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At the core of our business and operating systems, **FXM Research** mission is to support pharmaceutical companies and CROs with introducing new and approved FDA medications successfully into the marketplace. We perform this efficiently and effectively by providing the highest quality service in a timely fashion and at the lowest possible cost.

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- We do whatever is necessary to accommodate our subjects' school and/or work schedule, which maximizes compliance and retention.
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Clinical Researcher
The Authority in Ethical, Responsible Clinical Research

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PEER REVIEWED

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Clinical Research Performance and the Use of Metrics

GUEST EDITOR'S MESSAGE

Erika J. Stevens, MA

Erika J. Stevens, MA, (erikastevens1@gmail.com) is senior managing director of research technology in the Research and Compliance practice of FTI Consulting, a member of the Association Board of Trustees for ACRP and its liaison to the Editorial Advisory Board for *Clinical Researcher,* and president of the New York Metropolitan Chapter of ACRP.

The modern increased push for performance cuts across all industries, including clinical research. Understanding performance and the components which define performance improvement helps us to describe the appropriate selection, use, and interpretation of metrics.

Performance is defined as a multidimensional phenomenon that includes economy, efficiency, and effectiveness in business processes.[1] Applying this principle to clinical research, one should consider the benefit of decreasing overall research study costs, the speed at which trials are conducted, and the overall effectiveness of treatment to research patients.

Performance improvement is a method for analyzing performance problems and the process of setting up systems to ensure good performance.[2] The ability to measure a business process output, increase efficiency, or increase overall effectiveness is a key driver of performance improvement. Organizations seeking to solve a performance problem frequently implement a specific intervention, without fully comprehending the root cause of the problem or assessing the impact of the change.[3]

The ability to evaluate the impact for an organization in optimizing performance is applicable to clinical research. For example, reducing cycle time in clinical research could provide opportunity for efficiency and reduction in cost, but will it improve the effectiveness of the investigational product?

Three Perspectives

For "The Evolving World of Metrics" portion of this issue, the selected authors illustrate varied perspectives on the value and interpretation of metrics in clinical research. The increased push for performance improvement in clinical research is driven by metrics, but defining and applying metrics remains a challenge. These subject matter leaders provide insight into the complexity of describing, selecting, and interpreting metrics for clinical research performance improvement.

From a site perspective, Dr. Jeff Kingsley from IACT Health leads this issue with an overview of the terminology of measurements, metrics, and key performance indicators (KPIs). Of special note, the use of a "balanced scorecard" to measure clinical research performance is defined in this article.

In addition to scorecards, a thorough understanding of how the aforementioned KPIs function is essential in defining metrics for clinical research, and Drs. Sahai and Sahni from Velos describe a method for selecting appropriate KPIs. Their examination of this topic includes considerations for using data and variables which can be measured objectively.

Finally, Linda Sullivan from Metrics Champion Consortium explores the efficacy and use of performance metrics. The use of metrics, as discussed, should be in "the interest of better study execution, industrywide."

Readers of these articles are encouraged to keep in mind that improving the performance of clinical research may be measured through the use of metrics; however, interpreting the cost, benefit, and impact of tracking those metrics may not be as easy as it sounds.

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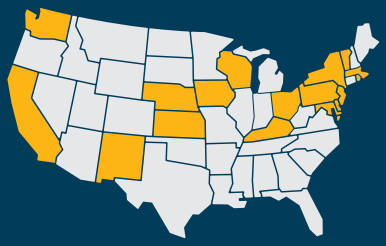
BY THE NUMBERS

A glimpse at some of the latest trends driving changes in the clinical research enterprise.

A recent report shows that the U.S., with nearly **115** specialty contract research organizations (CROs), has emerged as the primary hub of specialty CROs. This is followed by Europe, with about **60** CROs. Meanwhile, India and China, whose CROs offer optimized service portfolios at relatively higher costs, are emerging as new destinations; the level of activity in these nations, however, has been fairly limited so far.

Source: Research and Markets, www.researchandmarkets.com/publication/mzochnp/3623249



Since August 2015, **7 more states** (Connecticut, Georgia, Idaho, Maine, New Hampshire, South Carolina, and West Virginia) have adopted legislation permitting doctors to prescribe treatments for terminally ill patients that are being used in clinical trials, but are still awaiting final approval by the U.S. Food and Drug Administration, bringing the total of such states to **31**. **16** additional states are considering the law this year.

Source: Right to Try, http://righttotry.org/in-your-state/

The average total commercial investment for a medical device in development **48** or more months is **10 times greater** than the average commercial investment for devices in development for 23 months or less. The increase in budgets is largely due to the lengthy duration of complex Class III device development.

Source: Marketwired, www.marketwired.com/press-release/-2129725.htm

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[DOI: 10.14524/CR-16-4033]

PATIENT-CENTRIC TRIALS:
Numbers Don't Always Tell the Full Story

"Undertake a Clinical Trial at Your Own Risk," says a recent headline emblazoned across the pages of *U.S. News & World Report.* The subhead is not any better: "Volunteer: It 'may very well take a boycott' to get compensation for research injuries."

Jim Kremidas (jkremidas@acrpnet.org) joined ACRP as its new executive director in October 2015.

The article tells the story of a 65-year old woman who underwent a cancer trial at the National Institutes of Health (NIH). According to the magazine, the trial subject assumed she would be well cared for at the facility if the trial went bad. Instead, she found a notice on the final page of the 21-page consent form advising her she would not receive any long-term medical care or compensation if she were injured in the trial. The trial participant "had stumbled into a black hole of medical ethics," the magazine says.

Clearly, this is not the way we want to see clinical trials portrayed in the mainstream media. Potential trial participants see this kind of coverage and understandably become more wary to participate.

What's the answer? I suggest at least part of the solution is wider adoption of patient-centered clinical trials. We need to be ever more vigilant before, during, and after the informed consent process; but how do we best quantify better subject outreach and education?

In Search of the Full Story

We take a look at metrics in this issue of *Clinical Researcher.* Few would disagree when we stress how important they are as part of the safe, ethical, and effective conduct of clinical trials.

Numbers don't lie…however, they don't always tell the full story. For example, let's consider the patient-centric approach to trials and medicines. It's becoming a more and more popular concept. You don't have to look very far to find references to it in clinical trial–related publications—from journals to more mainstream outlets.

On a gut level, most of us would probably agree that a patient-centric approach improves trial outcomes. That's the easy part. The hard part is finding any metrics, or other tangible proof, supporting that thesis.

On a gut level, most of us would probably agree that a patient-centric approach improves trial outcomes. That's the easy part. The hard part is finding any metrics, or other tangible proof, supporting that thesis.

So far, the support is more anecdotal. I had the privilege to work with Eli Lilly and CISCRP on its Hero Campaign. It was an attempt to frame clinical trial participation as a "pay it forward" activity. In other words, today's clinical trial participant is helping tomorrow's patient. We split our approach down the middle. In one half, we raised awareness of the campaign using traditional, broad-blanketing methods of outreach. In the other half of the trial, we took a more proactive, patient-centered approach with more aggressive educational materials and other related strategies. Our results were clear: We enjoyed much faster enrollment rates with our more patient-centric approach.

Numbers Alone Fall Short

Unfortunately, those kind of metrics remain rare. Further, I'd be the first to admit that the CISCRP results are far from conclusive from a purely evidentiary standpoint. However, I also believe we can't rely on numbers alone to make the case for the patient-centric approach.

It's often too easy to miss the numeric benefits of a patient-centric trial. For example, how can we expect a super-busy doctor to notice that the patient-centric approach produces one patient every four weeks versus five weeks without it? That's a 20% improvement, but it is not something easy to register.

Some aspects of the patient-centric approach are, I hope, self-evident. It is important to make sure patients clearly understand the pros and cons of a potential trial. They deserve transparency. We owe it to them and we owe it ourselves to advance our important work.

I encourage you to take a look at Steve Ziemba's Chair's Message (page 8) where he takes an interesting look at patient-centricity from a genomic perspective.

Investing in Today's CRA Talent to Ensure a Stronger Tomorrow

The importance of Clinical Research Associate training to support effective trials

Monique Heiser Wong, *Senior Manager, Clinical Development Services, Covance Inc*

The clinical trial landscape is witnessing an increase in Phase III trials that average more than 3,500 patients. As more of these large trials continue to emerge, many contract research organizations (CROs) and sponsors are struggling to recruit qualified clinical research associates (CRAs) to support the influx of work.

Lack of experienced talent represents one of the main challenges facing the market, impacting sponsors and CROs alike with increased costs and extended timelines. Yet the urgent need for qualified CRAs will continue given that the demand in the field is projected to grow by 36.4% from 2012 to 2022[1] in the U.S., an issue also reflected worldwide.

Examining Recruitment Barriers

The clinical trial industry is acutely aware of the pressures. To stay abreast of this urgent situation, as noted in the Association of Clinical Research Professionals (ACRP) position paper, *A New Approach to Developing the CRA Workforce,* the industry needs to assess current standard operating procedures (SOPs) and examine barriers blocking new talent from filling positions.

At Covance, we followed this guidance and brought together our leaders to holistically assess the market and our current investments. We found the industry truly lacked a harmonized global training program to develop CRAs—early in their careers—creating a major hurdle for job seekers. Furthermore, many scam training programs offer dubious certifications to CRA candidates interested in building skills within the field.

Proactively Growing the Talent Pool

Recognizing this gap in training, we developed a global program to attract and retain talented people: the Covance Monitoring Excellence Academy (MEA). We wanted to give candidates from around the world the opportunity to grow into the CRA role, which ultimately enriches our lifeblood for the good of patients and transforms how we manage clinical trials.

The academy is more than a simple training program. MEA establishes an accelerated path through tailored scientific courses, interactive modules, hands-on experience, and an ongoing mentoring program. Trainees receive a solid foundation that lays the groundwork for a rewarding career path.

Building the Pathway to Success

The Covance Monitoring Excellence Academy is designed with two pathways to hire staff and train them in a standardized global fashion. The first path focuses on what we call the CRA "Assistant Role." These candidates have the relevant education but limited experience in a clinical research setting. With guidance from experienced team members, they can work at in-house roles and learn all the aspects of being a CRA, creating the perfect opportunity for recent graduates looking for a fast-tracked career path as a CRA.

Industry experienced staff, such as research nurses, site study coordinators, or clinical research coordinators are ideal for the second path. Here, the MEA courses teach them how to effectively

manage sites in clinical trials as a CRA. In many cases, these staff are remote employees, working from their home offices while in the MEA program.

Regardless of the pathway, we've found that trained staff feels empowered to bring a more consistent approach to how they monitor and manage sites, reinforcing our drive for quality, accuracy, and excellence. And, the CRA team, having diverse backgrounds with varied experience levels, offers a more innovative, holistic, and unique perspective, using a "critical eye" to judiciously manage our trials—a true value to everyone.

A Flexible Curriculum, Focused on Growth

The MEA program offers tailored tracks based on a candidate's individual level of industry knowledge and experience. Over a three-to six-month period, participants advance their clinical operation competencies through a comprehensive blended face-to-face and web-based curriculum:

Regional Training Modules	Allows candidates to participate in training modules based on experience in the industry–ranging from team roles and responsibilities to clinical trial design to remote monitoring
Clinical Foundations	Provides an overview of activities, processes, and components of a clinical trial, emphasizing the roles and responsibilities of the sponsor, sites, ethics committees, and CRAs
Peer Support and Observational Training	Offers participants the opportunity to partner with and observe skilled CRAs to further develop competencies, expand critical thinking skills, and gain co-monitoring experience
Regional Case Studies, as applicable	Encourages learning via scenario-based training case studies created from corrective and preventive actions (CAPAs) and examples from Clinical Quality Control (CQC) visit findings

Supporting Employees, Clients, and Trials

Through the MEA program, graduates gain comprehensive real-world experience and a thorough understanding of GCP and ICH regulatory requirements, all while working in a supportive network of skilled and trained CRAs.

