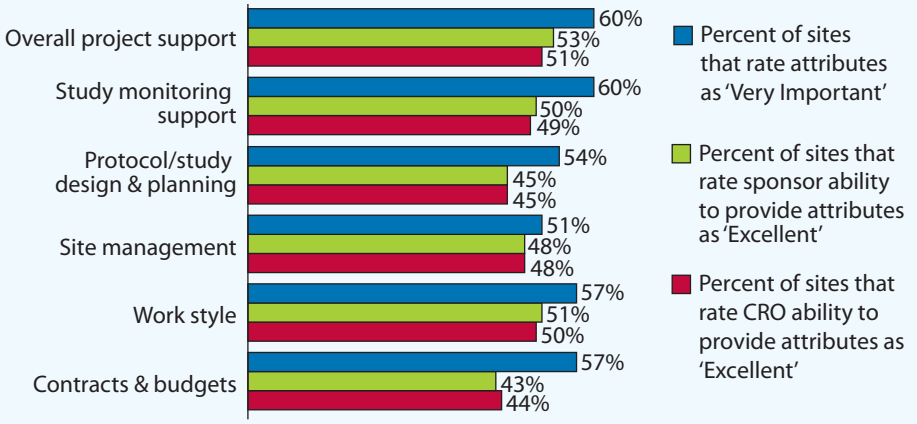
CRAs are often spread too thin and are not familiar with the condition under study. Many CRAs can't even pronounce certain indications or common medications during a site selection visit. Some CROs are better than others but, while this may be just a perception, it seems that sponsors are going for the lower cost CROs, and with lower cost comes lower quality."

Among the lowest scores in the survey were for having low monitor turnover, with 26% of investigators expressing dissatisfaction with CRO delivery in this area. Charles Wilcox, Ph.D., executive director of the California-based Pharmacology Research Institute (PRI), which has sites in Encino, Los Alamitos and Newport Beach, said reducing CRA turnover rates was one of the most important ways that CROs could improve their site relationships.

"In both 2015 and 2016, we averaged just under six different monitors per study when working with CROs, which resulted in 100% uncompensated costs for duplicating efforts and re-doing things repeatedly and often with painful inconsistency of rules, guidelines and specific requirements from monitor number one as compared with monitor number five on the same study with the same CRO," said Wilcox.

Another area identified for improvement is clear study initiation visit and training, which ranked among the top five most important attributes, yet CRO performance fell 15 percentage points below expectations. In a new attribute for 2017, fewer than half of investigators (47%) said CROs provide effective risk-based monitoring (RBM) processes and in interviews, many expressed concerns that budget amounts don't typically cover new site responsibilities associated with RBM systems being implemented.

Overall category rankings



Source: CenterWatch 2017; n=1,376 global investigative sites

Looking forward

Survey results show that CROs have steadily improved the quality of their working relationships with sites during the past four years and now perform at the same level as sponsor companies. Yet improvements are needed in areas investigators consider critical to successful study conduct. In particular, as protocols become more complex, it has become increasingly important for CROs to ensure they provide sites with well-trained, professional CRAs and organized study support.

The survey results also suggest the value of CROs understanding site needs and engaging with investigators to address challenges and provide solutions that can improve drug development processes.

"Traditionally, most of the clinical research processes were there for the benefit of the sponsor or CRO. Increasingly, there is a recognition that we have to make it easier for the sites in order for our trial to be successful. I think that is a change of approach," said Parexel's Evans. "There is a lot more work to be done. What you are seeing in this survey is only the tip of the iceberg. This is an evolving aspect in the clinical trials market and I think we will see much closer relationships between CROs, sponsors and sites going forward."

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