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Sites facing mixed operating conditions

Competition intensifying; select study conduct segments struggling

By Karyn Korieth and Annick Anderson

A new CenterWatch survey presents mixed signals about current operating conditions at investigative sites and reveals a complex picture of a market in flux.

Overall clinical trial volume and site profitability have grown, but at the same time, as drug development programs have become more complex and target smaller patient populations, competition has intensified for the pocket of clinical trial activity considered the "bread and butter" of the industry.

"There is a lot of change coming to clinical research," said John P. Neal, CEO of Preferred Clinical Research Sites Network (PCRS Network), comprised of 115 investigators from more than 50 independently owned sites across the U.S. "Our members have increased both revenue and profits during the last few years. That hasn't necessarily been the same condition throughout the industry, though. Competition is high and going to get much higher. It is becoming more difficult for individual, non-aligned sites to attract enough studies to remain viable."

Investigators generally express optimism about the study conduct market outlook due to healthy R&D pipelines, and a significant majority (63%) anticipate that their profit margins will continue to grow. Yet experienced investigators also express concerns about the climate for clinical research becoming more difficult due to increasing workloads and insufficient budgets. The majority of survey respondents report they won't expand their staffs this year.

Median number of active clinical trials in 2015

Source: CenterWatch, 2015; n=252 investigative sites

"We have a positive outlook for the future," said Jeremy Rigby, executive director of Advanced Clinical Research (ACR), which has seven locations in Utah and Idaho. "Studies are becoming more complex and difficult, but we are doing our best to be adaptable to that and learn how to execute these studies in a more competitive and difficult environment."

Mixed-picture of activity levels

CenterWatch recently completed an online survey, conducted in collaboration with the Association of Clinical Research Professionals (ACRP), of 252 investigative sites about their staffing levels, research activity and financial operations. Respondents averaged 15 years of clinical research experience. The majority of the respondents (84%) came from North America, with another 9% from Europe and 8% from the rest of the world. Nearly two-thirds of the respondents were small sites (164), defined as sites that managed 10 or fewer active clinical trials in 2015, while 77 respondents represented large sites.

CenterWatch carries out an extensive survey of investigative sites every two years to establish industry benchmarks for site operations and to give investigators, sponsors and CROs a chance to better understand the overall health and structure of this landscape.

Surprisingly, analysis of CenterWatch's 2016 site operations survey uncovered conflicting data points concerning clinical trial activity levels at investigative sites.

CenterWatch survey respondents re-

Median number of patients enrolled in 2015

Source: CenterWatch, 2015; n=252 investigative sites

ported a 21% increase in clinical trial volume in 2015 compared to 2010, which was the year sites had begun to recover from the effects of a global economic downturn. The average number of trials conducted per site increased from 14 to 17 between the two surveys. Separate CenterWatch analysis has found that industry spending on study grants for FDA-regulated clinical trials will exceed $14 billion this year, a 2.2% increase over 2014 levels, and the number of newly initiated Investigational New Drug (IND) programs has reached an all-time high. Extensive interviews with experienced investigators also suggest robust clinical trial activity during the past two years, with sites seeing an increase in the number of study grant opportunities available and expansion in specific areas including vaccine studies, neurology and immunology/anti-infectives.

"All research went through a drought. Sites were closing. But during the last couple of years, it's gotten much more favorable," said Nanci Hook-Seid, CEO of the California-based SDS Clinical Trials, where clinical trial volume has doubled in the past two years.

Yet survey respondents reported that the total number of active clinical trials fell by one-third between 2013 and 2015, from an average of 25 to 17 trials per site. The number of newly initiated trials, however, remained steady at 12 trials for both 2013 and 2015. In addition, the number of patients enrolled by a typical site decreased from 2013 to 2015, from a median 76 to 70 participants. To find those study volunteers, the typical site screened a median of 200 patients in 2015, a number that remained unchanged compared to 2013.

The decline in reported activity levels could be explained by differences in sample size and composition between the two surveys. In addition, two-thirds of respondents in 2016 were from small sites, with 40% of these sites representing physician-run practices that conduct clinical research part-time. Only 14% of small sites were part of a site network. Industry analysts have noted that small sites today face greater difficulties than larger sites or those that are part of a network in attracting new studies.

At the same time, a higher proportion of clinical trials are now funded by small pharmaceutical and biotechnology companies, which increasingly target specialty and rare diseases for small patient populations. These types of studies tend to gravitate toward community-based doctors, often with specialty practices, who may not be experienced investigative sites. Meanwhile, competition for typical clinical trials that provide investigative sites with regular income has increased among experienced investigators as the site landscape has consolidated during the past few years.