THE MONITORING EXCELLENCE ACADEMY ONBOARDING TIMELINE

Weeks 1–4

Onboarding, Orienting, and Project Training

- Hire CRAs, assign projects, and develop individual Skill Set Development and Support Plans
- Pre-identify studies for trainee placements
- Determine which trainees can be accelerated based on initial skill set

Months 1–4

Foundation Training, Observation, and Co-Monitoring Visits

- Competency training
- Project check-in at 30/60/90 days
- Emphasize individualized observational learning

Months 4–6

Care Quality Commission (CQC) Assessments

- Focus on peer support
- Identify CRAs who can work independently

Ongoing

Continued Development and CRA Education

- Ongoing skills training as needed

"The MEA gave me the necessary training that helped me make the jump from study coordinator to CRA. I feel that I have the right tools to excel in my role as a new CRA with continuing support from my trainers, mentors, and other CRAs from the program."

-Recent MEA graduate

Participants work with a regional point person who provides real-time support when questions arise and ensures the individuals understand all aspects of the clinical trial monitoring through the MEA program period and beyond—before accepting any individual assignments. This process ensures the highest data quality for more successful site performance.

Providing the First Line of Defense

"In any clinical trial, data integrity and patient safety are our top priorities," said Dr. Rob Davie, Vice President and General Manager for Global Phase II-IV, Clinical Development. "As dedicated research professionals who are knowledgeable about the science of monitoring and its collaborative nature, CRAs represent the first line of defense. That's why we work hard at Covance to invest in talent through the Covance Monitoring Excellence Academy."

With deep experience, a reputation for quality, and therapeutic area expertise across the entire development spectrum—from nonclinical through Phase IV and safety monitoring—Covance understands the essential role of skilled CRAs in successful trials. "Clients can expect to partner with innovative individuals committed to ongoing quality in clinical research," said Davie. "Likewise, CRAs can expect that we'll reward their efforts from the moment they walk in the door."

As a partner in this collaborative, talent-building process, we continue to hear from our clients how satisfied they are with the MEA coursework and the knowledgebase of their new enthusiastic CRAs.

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1. Bureau of Labor Statistics

[DOI: 10.14524/CR-16-4032]

Leading the Charge for Change

We are living in an exciting time in the field of clinical research. There are changes occurring that will alter how medical care is provided, and it is the work of clinical research professionals that will lead these changes.

Steven Ziemba, PhD, CCRC, CPI, (ziemba.steven@mcrf.mfldclin.edu) is the associate director of the Marshfield Clinic Research Foundation in Wisconsin and Chair of the 2016 Association Board of Trustees for ACRP.

Genetics has certainly made an impact in medicine. It has not been so long since we first sequenced the entire human genome, and now the first studies using the CRISPR gene editing technique have been approved.

Certain aspects have led to ongoing revolution in terms of how we are applying advances in genetics, with two having perhaps the most prominence. The first is that, as evidenced by CRISPR, we have new and highly effective techniques that can be put to use (the advent and use of Big Data is another example). The second aspect is cost. The first human genome to be sequenced, in 2003, came at a cost of $2.7 billion and took years of work. Presently, the technology exists to complete a genomic sequence in days at less than $1,000.

Applying What We've Learned

One direct application of genetics is precision medicine. This component of medicine may also have the greatest impact on clinical research now and in the future.

Traditionally, medical advancement has relied on the results of large studies that determine treatments for a group of people with a given diagnosis. It is an effective, if not ponderous, process; however, there will be individuals who may not have an optimal response, no response, or may experience adverse events as a result of the treatment.

Our focus is shifting from treatments intended to work for everyone, to treatments specialized to individuals. We are seeing the impact on clinical research now, with the ongoing Molecular Analysis for Therapy Choice (MATCH) Trial, a federally funded cancer clinical trial that seeks to pair treatment with the results of analysis of more than 4,000 genetic variants across 143 genes in the participant's tumor.

Our focus is shifting from treatments intended to work for everyone, to treatments specialized to individuals.

Relocating the Center

Meanwhile, patient centeredness is a unique development in clinical trials. The historical context of medical research has focused on the development of new ideas by scientists and physician-investigators, involvement of federal and industry sponsors, and the work of clinical research coordinators, study monitors, research nurses, data managers, regulatory specialists, and myriad other professionals to see a study through.

The study participant was expected to enter the process only after a study had gone through development and launch. Certainly, there have been successful studies conducted via this approach, but the demands placed on the participant may have not been carefully considered.

The advent of the Patient Centered Outcomes Research Initiative (PCORI) has changed this mode of thinking by making the patient, and by extension study participants, a partner in the drafting of the research question, through study design, and interpretation and dissemination of study results. Such input will inevitably grow as clinical research progresses.

You are the Linchpin

These are only a few of the examples demonstrating the evolution of the clinical research field. Others include new classes of drugs and improved medical devices, telemedicine and healthcare apps, translational and comparative effectiveness research, and adaptive research design.

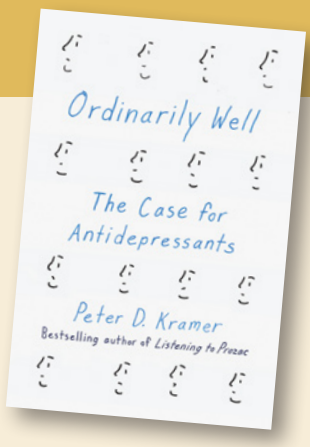
I am privileged to serve as the Chair of the ACRP Board of Trustees (ABoT) at this exciting time in our history. My colleagues on the ABoT and on the Academy Board have made it a personal mission to guide our organization in serving clinical research professionals. Similarly, the ACRP staff have demonstrated commitment, ingenuity, and innovative thinking in terms of educational offerings, the annual Meeting & Expo, and the accredited professional certification program in serving as the voice of our profession.

Above all, however, it is the clinical research professional who serves as the linchpin in leading the innovation that is advancing our medical knowledge. Thank you for your commitment to the field and to ACRP.

[DOI: 10.14524/CR-16-4029]

Prozac Author Calls for Reassessment of Clinical Trial Efficacy

James Michael Causey



Peter Kramer, author of the controversial *Listening to Prozac,* is back with another book that once again tosses the cat amongst the pigeons to challenge some current thinking regarding the testing and efficacy of antidepressants. Kramer is a psychiatrist and Brown Medical School professor. *Clinical Researcher* Editor-in-Chief James Michael Causey spoke with him in late June, a few weeks after his new book, *Ordinarily Well: The Case for Antidepressants,* was released to largely positive reviews. The interview transcript has been edited for space and clarity.

Clinical Researcher: Throughout the book, you stress the importance of randomized trials to the development of antidepressants. Why is that?

Peter Kramer: I think from the start, from the earliest development of psychopharmacology, people understood that it was going to be harder to specify what was going on with mental health treatment and behavioral medicine, and harder to convince people of whatever was going on. Some of the earliest organizing, specifying of parameters, and so on that's in clinical research in terms of randomized trials was done in mental healthcare. [It] was always understood that these interventions were going to be highly dependent on this technology, the randomized trial.

[In terms of] the whole range of treatments in psychology, the randomized trial has been important for almost as long as there have been randomized trials. Certainly for as long as there had been modern psychotherapeutic drugs.

CR: In the book you suggest how the pharmaceutical industry has largely abandoned drug development in psychiatry. You wonder if randomized trials are playing a part in that. Can you talk a little about that?

Kramer: I'm not privy to the discussions with any pharmaceutical companies, but I was just reasoning the way I think an executive would reason, which is, first of all these companies are coming under attack because there's such an anti-pharma contingent. Secondly, the patients just aren't there. Especially with depression, the antidepressants are so widely used that patients who are likely to respond to them have already responded. …It's not even clear whether clinicians should be sending patients into these trials without first trying already well-established remedies—both medication and psychotherapy.

CR: Do you think we need to change the structure, very broadly speaking, or the approach of clinical trials as they assess antidepressants?

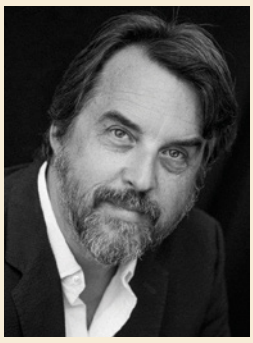
Kramer: Well, I guess the answer is yes. There are problems we haven't talked about. Arguably there's a placebo effect. …I know some people in the field have tried to jerry rig or create very complicated ways of trying drugs where a bigger percentage of people would be on active substances and fewer would be on placebo.

I think, partly, we ought to be working with drugs where there's a good case that we've done a good job of the animal trials…so that you're testing drugs for which the justification is very strong. Then I think you might need a long period of uncontrolled trials before you start going to placebo, and that gives a somewhat greater justification for people who refer patients in.

If we develop biological markers for depression that are really telling us what we're doing, that will make clinical trials easier, and maybe it would be a powerful enough technology to overcome some of the other difficulties that I write about.

CR: The book just came out [June 7], but I wonder if there's going to be any kind of defensiveness from the clinical trial world. Have you gotten any reaction yet, or expected a reaction?

Kramer: I haven't. I hope I'm fair. I take that trip to a research center [in the book]. I don't think it's the best way to go about doing things, but I do try to represent just how professional and excellent some of the functions are.



James Michael Causey (mcausey@acrpnet.org) is editor-in-chief for ACRP.

AT PRA, WE'RE FAMILY

A look inside PRA's "boomerang" phenomenon

Employees gather for a grand opening celebration.

We'll be the first ones to admit, we've had CRAs quit. They've even left PRA for other CROs. Sure, there's the allure of new opportunities, new studies, new systems. But at PRA, we've noticed one big difference. They "boomerang" back. At a rate of 6.5 former employees per month, in fact.

Believe us, we were surprised by this number too. It's not often you find an employee that has left so eager to come back. But they are.

Why?

Great question, glad you asked. The answer is simple, and we hear it overwhelmingly from our CRAs. "PRA is home, and the people here are family."

So what makes PRA home?

True, PRA is 11,000+ employees. We have offices all over the world. But there's one thing we never do. And that is forget that every single person that works here is part of the family. We don't define our employees by a number. We define them by the incredible work that they do.

PRA is home, and the people here are family.

Experience Nicole's CRA journey at DiscoverYourPRA.com.

Being a CRA asks a lot. Being a CRA means missed family dinners, missed soccer games, and just missed time. Time with loved ones, time with spouses, time with kids. And that's tough. It's more than tough. But that's why we do everything we can to give our CRAs flexibility when they need it. We try as best as we can to keep them close to home and work with their schedules so that they miss as few of those soccer games and dinners as possible. At PRA, we know how important family is, because at the end of the day, we consider every single person that works here family.

Really though, why would someone leave and then come back?

They come back because we welcome them back. We don't consider CRAs that have left to be outcasts. We know that our managers are incredibly supportive, our systems are top-of-the-line, and our teams are always there to help each other. But we also know that everyone longs to see or do something new. We don't exile someone for that. We encourage all of our employees to ask questions and challenge norms. We want our CRAs to discover, create, and most importantly, innovate. When CRAs return to PRA, we know that they've explored other places. They've worked on other studies and used new systems. We are happy to welcome back their input on how we can make PRA better.

So many people come to PRA because they want to do some good in the world. They want to go home each night knowing that they have truly made a difference in the world, while at a place they love working. So many people stay at PRA because, not only do they get to shape the future, they get to do it in a place they truly love. And we are happy to have them.

