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Is clinical trial design complexity behind the high turnover rate for principal investigators?

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By Craig Morgan

I can make more generals, but horses cost money.
-Abraham Lincoln

Principal Investigators (PI) may not be the generals Abraham Lincoln had in mind when he made this statement, nevertheless they are one of the key players in the clinical trial efficiency equation - ultimately responsible for the conduct of the trial at the investigative site. Achieving operational efficiencies at investigative sites is ground zero in efforts to control costs and ensure successful clinical trials. Given today's challenging economic environment, and the fact that human clinical trials are the most time-consuming and expensive part of the drug development process, industry stakeholders are anxious to rein in timelines.

The PI is responsible for all clinical research activities at a study site. Those responsibilities are two-fold: 1) assure that the study subjects receive appropriate study-related medical care, and 2) assure that all study-related activities follow the principles of Good Clinical Practice (GCP) – internationally recognized ethical and quality standards that serve to assure that the rights and well-being of trial participants are protected, and that the results of the clinical trials are accurate and credible.

Unfortunately, the pharmaceutical industry is experiencing a shortage of experienced PIs. As PIs have a huge impact on the success and efficiency of a study, sponsors are hesitant to use inexperienced PIs to oversee a study site. Yet, the data overwhelmingly suggests that many PIs choose not to continue with clinical trial research. Lack of experienced PIs can contribute to inefficiencies in site selection, qualification, training, and start-up that result in cost increases for sponsors.

What are the underlying causes of the shortage and what can be done?

The Principal Investigator Shortage

Before beginning participation in a clinical study, investigators must sign an FDA form 1572 to certify that they will abide by the guidelines detailed in the Code of Federal Regulations for the use of drugs in an investigational setting. A recent assessment by the Tufts Center for the Study of Drug Development (CSDD), based on FDA form 1572 filings in a public database maintained by the FDA's Center for Drug Evaluation and Research (CDER), found that there are nearly 40,000 unique active investigators worldwide that have conducted at least one FDA-regulated clinical trial. Roughly half of these 40,000 were new to the job in 2013, the most recent year for which data are available. In addition, although the highest turnover rates are observed among the least active investigators, turnover rates have been getting progressively worse among more active investigators. Other findings from this analysis suggest that a relatively small number of PIs are overseeing more trials every year:

- Only 10% of form 1574 filers conduct more than 5 studies per year.
- The percentage of form 1572 filers per year that are first-timers seems to be increasing – the above-cited 50% figure for 2013 was up from 40% four years earlier.
- Growth in the number of unique investigators is beginning to decelerate: the most recent four-year annual growth rate was 3.3% compared with the prior four-year period of 4.1% and an average of 5.6% over the last 15 years.
- During the 2009 – 2013 period, the numbers of active investigators in India and China, areas once expected to see the most dramatic relative growth, have declined by 16% and 5%, respectively.

According to Ken Getz, associate professor and director of sponsored research at Tufts CSDD, "Since 2006, 55% of PIs in Europe, 53% in Asia/Pacific, and 40% in North America have not conducted another clinical trial." This high level of PI turnover is very concerning for the industry. The high percentage of inexperienced investigators suggests that most investigators are not in the industry long enough to master their profession.

Another concern is that the experienced PI pool seems to be aging. Data from 2002 showed that only 8 percent of investigators conducting industry-sponsored clinical trials were younger than 40 years, and inadequate numbers of new investigators were available to replace the older generation. According to Tufts CSDD the average PI's age has risen from 43 years to 50 years.[1] Recent data from the National Institutes of Health (NIH) paints a similar picture – there are not enough new PIs to replace those planning to retire. AMA and NIH data show that the demographics of physician-scientists have shifted dramatically over the past decade, with the proportion of NIH-funded PIs in their 60s and 70s soaring and the share under 60 declining.[2]

So why is there such a high turnover rate for PIs? And why are the numbers of young physicians entering the field declining?

Causes of Principal Investigator Turnover

High PI turnover seems to be primarily centered around the fact that it has become a very demanding job without adequate compensation, financial or otherwise. "The fundamental problem, says Getz, is the needlessly complicated design of clinical trials shaped by complex regulatory requirements from the FDA." Due to risk aversion and a challenging economic environment, sponsors are putting pressure on PIs to deliver more with less.[1]

- Narrow subject eligibility requirements make subject recruiting difficult.
- New technologies increase costs for sites: Electronic Case Report Forms (eCRFs) move data entry costs from the sponsor to the investigator; eDiaries generate reminder phone calls.
- HIPAA, ICH, etc. are increasing regulatory compliance costs both directly and through more stringent sponsor and IRB requirements. HIPAA, in particular, increases the cost of subject recruitment and informed consent.
- Study budgets are flat while procedures per subject are increasing.