"We have to fight for our place to conduct a trial, even if we are a top-enrolling

site in something of that same indication. We have to prove our metrics," said Charlotte Tuttle, director of Regulatory Affairs at SDS Clinical Trials.

Some experienced sites also report limiting the number of new clinical trials they accept to avoid overworking current research staff or the need to hire additional staff, which would ultimately lower profit margins. At the Tennessee-based Holston Medical Group, director of Research David Morin, M.D., said the site has seen a "self-imposed" decline in trial activity because they are careful not to take on so much work that it interferes with the sites' ability to recruit subjects and stay productive.

"The question for us was not how many studies we initiated, but how well those studies enrolled and were conducted," said Morin, who co-founded a company called Trike that has developed an analytic software tool called SiteOptex to better understand the impact of operational workload on productivity. "We conducted analysis that showed I was over-allocating coordinator workload, so I decreased the number of studies at Holston Medical Group. Sometimes less is more. Our revenue is about the same, but we have fewer coordinators overall [who are] more focused on fewer studies."

Overall, survey respondents reported responding to an average of 21 requests for proposals in 2015, negotiating about 12 contracts and being awarded 10 of those agreements. On average, two initiated clinical trials were cancelled; investigators reported that contracts were canceled before the study began and after the first patient had been enrolled.

Increase in staffing levels

Globally, the size of a typical site increased by five positions between 2013 and 2015, reaching a median of 15 full-time employees. As study workloads have increased, many sites have added support staff to both ease the burden on coordinators and increase speed and data quality. Over the past two years, survey respondents indicated that growth in staffing levels was driven mainly by adding positions other than core clinical research positions, such as IT specialists, financial managers, regulatory experts and office administrative support.

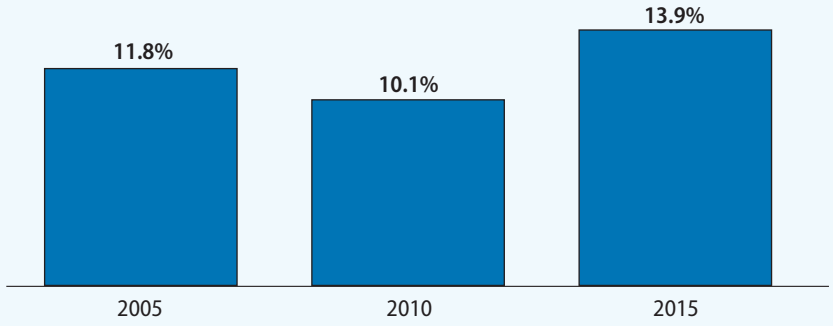
"We have had to add staff to make sure that our enrollment doesn't suffer and that the coordinators can handle the volume of visits. We've brought on board regulatory specialists and recruiters, which allows the coordinators to focus on the visits and on the additional documentation requirements that sponsors are imposing," said Ana T. Marquez, CEO of Marquez Clinical Site Partners, which has a division that manages a site network with 13 locations across the state of Florida.

William B. Smith, M.D., president and principal investigator at Volunteer Research Group/New Orleans Center for Clinical Research (VRG/NOCCR) said investigative sites can improve profitability and efficiency by better matching the background and training of staff members who perform different tasks to the requirements of the trial.

"We train our staff for certain areas so they become very specialized and efficient versus having coordinators who do it all. We have dedicated recruiters, data-entry, regulatory and lab-processing staff. We then use more expensive RNs, nurse practitioners and physician assistants for tasks where they are needed. This allows the coordinators to actually interact with the subjects and manage the trial without spending so much of their time doing clerical or more mechanical tasks that someone else can be trained to do at a lesser pay scale," Smith said.

Only one-third of survey respondents, however, plan to increase staff this year. Among those respondents planning to add staff, increases are generally planned for core clinical research positions including study coordinator, sub-investigator and/or principal investigator positions. Those positions where planned increases in staff are least likely include marketing/business development staff, office administrative staff and executive director positions.

Investigative site operating margins



Source: CenterWatch Surveys

Large sites most poised for growth

Sites of different sizes varied in their plans to expand operations this year. Large sites, which have become valuable and attractive acquisition targets for CROs and private equity-supported site networks during the past year, are the most poised for growth as more than one-third (37%) plan staff increases in 2016. The typical large site enrolled more than twice as many patients and conducted almost nine times the number of clinical trials (44) as the average small site (5) last year. Large sites also support more infrastructure and a greater number

of support staff than their smaller counterparts; they usually are the most invested in running their sites as a professional business and the most organized when it comes to adjusting their capacity upward or downward to accommodate need.