For more information, please visit DiscoverYourPRA.com

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This test expires on August 31, 2017

(original release date: 8/1/2016)

In this issue of *Clinical Researcher,* the three articles that follow this page have been selected as the basis for a Home Study test that contains 30 questions. For your convenience, the articles and questions are provided in print as well as online (members only) in the form of a PDF. This activity is anticipated to take three hours.

Answers must be submitted using the electronic answer form online (members only, $60). Those who answer 80% of the questions correctly will receive an electronic statement of credit by e-mail within 24 hours. Those who do not pass can retake the test for no additional fee.

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Measurements, Metrics, and KPIs: Achieving a Balanced Scorecard

PEER REVIEWED | Jeff Kingsley, DO, MBA, CPI

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Pharmaceutical, biotechnology, and medical device sponsors and contract research organizations (CROs) are hiring sites to do one thing: produce high-quality data. In pursuit of that single and seemingly simple goal, research sites have to do hundreds of things, including training highly competent researchers, recruiting numerous appropriately qualified research subjects, and managing complex nuances of the research protocol.

It's difficult enough to implement the processes and functions necessary to obtain high-quality data, but if you succeed in implementing the myriad policies and procedures needed, you will have only come half way to the goal.

LEARNING OBJECTIVE
After reading this article, participants should be able to design a balanced set of key performance indicators (KPIs) that maximize the participants' ability to achieve a strategic victory.

DISCLOSURES
Jeff Kingsley, DO, MBA, CPI:
Nothing to disclose

A procedure is only valuable if it is producing the desired results, and if you are not measuring the results, you will have no idea if you are winning. Further, each procedure you add may have negative implications for your other procedures—these are the inevitable "unintended consequences."

In such a research environment, key performance indicators (KPIs) are needed, and a tool known as a "balanced scorecard" is a must.

Why Measurements Matter

As clinical researchers, we know that in order to determine the safety and efficacy of an investigational product, medication, or device, we have to study it, and studying it means measuring it. We have to measure its safety against other medications or devices in its class, as well as its efficacy.

If we invent a new potential antibiotic in an existing class of safe and effective antibiotics, we have every reason to believe it will work. Yet we also accept that we positively cannot proceed without first studying this new potential antibiotic. We accept this as fundamental to the industry in which we work.

In our work life, we invent new processes to fix the ills of our businesses. These processes are designed well and should certainly work. However, all too often we implement processes and walk away. We often simply make the assumption that the processes will work. It is far too seldom that we take the time to then study the intervention, measure the results, and evaluate the effect on our other processes. It is equivalent in our clinical research world to considering matters of efficacy and side effect profiles. Too seldom do we pay attention to our own performance with the same rigor we apply in clinical research.

Interestingly, the simple act of measuring things improves the thing being measured, even in the absence of a meaningful intervention. This is equivalent to the placebo effect in our clinical research trials. This is known as the Hawthorne effect, and is sometimes explained as "what gets measured gets done," going as far back as now famous experiments from the 1920s.[1] According to one description of the experiments, "By the time everything had been returned to the way it was before the changes had begun, productivity at the factory was at its highest level."[2]

A Primer

A measurement is concrete, usually measures one thing, and tends to be quantitative. A metric describes qualities and requires a measurement of baseline characteristics. As an example, I can measure the amount of gas in my car and I can measure the distance I've traveled. The number of miles I've driven per gallon (MPG) of gas used is a metric, and is far more valuable than simply knowing the individual measurements that went into it. A key performance indicator (KPI) is the next improvement in measurement.

A KPI is a metric that is deemed to be a critical evaluation of the success of a process. There may be many measurements and metrics that are useful regarding that process, but there should only be one or two KPIs that provide a high-level, quick evaluation of the performance of that process. Is it doing well, or is it doing poorly?

You can think of a KPI as having your finger on your pulse. If during a normal part of your day your pulse is between 60 and 100, you're probably doing just fine. However, if your pulse (a KPI in healthcare) is outside that range, then it's time to dig deeper with more measurements and metrics to determine the cause. This is the same way you should measure the health of your organization.

A balanced scorecard is the collection of KPIs that look at the health of your organization from multiple different perspectives at the same time. Maintaining each of these KPIs within their desired range maximizes the health of your organization. (See Table 1 for a summary of terminology related to this article.)

It's important to note also that metrics, KPIs, and the components of your balanced scorecard can be either leading or lagging indicators. If your metric is a lagging indicator, it's providing you with information about what happened in the past without any remaining time to intervene and improve performance (leaving the opportunity to affect change in the future only). A leading indicator is a metric that is providing you with current data that are predictive of future outcomes.

Your leading indicators can provide you with an opportunity to intervene and impact performance before it is too late. Leading indicators give you the opportunity to affect change actively.

The balanced scorecard was a concept first discussed by Robert S. Kaplan and David P. Norton in *Harvard Business Review* in 1992.[3] It's important to note that as you work to improve one metric, you can many times worsen others. For example, if a business is concerned only about its financial performance, it can achieve its financial targets at the expense of employee satisfaction and engagement along with the quality it's providing to its customers and many of its stakeholders. Similarly, it's easy to imagine achieving our operational measures at the expense of our financial performance.

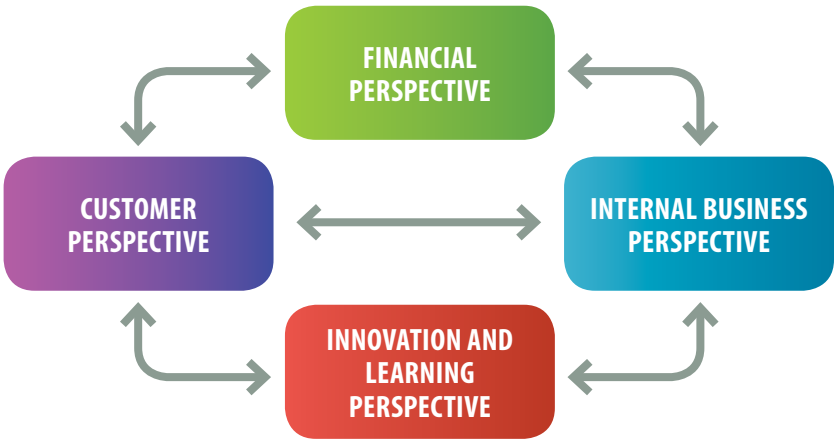
TABLE 1: The Terminology of Measurements, Metrics, and KPIs

Item	Description	Example
Measurement	Concrete, usually measures one thing, usually quantitative	Total number of research coordinators
Metric	Informs qualities because of a reference to a baseline state	Coordinator retention rate
Key performance indicator (KPI)	A metric considered critical to inform the success of a process or function	Coordinator satisfaction score
Balanced scorecard	A cluster of KPIs deemed to be the balancing point of ultimate success in the organization	Net profit margin Employee satisfaction % enrollment goal attainment % error rate
Lagging indicator	A metric that provides historical data and the ability to affect change in the future only	Net profit margin
Leading indicator	A metric that provides present data and the ability to affect change in the present condition	% error rate

Kaplan and Norton argued that a balanced scorecard consists of four distinct perspectives (see Figure 1 for a simplified visualization). These are the customer perspective, financial perspective, internal business perspective, and future perspective (innovation and learning). The balanced scorecard allows us to see when we're improving in one area at the expense of another, and it provides us with an ability to see where all of our important domains are maximized.

That Kaplan and Norton used four domains is irrelevant. Additionally, the four domains that they chose are less relevant than the domains that are pertinent specifically to any given industry (see Table 2 for some possibilities). For example, Southwest Airlines is renowned for putting its employees first, and certainly would list the employee perspective as one of its domains in a balanced scorecard.

FIGURE 1: Simplified Balanced Scorecard



All too often we implement processes and walk away. We often simply make the assumption that the processes will work. It is far too seldom that we take the time to then study the intervention, measure the results, and evaluate the effect on our other processes.

Suffice it to say that each business needs to choose which perspectives are most important in its unique case. Four balanced perspectives may be a good recommendation, but three or five would work just as well. Each of these perspectives should be tied directly to a mission-critical strategy of your organization.

A Few Words of Caution

First, just because we can measure something doesn't mean that we should. It's very easy to allow ourselves to begin measuring just about everything in our surroundings. Always ask yourself why you are measuring something. If the thing you're measuring is not directly linked to some mission-critical performance factor, consider stopping that measurement.

Measuring things takes time and effort from you and your team; be cautious not to focus that time and energy where there is little benefit. Determine in advance what your desired outcome is. What needs to be measured in order to monitor and improve performance on the desired outcome?

Sometimes, what really needs to be measured can be difficult. There's a tendency to measure what's easiest, and "the easy to measure drives out the hard, even when the latter is more important."[4] The thing you really should be measuring may not be the easiest. If you have the capabilities to measure the right thing, always do so.

Second, always be wary of unintended consequences, since "human beings adjust behavior based upon the metrics they're held against."[5] If the only thing you speak with your team about is enrollment, your team members will likely pay more attention to enrollment numbers than they will to the quality of the data. You will also increase the likelihood of fraud at your site. Fraud is rare, but if all you focus on is enrollment, then the risk of fraud in your organization will be higher than an organization that focuses on quality. It's an unintended consequence of a narrow focus on enrollment.

TABLE 2: Possible Domains of Importance to a Business

Sample Domains	
Customer Domain	A site's customers are sponsors and CROs. What KPIs ensure these customers are satisfied? Better yet, what KPIs ensure that the customers are ecstatic with the site's services?
Internal Domain	How does one know that a business is functioning at its highest capability and in a fashion that ensures long-term success? This domain can be where the business leader focuses on his or her team, if the feeling is that an exceptional team is key to the business strategy.
Financial Domain	What KPIs ensure the maximum financial health of the business or business unit?
Vendor Domain	To be successful beyond research considerations, a site needs to provide exceptional service to the remaining medical community and to that community's patients. What should be focused on to ensure value is provided to this domain?
Innovation Domain	As the saying goes, "If you aren't growing, you're dying." Businesses need to continuously innovate and adapt to remain healthy. What should your organization be focusing on?

A Site's Balanced Scorecard

Let's design a balanced scorecard for a research site.

1) WHAT ARE OUR MISSION-CRITICAL DOMAINS?

These domains need to take into account all stakeholders and the site's strategy. After choosing your domains, you should be able to confidently state that a balanced strategy to win in all the domains chosen maximizes your success. If you can still come up with a scenario where you can fail at your strategy, then consider whether you have chosen a balanced collection of domains.

2) WHAT ARE THE MOST SIGNIFICANT KPIs TO MEASURE WITHIN EACH DOMAIN?

To choose your KPIs, first consider what the functional areas touching this domain are in your operating model. Next, decide what result or outcome you wish to achieve in each area, and think about the activities or actions that drive that result. Finally, identify the measurements or metrics that let you know that the right activities are being performed, and that the right outcomes are resulting.

As stated at the beginning of this article, research sites are hired by sponsors and CROs to do one thing and one thing only—produce high-quality data. To produce data, sites need to recruit patients, and it is mission-critical that customers be served well. Therefore, the customer perspective should be part of the balanced scorecard, and should contain KPIs regarding enrollment numbers and data quality.

A sample KPI regarding enrollment numbers could be *percent of time achieving sponsor goal enrollment,* and a sample regarding the quality of the data would be the *percent error rate.* Now, the percent of time achieving sponsor goal is, by default, a lagging indicator, since you can only calculate that once goal enrollment was achieved. If the enrollment window closed prior to achieving goal enrollment, you no longer have any ability to intervene regarding that specific research trial.