Regarding this last point, sites have seen increases in paperwork, protocol complexity leading to challenges with patient recruitment, management and performance metrics, patient screening and informed consent complexity, site staff GCP and IT training requirements, and compliance requirements.[3,4] Site budgets, however, have not increased to address all this added overhead. Adding to the problem is the fact that a complex reimbursement process for patient care costs from clinical trials often results in inaccurate and late payments to sites.

As Terry Poling, medical director Heartland Research Associates, puts it, "Things have gotten more complex and complicated. I regret not enjoying the golden days—10 years ago. Today's landscape is financially tougher. We've seen an increase in demand, but the costs have increased more than the rewards. Twenty years ago, it was simpler to start up—if I were faced with the current demands, I would not have survived."[5]

Practicing physicians might decide to participate in a trial to make some extra money and gain access to new therapies for their patients, only to find that they lack the resources and time required to effectively serve in the PI role. Essentially, they realize that serving as a PI while maintaining a medical practice is more than they bargained for, and they thus join the growing ranks of the "one and done" PIs. The complex task of seeing a clinical trial through from beginning to end is making the clinical research career path unattractive for many, contributing to the aging PI population.

Additionally, sites are being overloaded by sponsors with multiple eClinical technology solutions that do not communicate with each other. A 2016 study by CenterWatch revealed that sites used about 10 different software applications to manage clinical studies in 2015. Jeremy Rigby, executive director of Advanced Clinical Research, says "I am a proponent of these technologies. But the difficulty is the need to use so many different systems, which are hard to keep track of and don't talk to each other. All of these systems work differently, have different login credentials and require training." Instead of supporting improved efficiencies, these technologies end up adding to the complexity of conducting trials by requiring interaction with third-party vendors and increasing training needs.

What Can be Done?

Can generals really be made? While efforts to attract and train new investigators are certainly important, they do not address the root cause of the experienced investigator shortage. To adequately address the problem, we must develop solutions to the fundamental causes of the problem that were detailed in the previous section. According to Getz, "While efforts to hire and train more investigators are helpful, they are not addressing the root causes of the problem. They are point solutions — they touch on areas downstream, but don't touch on root causes like regulatory burden and performance inefficiencies, and it is that protocol or blueprint that needs to be improved."

A fundamental shift by stakeholders is required to address the root cause of this problem in many different aspects of the logistics of running clinical trials. Some suggested changes include:

- Provide a support structure for new investigators in areas such as the completion of contracts and regulatory documents.
- Sponsors need to make sure that new investigators understand the technical, ethical and business differences between clinical research and their regular medical practice. Meetings with new investigators early on should facilitate this.
- Investigators need to perform due diligence to identify all the hidden costs involved in performing the study before budget negotiations with the sponsor commence. Sponsors need to understand that including these costs in the budget is in their own best interest.
- Payment schedules from sponsors to site need to be timely and accurate. Guaranteed investigator payment within a reasonable timeframe should be standard.
- Sponsors need to start treating investigators as partners in their business, investing in and developing long-term relationships with investigators.
- Regulatory agencies need to take steps to streamline and reduce unnecessary complexity in the regulations which govern clinical trials.
- Provide support structures that enable practicing physicians to more easily serve as PIs.
- Sponsors should seek a more integrated approach to IT technologies that are designed to aid clinical trials. The presence of multiple applications and platforms that are not connected to each may serve to add unnecessary complexity to the business of conducting clinical trials.
- Regulatory agencies could create a centralized website accessible to all study sponsors where investigators could upload their GCP training credentials, thus avoiding the need for repeating this training unnecessarily for every study.

Conclusion

Fortunately, some companies are developing technology solutions specifically designed to address site and CRO engagement needs. Study start-up activities from site activation through patient recruitment and into first subject first visit (FSFV), can be particularly challenging for PIs and study staff. They want to deliver high levels of performance but may be overwhelmed in the flurry of startup activity. To perform well, sites need timely access and visibility into workflow steps, including key documents and crucial tasks. Additionally, sites need objective evidence of the key drivers of study startup (and metrics) to meet sponsor expectations and make the right service quality investments. The same can be said for CRO engagement. Visibility into the operational workflows, key tasks, documents, and bottlenecks are critical elements in fueling the partner ecosystem required to deliver clinical trials successfully.

Technology solutions, particularly cloud-based, are increasingly becoming a key differentiator for sponsors looking to invest in site and CRO engagement, ultimately resulting in lower costs and less turnover. Aiding this technology adoption is much needed regulatory agency support to eliminate duplicate, time-consuming tasks and improved supported structures for PIs needed to move the industry forward.

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Craig Morgan is a technology and life sciences management professional with more than 15 years experience in the application of informatics and bioinformatics to drug discovery. He currently heads up the marketing and brand development functions at goBalto, working with sponsors, CROs and sites to reduce cycle times and improve collaboration and oversight in clinical trials.

Craig Morgan
Head of Marketing | goBalto