Many small sites, on the other hand, believe it's too risky to scale up in the current clinical trial environment as competition for studies has intensified. Less than one-fourth (23%) plan to hire study coordinators this year and only 10% will add principal or sub-investigators to their staff.

"Our bigger sites have seen growth because we are expanding our therapeutic indications. We are trying to find new ways to keep our revenue stream stable," said Marquez. "It's harder for smaller sites to grow because in order to grow, you have to invest in more staff. And it's hard to invest in more staff if your budgets are shrinking, which is what actually is happening."

A higher proportion of large sites (30%) also reported that they were part of a network, compared to 14% of small sites. Site networks typically provide its investigators with services that include business development, contract and budget negotiations and, in some cases, regulatory work. Affiliation with a site network has become important as CROs, which increasingly manage site operations for sponsor companies, have begun to buy investigative site networks or form strategic partnerships with high-performing sites in order to have closer involvement and more control over site conduct.

"It's becoming more and more difficult for individual, non-aligned sites—particularly where it's a single principal investigator with a small staff—to get the attention of sponsors and CROs and to be effective and efficient at conducting studies," said PRCS Network's Neal.

Small sites reported a 30.5% profit margin for 2015, substantially higher than the 3.4% for large sites. The difference is unsurprising since large sites typically reduce profit margins to grow their businesses and carry higher infrastructure and staffing costs. Despite the lower profit margins, a higher proportion of large sites were optimistic about their clinical research profits increasing this year (65%) than small sites (60%). Many industry experts believe that small and novice sites won't thrive in the long run unless they scale up and build infrastructure needed for sustainable growth.

2015 Site activity

	(All values are medians)
Total number of request for proposals (RFPs)	21
Total number of contracts negotiated	12
Total number of contracts awarded	10
Total number of clinical trials initiated (e.g., protocol approved by IRB and site ready to begin screening patients)	12
Total number of clinical trials for which site was actively recruiting and retaining study volunteers	17
Total number of initiated clinical trials that were canceled	2

Source: CenterWatch, 2015; n=252 investigative sites

Profit margins increasing

Profit margins at investigative sites have reached their highest level in a decade. The average reported profit margins reached 13.9% in 2015, a nearly four percentage point increase from 10.1% in 2010, as compared to 11.6% in 2005. A significant majority (63%) of investigators expect that their profitability will increase "strongly" (13%) or "somewhat" (50%) in 2016. One-out-of-four investigators expect their operating profit to remain the same.

In open-ended survey responses and during interviews, principal investigators and site staff indicated they have improved profit margins by making business-side improvements to boost operating efficiency. Sites report they maintain better control of overhead costs, particularly for staffing, and have become more savvy in negotiating budget contracts. Investigators also report paying more attention to payment schedules and pass-through costs.

"Sites have become more profitable because of a combination of two things. The industry is growing. Also, our own internal skill set with managing budgets and contracts has improved," said ACR's Rigby.

Investigators also have become more selective about the types of studies they accept. All of the investigators interviewed by CenterWatch said they routinely walk away from studies when strict inclusion/exclusion criteria would make it difficult for them to meet enrollment targets, which could then jeopardize being awarded future studies, or if the budgets wouldn't cover their expenses. Sites might find that conducting a complicated biologic study with low patient volume, for example, isn't financially feasible. At VRG/NOCCR, Smith turns down more than one-third of the trials the site is awarded based on the initial feasibility because either the initial information was inadequate to determine the site's capabilities or the budgets were inadequate. Other sites report similar decisions.

"We turn down five to six trials a year because the costs of running the trial far outweigh the potential income that might be generated," said Terry L. Stubbs, president and CEO, ActivMed Practices & Research. "Too many sites still operate on a shoestring and do not get the full costs of doing business. Those who run research as

a hobby often do not understand the costs affiliated with a trial."

Despite the higher profits, investigators report negative trends that have made the operating climate more difficult. More complex protocols, which increase workload and make it more difficult to recruit patients, longer studies, inadequate budgets, increased training requirements, growing documentation requirements and the need to manage multiple technology platforms have added pressures to site operations.

"We are a growth company. We are seeing growth in the number of trials and we are growing our revenue. But I don't want that to imply that the industry is getting easier. The industry is getting harder. It's becoming harder for research sites to be profitable and it's becoming harder for research sites to cash-flow. You can grow revenue and your accounts receivable balance can be growing much more easily than you are bringing cash in the door," said Jeff Kingsley, D.O., CEO of IACT Health, an integrated clinical research site network with nine locations in the Southeast.