Your percent error rate, however, can be tracked in real time. That makes it a leading indicator, allowing you to intervene and improve the quality of the data within an existing research trial prior to that research trial ending. For example, if you see that your percent error rate is unacceptably high in a given research trial, that enables you to drill deeper into that trial and try to determine the reasons why. Are the error rates higher because of trial complexity? Is there confusion regarding interpretation of the protocol? Do the staff site members require retraining?

Additional KPIs pertinent to your customers could include *total enrollment % of goal across all studies, % sponsor repeat business,* or *customer satisfaction rate.* What is important is that you choose where you want to focus. You can't be all things to all people. How do you want to best serve your customers?

The financial domain is certainly necessary for a research site's balanced scorecard. Research is financially challenging for sites; ignoring this domain could be perilous. Repeat the process above to choose the KPIs you believe will maximize the financial health of your organization.

On the other hand, a research site only paying attention to its financial perspective can produce a very short-term view of performance. That site may immediately improve its gross revenue and net income by taking on as many trials as possible, and by processing as many patients as possible through those trials. That site may maintain a lean staff size to further enhance its financial profit, but it's reasonable to assume such a model would run the risks of increased error rates, lower subject satisfaction, and increased employee turnover due to the overly lean staff size. The long-term view of performance could therefore show that site's model as being ultimately flawed.

The internal perspective can't be ignored. It would include KPIs regarding employee engagement, payroll, or perhaps length of employment. If your business, for example, determines that your more senior research coordinators consistently produce higher quality data and higher levels of subject recruitment, then it would be reasonable to create a strategy for your business regarding methods to increase the number of senior research coordinators. Your KPIs regarding this strategy would fall into this internal perspective.

However, if you want to compete for research trials on cost, then perhaps you need to keep your payroll costs as low as possible, and should choose different KPIs to help guide you in achieving your strategy.

Now it's Your Turn

You need to do the work from here. All sites and all strategies are different. Therefore, site leaders cannot all use the same balanced scorecard and the same KPIs to achieve their strategies. You need to use the processes discussed to determine your balancing point, and how you will research your own outcomes to know with certainty that you are balancing your success.

The balanced scorecard allows you to bind your short-term activities to a longer view on performance. Once you've initiated a balanced scorecard in your organization, this scorecard will alter the foundations of how you run your business.

Your scorecard translates your mission, vision, and strategy into operational metrics. Your scorecard will alter what you speak about in your meetings. It will increase alignment throughout your organization, so that your entire team is rowing in the same direction at the same time. Your scorecard will affect business planning so that financial budgeting is in alignment with strategic goals. It will create a mechanism for continuous improvement and your organization will have improved levels of learning.[6] You will have achieved the ability to research your own activities as well as you research investigational products, medications, and devices.

Conclusion

As clinical researchers, we measure things for a living, and yet as leaders of sites, small CROs, and small sponsor companies, we are amazingly poor at measuring our own behaviors. However, measuring our own behaviors is the only path to continuous improvement.

A balanced scorecard provides us with the capability to maintain a long-range review that integrates the perspectives most critical to long-term success. Focusing strongly on one perspective—and one perspective only—can produce outsized results for that perspective, but it's unacceptable to allow your other critical perspectives to suffer.

The ultimate win is achieved when you are able to maximize performance throughout your balanced scorecard. To do that, you need to push evenly in each of the domains you deem critical. As you improve one domain, others may slip a little in their optimal range. As you improve others, you may lose ground on your first; but remember the Hawthorne effect.

If we pay attention to all of our mission-critical perspectives, we will continue to make incremental improvements in each, and we will ensure that our end results are the healthiest they can possibly be.

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Strategies for Defining Key Performance Indicators in Research

PEER REVIEWED | Priti Sahai, MD | Rashmi Sahni, PhD

[DOI: 10.14524/CR-16-0010]

Few people would argue that clinical research provides value with respect to gaining a better understanding of diseases, driving innovation, identifying novel therapies, and improving quality of patient care. Recent years have seen steady growth and significant changes in the clinical research domain. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the pharmaceutical industry has invested more than half a trillion dollars in research and development since 2000, and more than 5,000 drugs are in development in the United States alone.[1]

With growth and change comes additional complexity. Protocols now have an increasing number of touchpoints and data variables; as of 2012, a typical protocol averages 13 endpoints and 167 procedures.[2] Studies are under more scrutiny than ever before, and there are an increasing number of regulations with which researchers need to comply to avoid receiving, for example, Warning Letters or Form 483 findings from U.S. Food and Drug Administration audits and inspections.[3]

The new regulations and scrutiny have resulted in an increased demand for approaches and solutions that improve efficiency without compromising quality. Key performance indicators (KPIs) that bridge the gap between strategies and results are integral to ensuring efficiency. While sponsors and contract research organizations (CROs) have made targeted efforts to establish KPI programs that help optimize clinical trial processes, costs, and timelines, the efforts at research sites have largely been sporadic and unsystematic.

This paper discusses strategies and best practices for developing a program at research sites that enables an organization to monitor research processes and outcomes in an efficient and effective manner. Using particular examples, this paper demonstrates that even as research site staff learn to carefully review KPI portfolios established by sponsors and CROs, they need to define and leverage context-specific KPI targets.

The Growing Importance of Effective Monitoring

There is a growing interest in KPIs, with many organizations either having implemented them already, or struggling now to implement them, or being keenly interest in doing so, but unsure how to proceed. Even with increasing awareness regarding metrics and KPIs, unanswered questions abound at these sites: What metrics should one measure? What KPIs would have significant impact on clinical research? What should one do after collecting the measurements?

No matter where a site stands with respect to KPIs, it is first important to understand the basics.

By definition, a metric is a standard of measurement, which may or may not involve a value (e.g., while accrual metrics involve numbers and absolute value, compliance metrics only indicate quality). Collecting metrics is only a starting point of a KPI program, as every metric is not necessarily a KPI; but what exactly is a KPI?

LEARNING OBJECTIVE
After reading this article, participants should be able to recall a few strategies for identifying relevant KPIs in research, and to use them for developing a KPI program that benefits a particular research site.

DISCLOSURES
Priti Sahai, MD;
Rashmi Sahni, PhD:
Nothing to disclose

A KPI is a type of metric that takes into account business values, context, and strategies. As Wayne Eckerson puts it, a KPI "is a metric that embeds performance targets so organizations can chart progress toward goals."[4] In other words, a KPI is a composite metric that is tied to targets and that indicates how an organization is performing relative to a specific objective.

For instance, if a site wants to improve accrual of patients in its clinical trials program, it can record the number of enrollments daily, monthly, or annually, whereby it obtains a metric. However, on its own, this metric doesn't give a sense of whether accrual targets were achieved, or how the site is performing over time.

On the other hand, if the site has its targets, but doesn't have the measurements that are required to give it a full picture, it is still no closer to monitoring its performance. A KPI, unlike a metric, would track screen failures and withdrawals, and check how accruals change over time.

A holistic KPI portfolio, involving composite and interconnected metrics, helps in leveraging measurements and monitoring ongoing processes for improving multiple facets of a clinical research program, including administrative, financial, clinical, and others.

So, What KPIs are Right for Me?

When initiating a KPI program, research sites often measure the wrong things—or end up measuring too much or too little—to be really effective. However, if site staff consider what KPIs are right for them seriously, they will be on the right track. Why? Because when it comes to KPIs, one size does not fit all, which is what makes finding the "right" approach a challenging process.

There is no standard way of developing a KPI program, and while site staff can learn from colleagues at other sites, they can't just copy what another site did without investigating whether it's right for their own particular needs. "What KPIs are right for me" does not mean that a site should ignore KPI portfolios developed by sponsors and CROs, or develop KPIs that correspond to subjective opinions. On the contrary, relevant KPIs for sites often align well with sponsor requirements, and are based on objective data.

"For me," however, is a call to make KPIs more context specific, and a reminder that the "one size fits all" approach does not work across sites. Indeed, a single KPI program often doesn't work across different types of trials, departments, and indications—even within the same organization.

Given the variety of disciplines, processes, and study designs associated with clinical research, it is important to have a holistic KPI program that takes into account different types of research and organizational goals. Furthermore, the staff of research sites need to look beyond their walls to ensure that their KPIs are aligned with the needs and goals of other stakeholders in the clinical research process, such as sponsors and CROs.

The overarching goal of all parties is to ensure optimal performance throughout the clinical trial process; to do this in an effective manner, the goal should be incorporated throughout the process, and not just upheld by specific entities or at specific time points.[5] Instead of seeking a magical number of metrics or attempting to create a list of universally useful KPIs, it is best to focus on strategies and considerations for designing a KPI program that works for an individual site today, but continues to evolve as the site's goals change over time.

Identifying Relevant KPIs

Determining relevant KPIs requires strategic planning and considerable effort. It is often tempting to select metrics that are the easiest to measure, but if they aren't the right ones for a specific site, precious time and effort will be spent on setting up a KPI program that doesn't yield results. As Abraham Lincoln famously said, "If I had eight hours to chop down a tree, I'd spend six hours sharpening my ax."

While there is support for the theory that measuring something provides motivation to make it better, there is also evidence to support that "every metric, whether it is used explicitly to influence behavior, to evaluate future strategies, or simply to take stock, will affect actions and decisions," and the end result may not be what an organization had hoped for.[6]

Picking up on the earlier example of accruals in a clinical trials program, let's say a site defined a KPI to track study enrollments across its entire research portfolio, and that it started showing a positive upward trend. Well, one may conclude that the KPI worked, and that the site is reaching its overall goal. Unfortunately, this is not entirely true.

The success of the KPI depends on what the site's overall goal was—if it was to simply increase the number of enrollments, then yes, the KPI worked.

New regulations and scrutiny have resulted in an increased demand for approaches and solutions that improve efficiency without compromising quality. Key performance indicators (KPIs) that bridge the gap between strategies and results are integral to ensuring efficiency.

TABLE 1: Dos and Don'ts for Identifying Successful KPIs

Do	Don't
✔ Identify the program's objectives before developing KPIs.	✖ Start with a consideration of metrics that are easy to track, but which may have no correlation to the overall objectives.
✔ Identify who will consume the results and how they will be communicated.	✖ Focus only on catching deviations, but rather look for information that will help to plan and avoid issues.*
✔ Be proactive in planning how the KPIs will be utilized to fulfil the program's objectives. This will ensure that the metrics are validated for effectiveness well before an organization collects and monitors more of the same.	✖ Monitor each and every metric, as it can create a lot of "noise" and become resource intensive; instead, focus on a select few that tie to the overall program goals.

** Joy Baker suggests that "best indicators assist in problem solving and lead to preventive actions (e.g., prevention of patient falls) rather than corrective actions after an incident or episode has occurred."[7]*

There is a growing interest in KPIs, with many organizations either having implemented them already, or struggling now to implement them, or being keenly interest in doing so, but unsure how to proceed.

However, if it was to increase the number of accruals (subjects who have completed or are completing a study) in order to have more successful study outcomes, then the site should also be tracking the numbers of consent withdrawals, screen failures, dropouts, and other early terminations to know whether there is an actual increase in accruals.

Table 1 summarizes some key dos and don'ts to keep in mind while identifying relevant KPIs.

Gathering Accurate Data

Even though there is no simple formula for determining relevant KPIs, experts recommend selecting KPIs based on data and variables that can be measured objectively and avoiding signals that are based on subjective qualifiers.[8] Besides realizing that KPIs are important to manage a more effective clinical research program, most sites should also recognize the need to have defined processes and accurate systems to obtain the data to support an effective monitoring program.

Having identified what one wants to measure, the next important step is to define the KPIs, including identifying sources of information. What makes the need to define KPIs critical is that often the data being monitored are in multiple systems, which are not harmonized in terms of their meaning or are not being collected in a consistent manner.

For example, it is not unusual to have many different interpretations applied to an "active" trial, or variations in how individuals or departments define the date that their trial became "active." If there is no standard way of interpreting this, then any KPI based upon time to activation would not be accurate or reliable. It is important, therefore, to make sure that site staff not only identify all of the KPIs to be used, but also provide accurate definitions for all to ensure clarity in communication and decision making.

Once KPIs have been identified, the logical next step is to figure out how the metrics will be captured and tracked. Many organizations have a clinical trial management system that captures critical data in a more consistent and reliable manner. In addition, sites may need to collate these data with data from other systems such as the electronic health record, institutional review board (IRB), or financial systems at the sites. While implementing these systems, organizations should take into account the adaptability of systems for capturing key metrics that will assist them in tracking their KPIs, and in being interoperable with other systems.

Utilizing Your KPI Program—A Continuous Process of Learning

It is not unusual to come across sites where staff have put a tremendous amount of thought and effort into identifying relevant KPIs and gathering accurate data, and yet they failed to realize benefits from the entire process. Launching a KPI program deceptively gives stakeholders the sense that capturing and monitoring the metrics is automatically going to help improve performance. Usually the failure to realize benefits can be traced back to a lack of planning in how to act upon the results from monitoring KPIs.

Figure 1 depicts how multiple components work together in the design of a holistic KPI program. The interconnected cycles indicate the significance of timely communication and implementation of findings.

Results of the information collected from the KPI program should be visible to all relevant stakeholders. It is equally important to rapidly implement findings from constant monitoring of KPIs. Through the timely implementation of findings, one can continue to validate one's discoveries and incorporate improvements into a continuous process of learning.

Meanwhile, what exactly does timely implementation of KPIs look like and what are its outcomes? Mark Donaghy provides valuable advice on when to incorporate performance metrics in a research program: "Performance metrics are the project management version of the data and analysis in a longitudinal clinical study. …Performance metrics programs produce the best results when established in the design phase of a clinical study. Application of the Deming Cycle (Plan – Do – Check – Act) encourages a planned, systematic, and explicit alignment of study endpoints with objectivity in performance data collection and analysis."[9] Donaghy reminds us

of the importance of building a performance metrics program before undertaking any major activity within a clinical trial.

The significance of measurement and monitoring of KPIs can be further demonstrated with concrete examples. It is well acknowledged that site staff want to track turnaround times in their study activation process. For instance, sites might want to measure the time to IRB approval or time to contract execution. In such cases, having a single number with an upward or downward trend isn't entirely helpful, unless there is an analysis associated with it and an appropriate plan for action.

Only analysis can shed light on the data that have been tracked. An organization, for example, might find out that the time to approval is increasing because of an influx of a large number of trials at the site, which would necessitate looking at the staff allocation ratio and improving it. Alternatively, an organization might learn that the increasing timeframe is due to numerous back-and-forth messages and incomplete submission packages, which, in turn, would call for action in improving the process for submission.

Another likely explanation is that the overall number is skewed because of a specific process instituted for early-phase studies, which would call for a closer look at that new process. Having the information available at one's fingertips helps identify the exact problem area and takes the guesswork out of it. Furthermore, timely action and ongoing monitoring of KPIs ensure that the learning process can continue to occur, and that an organization can show improvement in weeks and months rather than in years.

FIGURE 1: An Effective KPI Program – A Continuous Process of Learning

Conclusion: The Big Picture

Finally, it is important to remember that developing a KPI program is not a strategy unique to the research community. "Advancing research, scientific knowledge, and innovation," was specifically called out as one of the five major "Collect-Share-Use" goals in the *Federal Health IT Strategic Plan 2015-2020* released by the U.S. Office of the National Coordinator for Health Information Technology as part of the Health Information Technology for Economic and Clinical Health (HITECH) Act.[10]

Interestingly, the HITECH plan's other four goals, emphasizing the need for healthcare organizations to develop a holistic plan that integrates clinical and research perspectives, also have a direct or indirect links to clinical research. By incorporating KPIs that not only improve sites' financial and operational performance in clinical research programs, but also attend to clinical outcomes and research programs' integration with point of care, healthcare organizations will truly begin to realize the potential of translational research, and ultimately bridge the divide from bench to bedside.

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Are Performance Metrics About Doing the Right Things or Simply Doing Things Right?

PEER REVIEWED | Linda Sullivan, MBA

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National Public Radio's (NPR) *This American Life* in 2010 told an eye-opening story of General Motor's (GM) awakening to Japanese competition that was storming the automobile industry in the early 1980s.[1] The story focused on well-worn facts, namely, that at the time, GM was producing cars of questionable quality and poor resale value, whereas Toyota was turning out highly reliable cars and ultimately stealing massive market share (GM's market share fell from 77% in 1980 to 45% in 2009).[2]

The NPR tale tells of a culture of faster, faster, faster at GM plants, with little emphasis on quality, whereas the Japanese plants adopted the reverse philosophy—making quality its hallmark. Time and cost were critical factors for the Japanese automaker, and they were meticulously measured and scrutinized, but quality was never sacrificed to meet those benchmarks.

To the astonishment of American executives and workers sent to Japan to learn the Toyota way, Japanese line workers were able to stop the line at any time to prevent a problem from happening, or to immediately fix one that had just happened. The one cardinal rule in GM plants was to NEVER stop the line, ever. Doing so would likely result in a firing, because after all, poorly made cars would be fixed in the rework area. Interestingly, Toyota plants did not have a rework area—one wasn't needed. Moreover, Japanese cars were produced faster and at lower cost.

This story could be a parable for the current status of metrics in the clinical trials sector, an industry in need of transformation[3] and a re-imagining of how success should be defined and measured in an effort to improve study quality. In keeping with that theme, this article describes how stakeholders are changing how they do things for better execution of the many steps that produce quality clinical trials, as measured by standardized performance metrics.

This article also discusses the direction that regulatory agencies are taking to encourage greater risk mitigation and management techniques from the beginning of clinical trials to improve operations. Ultimately, what follows asks the question: Are we simply using performance metrics to determine if we are doing things right (according to the plan), or are we using metrics to improve the plan—doing the right things—from the beginning?

Critical Success Factors

Performance metrics based on standardized definitions are new to the world of clinical trials. Stakeholders have long maintained company-specific metrics, such as the percentage of clinical trials within a program meeting enrollment targets or the amount of time needed to lock a database, but in the interest of better study execution, industry-wide, standardized definitions are required. Such definitions have been lacking, making industrywide research difficult and creating confusion when different stakeholders attempting to collaborate have dissimilar definitions for similar functions.

The Tufts Center for the Study of Drug Development (CSDD) recognized this problem nearly two decades ago, when it presented findings from a workshop on the importance of using standardized performance metrics across the industry to benchmark productivity and motivate excellence among staff.[4] In its report, the center also noted that metrics are most effective when they help stakeholders look at the "big picture" and the overall trends, which is a departure from the continual practice

LEARNING OBJECTIVE
After reading this article, participants should be able to describe how to use a structured approach to determine the right metrics for improving clinical trial planning and execution.

DISCLOSURES
Linda Sullivan, MBA:
Nothing to disclose

of focusing on one particular metric or a group of metrics that may not lead to better performance.

Looking at the big picture, or more specifically, aligning performance metrics with critical success factors and key performance questions (KPQs) is the next horizon. This approach is fundamental to how the Metrics Champion Consortium (MCC), an industry group founded in 2006, operates. MCC brings stakeholders together to define standardized performance metrics, and helps identify what to measure and how to use those measurements to drive process improvement and mitigate risk, all by measuring the right things. This is a major departure from "measuring things right"—in check box fashion—simply because that is how it has always been done.

To start, MCC considers the concept of the critical success factor as the foundation, referring to what an organization must do to achieve desired outcomes and ensure successful competitive performance. Massachusetts Institute of Technology's Sloan School of Management is credited with developing this strategic approach in the late 1970s to help organizations seriously consider what is needed to improve operations. In a classic article in the *Harvard Business Review,* John Rockart describes the need for a critical success factor, as without it, executives are generally overwhelmed with data that are of little use in making critical management decisions.[5]

For the clinical trials industry, there are numerous critical success factors that focus on measuring the right things (see sidebar). One example is the expectation that all studies will have more than 85% of sites enrolling more than one subject (see Table 1). Once the critical success factor is determined, KPQs that align with organizational roles and responsibilities—such as those at the executive, program, and study team levels—can be developed. KPQs should provide insights about factors in a process that help users achieve success, processes, and/or data that need to be managed to ensure success, and recognize problem areas that need to be improved or fixed. Good KPQs include time, quality, and cost/efficiency performance aspects, and provide information to make decisions.

Specifically, at the executive level, a KPQ might be: What portion of studies within each program has 15% or more of sites enrolling fewer than two subjects? Table 1 shows other examples of KPQs for this critical success factor, along with metrics designed to answer them.

The metrics for this critical success factor and others were developed by MCC, which offers an array of peer-vetted, standardized performance metrics for clinical trials, laboratory, and imaging. Importantly, these metrics reflect what stakeholders want to measure, namely factors related to time, cost, and quality. Much like the automobile parable, however, stakeholders tend to overemphasize time-related metrics at the expense of quality, which often results in increased risk for rework as a clinical trial unfolds.

Critical Success Factor

"…the limited number of areas in which results, if they are satisfactory, will ensure successful competitive performance for the organization. They are the few key areas where 'things must go right' for the business to flourish. If results in these areas are not adequate, the organization's efforts for the period will be less than desired."

—John Rockart[5]

In the clinical trials sector, rapid drafting of the study protocol is a good example of a task where satisfying time-related metrics is highly valued. The protocol development team is rewarded for completing the protocol by a specified time, but does the protocol meet a set of quality requirements? When organizations do not assess protocol quality during the development phase, it is difficult to know. Furthermore, not including a quality measurement sends a message to the protocol development team that quality is not important.

With this scenario, it is not surprising that protocols often need rework, possibly amendments, within 30 days of completion. There is also an increased risk for an expanded timeline and budget. Mitigating or avoiding this situation—doing the right thing—may involve crafting a critical success factor that acknowledges the level of complexity of today's protocols.

By comparison, relying mostly on time-related metrics—doing things right—may show that monitors are behind schedule in completing study reports, but this approach is unlikely to address why they are behind. It could be the fault of a challenging protocol, which may be better detected by quality metrics used from the start. This is a key consideration, given that Tufts CSDD research shows that protocols, the basis of clinical trials, are increasingly complex.

In a typical Phase III study, Tufts CSDD found that the total number of endpoints rose to 13 in the 2011–15 timeframe as compared to just seven a

Critical Success Factors that Focus on the Right Things

- All studies have more than 85% of sites enrolling more than one subject
- Develop a quality protocol in a timely manner
- Use quality sites that deliver clean data in a timely manner while following GCP compliance regulations
- Ensure that sites have drugs and other clinical supplies onsite when needed
- Collect/Analyze safety and endpoint data required for submission
- Monitor and respond to subject safety events in a compliant manner

Source: Metrics Champion Consortium

TABLE 1: Key Performance Questions (KPQs) and Metrics at Different Levels

Critical Success Factor: All studies have more than 85% of sites enrolling more than one subject

Organizational Level	KPQs	Metrics that Answer the KPQs
Executive	What portion of studies within each program has 15% or more of sites enrolling fewer than two subjects?	Percentage of studies where 15% or more sites consent fewer than two subjects/ program
Program	What portion of sites from each study in the program has enrolled fewer than two subjects?	Percentage of sites in each study that have consented fewer than two subjects
Study Team	What portion of sites in the study has enrolled fewer than two subjects?	Percentage of sites in the study that has not consented at least two subjects

Stakeholders are changing how they do things for better execution of the many steps that produce quality clinical trials, as measured by standardized performance metrics.

decade earlier. Similarly, the total number of procedures jumped to 163, up from 97 in the 2001–05 time period.[6] With this big change, amendments are mounting up, and are costly.