Greatest cause of delays

More than half of respondents (56%) identified budget and contract negotiation and approval processes as the top reasons for study delays at investigative sites, a finding similar to previous years, and indicated that negotiations cause more frequent holdups to sites than enrolling study volunteers (42%) and retaining patients in clinical trials (11%). Although many sponsors and CROs have established preferred-site networks with pre-negotiated master agreements or invested in software systems that have helped accelerate start-up processes in recent years, improvements so far have fallen below expectations.

Investigators say negotiation processes are often slower when a CRO or other third-party is involved and said it can take weeks or months for a response to contract questions or budget requests. Most often, investigators report contract and budget negotiations take longer when the original budget offered fails to take into account the complexity or demands of the study or when fair market value rates don't cover the site's expenses. Delays also result when sites find proposed payment schedules unacceptable.

"Sponsors and CROs need to recognize that not all sites are created equal. If a site costs more, it's because they are actually creating a higher quality service for the sponsor that should be paid for. When we are doing these negotiations, they look at the typical fair market value, which is held artificially low by the sites that aren't producing a high quality service," said IACT Health's Kingsley.

Areas for improvement

Almost a quarter (24%) of respondents ranked better communication as the top way their relationships with sponsors and CROs could be improved this year. Leading sponsors and CROs have already begun new programs and initiatives to improve communication with investigators and ask sites for feedback on how to improve the quality of their relationships. In addition, many investigators credit the Society for Clinical Research Sites (SCRS) for giving voice to their major needs and concerns. Yet investigators continue to express frustration about their lack of access to decision-makers when problems or questions arise during a clinical research study and the length of time it takes to resolve issues.

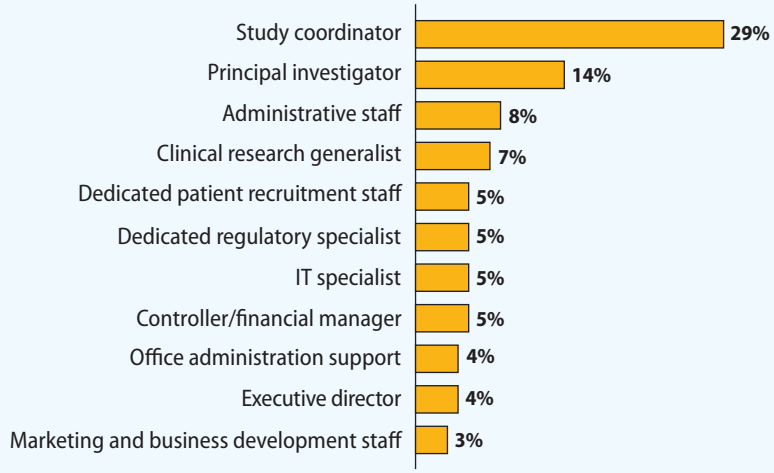
"When sponsors have requirements that don't make sense, or if they change course in the middle of a study and want something done in a different way, many times they don't explain why or understand what kind of difficulty the change is creating for us. Our main contact point is our monitor, who then tries to get information from the folks above her or him. But it's not always successful," said Judith Kirstein, M.D., medical director and principal investigator of Advanced Clinical Research-Utah.

Investigators also say their working relationships with sponsors and CROs would improve if they had more involvement in the study feasibility process before the protocol is finalized and better insight into industry pipelines so they can plan for upcoming studies.

"We are in a position to help with some of the practical aspects of inclusion/exclusion criteria and design of the study to help enrollment and trial execution go smoother for both the site and the sponsor. If the

Planned staff increases

Do you plan to increase staff in this position? Percent indicate 'Yes'



Source: CenterWatch, 2015; n=252 investigative sites

protocol is already finalized before we see it, then our years of experience with this population aren't of any value to the sponsor," said VRG/NOCCR's Smith.

Other top areas respondents would like sponsors and CROs to improve include contract and budget negotiations (14%), the quality/turnover rates of study monitors (14%) and streamlined technology processes (9%).

Looking ahead

The 2016 CenterWatch-ACRP site operations survey shows a complicated picture of the investigative site marketplace, where study volume and profitability has increased, but competition has also intensified. To remain viable, investigative sites must continue to improve operating performance and find ways to adapt to the changing clinical research marketplace, where studies will be smaller than many of the big blockbuster-type studies that took place in the past.

"Good quality sites that are paying attention to the trends and trying to anticipate where the marketplace is going will fare very well," said PRCS Network's Neal. "The naïve sites will have a tough go of it. If we look at the number of sites that are in practice today versus the number that will be in practice 10 years from now, I think that number is going to decrease dramatically."

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