Research indicates that sponsors implement at least one substantial global amendment for nearly 60% of all clinical trial protocols, which tends to reduce the number of patients enrolled. However, the tactic also extends clinical trial durations and costs to the point of averaging $141,000 for a Phase II study and $535,000 for Phase III.[7] The high cost of quickly made protocols plus subsequent amendments highlights the importance of seeking balance among time, cost, and quality metrics, all in an effort to influence performance and avoid rework.

Emphasis on Quality and Regulatory Influence

The emphasis on doing the right thing aligns well with industry efforts and guidance from regulatory agencies. In the past few years, agencies have released guidances and regulations focusing on ways to be more strategic about study planning and execution. Much of this effort encourages stakeholders to focus on quality from the beginning of clinical trials, rather than relegating it to a costly afterthought.

Interest in quality metrics started gaining traction several years ago, with input from MCC and from the Clinical Trials Transformation Initiative (CTTI), a collaboration between the U.S. Food and Drug Administration (FDA), Duke University, and multiple member organizations. CTTI launched its first Quality by Design workshop in 2011, with the intent of incorporating quality and risk management principles into clinical trials, similar to what had already become standard practice in other areas of drug development.[8] In particular, there was a strong focus on becoming proactive regarding the objectives of a clinical trial and the defining factors critical to meeting those objectives. This entailed gathering the right data, so stakeholders could take action to prevent or mitigate risks that could negatively impact study execution.

In 2013, the concept of assessing and mitigating risk was further advanced when the industry group TransCelerate Biopharma Inc. released the Risk Assessment and Categorization Tool (RACT).[9] The RACT framework provides organizations with a standardized means of assessing project-and protocol-level risk and quality before conducting studies.

Building on the RACT framework, MCC has taken a particularly comprehensive view of quality metrics as key to avoiding or mitigating risk. The MCC Risk Assessment & Mitigation Management Tool provides an approach for risk assessment, risk mitigation, and issue management.[10] Figure 1 details MCC's risk management process, which starts with conducting a protocol assessment, followed by gathering data for risk identification.

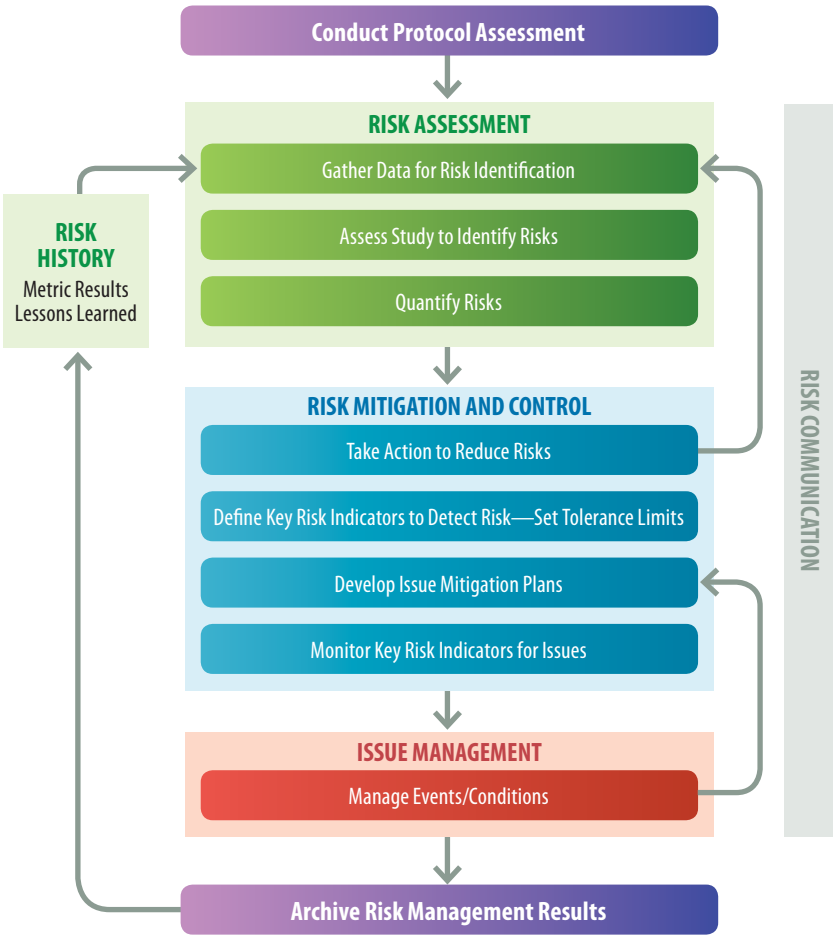
This MCC framework is rooted in a 2013 Reflection Paper from the European Medicines Agency (EMA).[11] In that document, the EMA describes the necessity of incorporating risk-based quality management at a very early stage in a clinical trial. Also, protocol design, use of technology, and other issues are deemed particularly important to mitigating risk. In that same year, FDA released its guidance on risk-based monitoring, stating that sponsors should be prospective in understanding the risks that could affect data collection and performance of critical processes, and in identifying critical data and processes.[12]

The next horizon is happening in November 2016, when the International Conference on Harmonization (ICH) E6(R2) guideline is expected to be released.[13] It is intended to replace the widely used R1 guideline implemented in 1997, which is commonly known as the Guideline for Good Clinical Practice (GCP). The intent of R2 is to keep pace with the changing scale and complexity of clinical trials, and to ensure greater use of technology to modernize approaches toward clinical trial design, conduct, management, oversight, and documentation to enhance human subject protection and data quality.

R2 will include many changes, with Section 5—Quality Management—particularly noteworthy. It stresses the sponsor's responsibility to ensure operational feasibility, avoidance of unnecessarily complex protocols, and efficient design of clinical trials.[14] It also states that the quality management system should use a risk-based approach. For example, risk mitigation activities may be incorporated into protocol design and implementation, and into monitoring plans.

With the implementation of R2, the clinical trials sector is expanding its interest beyond quality metrics to include risk indicators, and eventually, to predictive indicators. The new guideline will have far-reaching consequences, as risk management processes will become the core of clinical trial operations.

FIGURE 1: Metrics Champion Consortium Risk Management Model



Source: Metrics Champion Consortium (2015), adapted from EMA Reflection paper on risk-based quality management in clinical trials (EMA/269011/2013)

Doing the Right Things

Making improvements to clinical trial operations is all about asking the right questions. Is the protocol feasible? How do we select quality sites that can produce clean data? These are critical success factors for helping stakeholders look at the big picture, and if properly addressed, they help ensure better clinical trial execution.

For too long, the industry has repeated older processes, which tended to focus on measuring speed of operations while reining in costs. It has largely been a box-checking exercise to determine if stakeholders were doing things right (according the plan), without considering if they were doing the right things.

Because data continue to show that transformative action is needed, a newer approach is gaining traction—one built on a structure of critical success factors followed by key performance questions and metrics that answer them. This methodology is being supported by regulatory influence, all in an effort to move the needle toward process improvement and less rework, saving time and dollars, while improving study quality.

The high cost of quickly made protocols plus subsequent amendments highlights the importance of seeking balance among time, cost, and quality metrics, all in an effort to influence performance and avoid rework.

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HOME STUDY HS

The Evolving World of Metrics

OPEN BOOK TEST

This test expires on August 31, 2017

(original release date: 8/1/2016)

Measurements, Metrics, and KPIs: Achieving a Balanced Scorecard

1. **Per the article, metrics matter because of which of the following:**

1. The Hawthorne effect
2. Improving one process will frequently make a second process worse
3. Measuring things is fun
4. Leading indicators give us the ability to affect change in the present condition

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

2. **Per the article, a "balanced scorecard" for a research site can be defined as:**

A. A cluster of key performance indicators (KPIs) where profit is balanced with employee needs
B. A group of four KPIs prescribed by Kaplan and Norton in 1992
C. The collection of KPIs that look at the health of your organization from multiple different perspectives at the same time
D. A group of metrics that provide present data and the ability to affect change in the present condition

3. **A lagging indicator is:**

A. A metric that provides present data and the ability to affect change in the present condition
B. A metric that takes a long time to calculate, but is critical to the overall study success
C. A metric that provides historical data and the ability to affect change in the future only
D. A metric considered critical to inform the success of a process or function

4. **Which of the following are considered examples of metrics?**

1. Coordinator retention rate
2. Revenue per year
3. Miles per gallon
4. % error rate

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

5. **Which of the following is an example of a leading indicator?**

A. Miles per gallon
B. Net profit margin
C. % error rate
D. % enrollment goal attainment

6. **Besides the capture of evidence of improvements gained in particular areas at the expense of others, what other "ability" does a balanced scorecard allow?**

A. The ability to see where all of our important domains are maximized
B. The ability to place our customers' needs above all other needs
C. The ability to affect change in the present condition
D. The ability to measure metrics that are difficult to measure

7. **According to Kaplan and Norton, the "domains" of a balanced scorecard are:**

A. The different addresses where research activities are performed
B. Of little importance because they are different from business to business
C. Financial, internal, customer, and innovation and learning perspectives
D. The different perspectives of your business that you feel are mission critical

8. **The unintended consequences of holding people accountable to metrics can include which of the following:**

1. Unethical behavior because enrollment is the only critical metric
2. Financial failure because quality is the only critical metric
3. Employee longevity because employee satisfaction is the only critical metric
4. Improved quality outcomes because profitability is the only critical metric

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

9. **Which of the following is the best strategy to follow when choosing KPIs to measure within each domain?**

A. Measure the metrics that are the easiest to measure in the area
B. Identify metrics that let you know the right outcomes are resulting from the right activities
C. Measure the same metrics that the other sites do in our industry
D. Measure as many metrics as possible across the entire business model

10. **Benefits of a balanced scorecard include:**

1. Increasing alignment throughout your organization
2. Increasing alignment of financial budgeting with strategic goals
3. Increasing focus on employee needs over those of financial performance
4. Creation of a mechanism for continuous improvement

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

Strategies for Defining Key Performance Indicators in Research

11. **An increase in demand for KPIs in research can be attributed to:**

A. Marketing campaigns
B. More contracts and agreements
C. New regulations and scrutiny
D. Mounting social pressure

12. **An effective KPI program can potentially:**

A. Increase clinical trial costs
B. Optimize clinical trial processes
C. Extend the clinical trial duration
D. Elevate risks of doing studies

13. **A KPI is a type of metric that takes into account which of the following?**

1. Opinions
2. Business values
3. Context
4. Strategies

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

Find the most current online test at **www.acrpnet.org/homestudy**, including any revisions made after publication of this issue of *Clinical Researcher*.

14. **It is challenging to develop an effective KPI program because:**
1. One can't just copy KPIs defined by others
2. Sponsor requirements need to be assessed
3. Standard processes and designs already exist
4. A vast variety of trials and departments exists

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

15. **A holistic KPI portfolio is characterized by:**
1. Composite and interconnected metrics
2. The ability to monitor ongoing processes
3. An unlimited number of metrics
4. A variety of subjective inputs

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

16. **Which of the following are best practices for identifying successful KPIs?**
1. Identifying a program's objectives
2. Monitoring each and every metric
3. Identifying how results will be communicated
4. Maintaining a constant focus on catching deviations

A. 1 and 3 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 2 and 4 only

17. **While capturing and tracking metrics in research, it is important to:**
A. Create more Excel templates
B. Use interoperable systems
C. Employ additional staff
D. Get feedback from patients

18. **Why do sites often fail to realize the benefits of their KPI programs?**
1. Research site staff don't put in the required effort
2. Absence of timely communication
3. Carelessness or nonchalant attitude
4. Failure to implement findings

A. 1 and 2 only **C.** 2 and 4 only
B. 1 and 3 only **D.** 3 and 4 only

19. **For the best results, when should a performance metrics program be established?**
A. In the design phase of a clinical study
B. When randomized controlled trials are in progress
C. When a new treatment works well
D. While selecting patient populations

20. **One of the five major "Collect-Share-Use" goals noted in the *Federal Health IT Strategic Plan 2015–2020* is:**
A. Sharing electronic health information in the public domain
B. Advancing research, scientific knowledge, and innovation
C. Banning the use of health IT products
D. Promoting quantity over healthcare quality

Are Performance Metrics About Doing the Right Things or Simply Doing Things Right?

21. **A lack of standardized performance metric definitions can:**
1. Make industrywide research difficult
2. Create confusion for collaborating stakeholders
3. Enable industry benchmarking
4. Improve stakeholder communication

A. 1 and 2 only **C.** 2 and 4 only
B. 1 and 3 only **D.** 3 and 4 only

22. **According to the Metrics Champion Consortium, an approach that results in measuring the right things includes aligning which of the following?**
1. Critical success factors
2. Key performance questions
3. Performance metrics
4. Risk indicators

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

23. **When aligned with critical success factors and key performance questions, what do metrics provide?**
A. Valuable insights
B. Uncategorized information
C. Worthless data ranges
D. Unverifiable opinions

24. **According to John Rockart, the few key areas where "things must go right" for a business to flourish refers to:**
A. Performance targets
B. Critical success factors
C. Key performance indicators
D. Key performance questions

25. **Key performance questions should align with which of the following?**
A. Executive-level roles and responsibilities only
B. Program-level roles and responsibilities only
C. Organizational roles and responsibilities
D. Study team–level roles and responsibilities only

26. **Key performance questions should provide insight about:**
1. Factors that help you achieve success
2. Processes that need to be managed to ensure success
3. Areas considered unimportant to achieving success
4. Problem areas that need to be improved or fixed

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

27. **Key performance questions should include which of the following aspects of performance?**
1. Time
2. Quality
3. Color
4. Cost

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

28. **Which of the following is a result of using a combination of time, cost, and quality metrics?**
A. Decreased rework
B. Some increase in rework
C. No change in rework
D. Substantial increase in rework

29. **Which of the following are components of a risk management model?**
1. Risk assessment
2. Recruitment
3. Risk control
4. Issue management

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

30. **The ICH E6(R2) guideline will emphasize the sponsor's responsibility to do which of the following?**
1. Ensure operational feasibility
2. Avoid unnecessarily complex protocols
3. Design efficient clinical trials
4. Monitor all datapoints

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

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Preparing Your Research Departments for HIPAA Audits by the Office for Civil Rights

For those who do not know, the U.S. Office for Civil Rights (OCR) is the organization that enforces the Health Insurance Portability and Accountability Act (HIPAA). Since HIPAA's inception, OCR has established complaint mechanisms and levied fines on organizations that are not in compliance with HIPAA in predominately a reactive manner. Recently, the office has been migrating to a more proactive enforcement of HIPAA through compliance audits, including a pilot phase of auditing about 115 covered entities during 2011–12.

OCR has now refined its audit policies/tools, and is ready to enter into a second phase of audits. As with the first phase, the next round of audits will focus on compliance with the HIPAA Privacy, Security, and Breach Notification final rules. Supporting documentation for details in the following three paragraphs can be found at www.hhs.gov/hipaa/for-professionals/compliance-enforcement/audit/index.html.

Getting Ready for the Next Round

To prepare for these audits, OCR is currently gathering information about the universe of covered entities and business associates out there. This is being done through e-mail blasting (the press release says "We expect you to check your spam and junk mail folders for OROCRAudit@hhs.gov"), giving the covered entities 14 days to respond to validate/update their designated contacts' e-mail addresses. Also requested is completion by the covered entities of a pre-audit questionnaire (about the entities' locations, sizes, types of organization, etc.), as well as a list of its business associates.

OCR is clear that lack of response to this e-mail does not alleviate the covered entity from audit. This collection of information, along with supplemental information gathered about nonresponders, theoretically gives OCR the universe of covered entities to select from for either for-cause or random audits. The office states that it intends to audit a "wide range of covered entities and business associates," implying that large or small, urban or rural, hospital or single physician office, etc., are all potentially auditable sites.

Essentially, if selected for an audit, your designated official will receive notification (likely via e-mail) from OCR of the audit. Your organization will have 10 business days to upload all the requested materials to OCR's website. OCR will perform a desk audit on the submitted materials, and may supplement that with an onsite audit as well. Your institution will eventually receive a draft audit report to which you will have 10 business days (if you choose) to respond prior to the report becoming final.

We don't have a lot of information of what OCR's intent is after the final report is published (i.e., will it require corrective and preventive action plans? Will it assess monetary penalties or fines at that time?), but we will undoubtedly learn as the second phase of audits continues.

The 419-page audit protocol (April 2016 version) is available at www.hhs.gov/hipaa/for-professionals/compliance-enforcement/audit/protocol-current/index.html, and while it addresses all aspects of HIPAA, Table 1 highlights the areas either directly governing research privacy/security or tangential to it. The table then describes expected risks germane to research operations.

As with the first phase, the next round of audits will focus on compliance with the HIPAA Privacy, Security, and Breach Notification final rules.

TABLE 1: Risks to Research Operations, by Audit Area

Audit Area	Sampling Of Research Operations Risks
De-Identification	Was that dataset you said was "de-identified" actually de-identified according to the HIPAA standards at 45 CFR 164.514 (b)(1)-(2) in the *Code of Federal Regulations,* or did you just call it "de-identified" because it did not have names/addresses/Social Security numbers on it? The most common errors here are the failure to eliminate all elements of date except for year, no geography other than a state (i.e., city, county/parish, neighborhood, "within 50 miles of X," etc.), no ZIP codes beyond the first three digits (unless according to the most recent U.S. Census the population of those first three digits is less than 20,000 people, in which you must replace them with "000"), no age if greater than 89 (which means either left blank or changed to a range such as ">89" or "90+"), and no free text fields that could reasonably re-identify the individual (e.g., "This person is our current President," "This is the mayor's wife"). See www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs_deid_guidance.pdf for guidance.
Limited Dataset	Did your dataset contain any elements not allowable under the HIPAA definition of a "limited dataset" at 45 CFR 164.514(e)(1)-(3)? Did you have the required Data Use Agreement (DUA) in place prior to disclosing the dataset? Did the DUA address each of the regulatory required elements by HIPAA at §164.514(e)(4)? See https://privacyruleandresearch.nih.gov/pr_08.asp#8d for more guidance.
Verify Identity of Those Who Request PHI	Prior to releasing protected health information (PHI) to a third party pursuant to authorization to do so by a patient, did you adequately verify (according to HIPAA requirements at 45 CFR 164.514(h)) that the person you were disclosing to was actually on the list in the authorization? According to the U.S. Department of Health and Human Services, "the covered entity must establish and use written policies and procedures. . .that are reasonably designed to verify the identity and authority of the requestor where the covered entity does not know the person requesting the protected health information." Did you verify the identity of the individual who showed up at your door as being the actual person (i.e., researcher or monitor) or representative of the company (or government agency) allowed to receive information? While this may be done by your information technology department if you are providing your monitor a username and password, what is the policy when providing "over the shoulder" access to PHI? See https://aspe.hhs.gov/report/standards-privacy-individually-identifiable-health-information-final-privacy-rule-preamble/section-164514h-verification-identity-and-authority-persons-requesting-protected-health-information for more information.
Login Restrictions	Have you given your monitor his or her own password to log into your electronic health record (EHR) system for source document verification (which ordinarily requires a written agreement with your institution)? If so, have the monitor (and the monitor's company) been trained/notified on your HIPAA policies (i.e., no sharing/recycling of the login ID even when the monitor changes)? Especially if the monitor can log in remotely, what are your policies to address change of your monitor? How do you promptly know that your monitor has resigned or been reassigned, so that you can delete his or her login access?
Research Authorizations	First, your authorizations must have all required elements. While institutional review boards (IRBs) are generally well versed in the U.S. Food and Drug Administration (FDA) and/or Office for Human Research Protections (OHRP) requirements for informed consent, rarely do they validate that a HIPAA authorization has all required elements. In fact, IRBs are not even responsible to assure this, according to OCR guidance. Second, data cannot be released outside those elements. For example, if the authorization says PHI will be accessed by CRO X and the sponsor changes to CRO Y, you cannot release identifiable PHI data to CRO Y because your signed authorization specified only CRO X. Assure that you are only releasing PHI in a manner consistent with the limitations of the individual's signed HIPAA authorization. See https://privacyruleandresearch.nih.gov/authorization.asp for more information.
Waiver of Authorization	Verify that when the requirement for an individual's authorization to disclose PHI has been waived by an IRB (or privacy board), the board can actually validate that all the HIPAA criteria for such a waiver were documented and have been met. All too often, IRBs waive research consent (when allowable under FDA and/or OHRP regulations), but forget (or are not asked) to waive the requirement of the HIPAA authorization. This is a problem if you are releasing PHI pursuant to a study. Also, if you are a covered entity that released PHI pursuant to such an IRB (or privacy board) waiver or authorization, can you provide documentation of that IRB (or privacy board) waiver? Did it have all the HIPAA requirements (i.e., the date of the waiver and signature of the IRB chair—not the IRB administrator or other party, but the chair)? See https://privacyruleandresearch.nih.gov/IRBandprivacyrule.asp for more information. Also, as will be discussed in a different section, did you appropriately update your "accounting of disclosures"?

If selected for an audit, your institution will eventually receive a draft audit report to which you will have 10 business days (if you choose) to respond prior to the report becoming final.

David M. Vulcano, LCSW, MBA, CIP, RAC

TABLE 1 (continued): Risks to Research Operations, by Audit Area

Notice of Privacy Practices	Your institution most likely has the HIPAA-required Notice of Privacy Practices to give to your patients, but are your research activities/disclosures consistent with this notice? Many researchers are surprised to find language such as "we will not sell your information to any third parties without your authorization," when their institution is actually doing so for research purposes. There are many things in this document that could impact your research use of data, therefore the document should be reviewed and revised accordingly.
Preparatory to Research and Research with Decedents	Access to PHI in the "preparatory to research" category is for items such as assisting in the development of a research hypothesis, preparing the protocol itself, preparing for a protocol such as feasibility, and/or aiding in research recruitment such as identifying prospective research participants who would meet the eligibility criteria for enrollment into a research study. When a researcher accesses PHI for purposes preparatory to research, the covered entity is required by HIPAA (at 45 CFR 164.512(i)(1)(ii)) to obtain representations from that researcher that 1) the access is solely to prepare a protocol or similar preparatory purposes; 2) he or she understands that the PHI cannot be removed from the covered entity; and 3) that PHI requested is necessary for research purposes. This written attestation is required, regardless of the researcher being part of the covered entity's workforce or not. The OCR auditors may also want to see if the covered entity let a third party (i.e., individuals not on the covered entity's workforce) contact potential subjects for recruitment purposes and, if so, was it done appropriately. See www.hhs.gov/hipaa/for-professionals/faq/317/can-the-prepatory-research-provision-be-used-to-recruit-individuals-to-a-research-study/ for more information. Similarly, for access to PHI of decedents for research purposes, HIPAA (at 45 CFR 164.512(i)(1)(iii)) requires the covered entity to receive similar attestations that include 1) the PHI used will be solely for research; 2) documentation of death as requested; and 3) that PHI requested is necessary for research purposes. See https://privacyruleandresearch.nih.gov/pr_08.asp#8f for more information. The auditors are entitled to see your policy on obtaining the required representations, and that you have actually obtained them prior to allowing access for these respective purposes.
Non-EHR Storage Security of PHI	When PHI is held outside the secure environment of the EHR system, are those data secured in compliance with HIPAA security provisions? In research, we use lots of laptops, paper, portable media, and offsite storage of PHI. For the proverbial "research laptop," passwords are not enough to meet the standards—you must encrypt.
Business Associates	The use of "business associates" (as defined by HIPAA) is not prevalent in research because research is not a covered function of such associates (see *Federal Register,* Vol. 67, No. 157, from August 14, 2002, page 52353; and the December 2015 installment of this column by its regular author, Brent Ibata). About the only use for research purposes is to have a third party de-identify a dataset that will be eventually used for research. If you do use a business associate in such a manner, you must be sure that your agreements contain all required elements of HIPAA and the Health Information Technology for Economic and Clinical Health Act. You also have to show that the agreements were in place before PHI was disclosed. See www.hhs.gov/hipaa/for-professionals/covered-entities/sample-business-associate-agreement-provisions/index.html for more information.
Accounting of Disclosures	Many researchers are surprised to learn about the "accounting of disclosure" (AoD) requirement of HIPAA (45 CFR 164.528(b)(3)). Every patient of a covered entity has a right to see who their identifiable PHI was disclosed to without their authorization and/or for reasons outside of treatment, payment, and healthcare operations (all as defined by HIPAA). Research is specifically included in this when the release is not done pursuant to a written authorization (when the patient would know of the disclosure, as he or she had requested it). When a researcher accesses identifiable PHI for research purposes under these circumstances (e.g., not as a limited dataset, but under an IRB waiver of authorization, preparatory to research purposes, etc.), this must be logged with certain fields (such as the name and address of the researcher, the description of the PHI accessed, the date[s] of access, the reason of disclosure [i.e., the research purpose], etc.). If the researcher accesses more than 50 records, the covered entity can alternatively create a "bulk" or separate log (to avoid having to mark each individual record), which requires some additional fields (i.e., record selection criteria, name and address of sponsor, and others). Thus, if the organization opts in to maintaining an alternative log (instead of individual logs) for a researcher accessing 50 or more records, patients requesting their AoDs will get a list of those researchers (and accompanying information) known to have accessed their records, as well as (if utilized) a list of researchers (and accompanying information) who MAY have accessed their records. You will have to show that you appropriately logged these disclosures, that the logs (either individual access log or abbreviated access log for accessing 50 or more records) had all required elements, and that you maintained these logs for the required six-year minimum timeframe. See https://privacyruleandresearch.nih.gov/pr_08.asp#8k for more information.

All too often, IRBs waive research consent (when allowable under FDA and/or OHRP regulations), but forget (or are not asked) to waive the requirement of the HIPAA authorization.

Every patient of a covered entity has a right to see who their identifiable PHI was disclosed to without their authorization and/or for reasons outside of treatment, payment, and healthcare operations.

Conclusion

While Table 1 captures the major ways HIPAA audits intersect with the research universe, HIPAA's vast breadth could certainly yield other target areas not as clearly defined in the audit tool (e.g. the Omnibus Rule revision of HIPAA in 2013 limiting the covered entity's sale of PHI at a profit without patient authorization to sell it at a profit).

Undoubtedly, we are obligated to follow the rules that society has set for respecting the privacy of individuals and the security of the identifiable health information they have entrusted us with. Researchers take on this obligation especially when the research operations put this information at a greater risk of breach than if there was no research taking place.

If you are part of a larger organization, you are likely fortunate enough to have dedicated compliance officials/resources either handling much of this, or capable of helping to handle it with mutual assistance. If your organization does not have such resources, you will have to rely more on wisdom and best practices being passed on from sponsors and/or more experienced sites, or learning opportunities coordinated/communicated by professional societies.

At any rate, you should determine your risk areas here and always strive to be in that mythical state of "constant audit preparedness."

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State-of-the-Art Pharmacy Services

IN A PHASE I CLINICAL RESEARCH UNIT

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Phase I clinical studies form an important foundation for drug development and eventual approval of life-saving therapies. Potential drug candidates are screened for entry into Phase I trials by extensive *in vitro* testing and tolerance in several animal species. Early *in vitro* testing establishes potential mechanisms of action, such as binding to a receptor or enzyme. Animal toxicology at large doses is used to determine a small, safe starting dose for first-in-human trials.

Given the pressures to develop drugs more quickly, Phase I studies have in recent years incorporated sophisticated pharmacodynamics assessments and biomarkers to better understand the safety and pharmacology of a compound prior to initiating Phase II studies in patients.

A typical Phase I program will consist of a series of studies to carefully define the safety and pharmacokinetic (PK) qualities of a compound in humans, beginning with a single-dose per subject and then increasing the dose in subsequent cohorts of volunteer subjects until either a maximum tolerated dose (MTD) is identified,[1–3] calculated exposure limits based on animal toxicology, or a pre-established biological endpoint has been reached. The latter is often an estimation of the eventual effect in the targeted patient population.

Such a study is then typically followed by a multiple-dose per subject scheme of escalating doses in volunteers to further characterize the safety and PK aspects of the compound at steady-state conditions. Additional Phase I studies, including those intended to gather AME (absorption, metabolism, and excretion), drug-drug interaction, food effect, and even maximum tolerated dose data in subjects, may also be conducted.

Given the pressures to develop drugs more quickly, Phase I studies have in recent years also incorporated sophisticated pharmacodynamics assessments and biomarkers to better understand the safety and pharmacology of a compound prior to initiating Phase II studies in patients.[4]

This article reviews the role of the pharmacy in a modern Phase I clinical research unit (CRU). The setup described in this paper may also be applicable in some instances to Phase II and Phase III trials; however, the U.S. Food and Drug Administration (FDA) has issued a specific guidance for current Good Manufacturing Practice (cGMP) for Phase I investigational drugs.[5] Additional regulatory guidance for Phase I pharmacy units can be found in the *United States Pharmacopeia* (USP) standards.

This paper also reviews an ideal suite of pharmacy services in the CRU. A literature search via PubMed revealed no publications specifically discussing pharmacy services in a Phase I setting.

While considering the rest of this article, one should bear in mind the fundamental principles of the Declaration of Helsinki,[6] and the fact that the tenets of ethical research are also applicable to healthy volunteers participating in Phase I studies.

The Pharmacy's Role in Phase I Research

Phase I service units typically have a number of dedicated resources, including in-patient research beds, telemetry units, adaptable procedure spaces, a Clinical Laboratory Improvement Amendment (CLIA)-certified clinical safety laboratory, and a fully equipped sample processing laboratory. Ideally, a centralized atomic clock system throughout ensures uniformity of timed study events.

A physician serves as the principal investigator for each study, and is supported by physician sub-investigators and by project managers, clinical research coordinators (CRCs), and pharmacists to ensure proper study conduct and collection of quality research data. Additional support staff can include nurses, phlebotomists, paramedics, lab technicians, medical technicians, pharmacy technicians, floor monitors, and operations supervisors.

Ideally, the pharmacy in such a space offers adequate workspace that is under high-efficiency particulate arrestance (HEPA) filtration. Additionally, the pharmacy should have an International Organization for Standardization (ISO) Class 7 clean room with ISO Class 5 laminar flow hood for compounding sterile products, and a spacious compounding suite for preparing oral and topical dosage forms.

The pharmacy must have secure drug storage for active studies, with additional space for long-term storage of retention samples available in separate areas. All drug storage areas should have limited access and continuous temperature and humidity monitoring.

Pharmacy Staff

Since the main purpose of the CRU is often the testing and evaluation of investigational drugs, the preparation and dispensing of test articles should be done by professionals best trained for this task. CRUs that are located within academic medical centers typically receive and distribute investigational drugs through the established pharmacy services at those institutions, with assigned pharmacy staff who are familiar with

research procedures. However, many stand-alone Phase I CRUs have no such precedent for pharmacy operations, and often non-pharmacy staff, such as registered nurses or CRCs, will handle drug preparation and dispensing within the unit.

Because of the demands of research, a pharmacy should operate seven days a week, and be staffed by full-time licensed pharmacists and certified pharmacy technicians. Ideally, pharmacists should report directly to the medical director of the CRU, which allows input and quick resolution of any issues with minimal obstacles.

This management structure fosters the critically time-dependent nature of procedures in clinical research, which include the time of dosing and PK samples. Delayed resolution of issues or omissions can result in protocol violations that compromise the integrity of the study objectives.

A lead pharmacist should be assigned to each protocol, and a pharmacist should attend all study initiation and study progress meetings. Table 1 shows tips for clinical researchers to follow in order to best utilize pharmacy service professionals.

TABLE 1: Tips for Clinical Researchers to Follow in Order to Best Utilize Pharmacy Service Professionals

Comprehensive, documented audit trail from drug receipt through study closeout reconciliation, including sponsor-approved product destruction or return
A clear understanding of the protocol and investigational drug distribution requirements (correct drug, correct dose, correct patient, correct time, correct route of administration)
Quality control and quality assurance oversight
Implementing mock/practice sessions for complex procedures
Ongoing communication with other members of the study team

Pharmacy Facilities

The main pharmacy should be used primarily for preparing and storing investigational drugs needed for active research protocols. Drugs should be stored in locked cabinets, refrigerators, or freezers. Controlled substances should be stored in secure, locked cabinets, separate from other investigational drugs.

Ideally, -20°C and -70°C freezers are used to provide cold storage and are continuously monitored by independent electronic systems with automated alerts sent by phone, text, and e-mail should out-of-range temperature excursions occur. Cold storage units should be backed up by dedicated emergency generators capable of supplying power for 20 uninterrupted hours. Further, all drug

storage areas of any type should have continuous temperature and humidity monitoring with immediate alerts generated.

The pharmacy should have a yellow light system available that can be activated when compounding or dispensing light-sensitive drugs. A separate compounding suite could house analytical balances (for example, a Mettler-Toledo XS105DU, which has a minimum weighing capabilities of 200 mg) and microanalytical balances (for example, a Mettler-Toledo XPE56, which has minimum weighing capabilities of 2 mg), for accurately preparing capsules and powder-in-bottle dosage units.

An ante-room and clean room with ISO Class 5 laminar airflow workbench can complete the main pharmacy area and be used for preparing sterile products. All pharmacy equipment must be certified and/or calibrated by outside vendors according to manufacturer recommendations and/or applicable Good Clinical Practice (GCP)/cGMP standards.

Finally, it is best that all pharmacy areas are secured by ID badge or key access with video surveillance, and access should be strictly limited to pharmacy staff and the medical director of the CRU.

Many stand-alone Phase I CRUs have no precedent for pharmacy operations, and often non-pharmacy staff, such as registered nurses or CRCs, will handle drug preparation and dispensing within the unit.

Protocol Review

Pharmacists should be involved in reviewing and contributing to research trials from the earliest stages of protocol development. Once a draft protocol is received, the pharmacist should be placed on the distribution list with other team members to provide crucial feedback to the medical director and to the medical and scientific affairs staff. Pharmacists may also be asked to provide guidance on test article procurement, storage, handling, and dose preparation prior to the initial draft protocol.

Often, the first task is to decide whether the CRU can execute the study properly and recruit the necessary subjects and/or patients for the study. Recommendations believed by the study team to be necessary to successfully carry out the study should be supplied to the sponsor. These recommendations often include slight alterations in subject inclusion or exclusion criteria, based on prior experience with similar protocols, or pointing out various inconsistencies within the protocol that could interfere with successful execution.

While pharmacists can review the entire protocol, they should focus their specific expertise on sections pertaining to safe dose selection (usually based on the "no observed adverse effect" level dose found in animal species), dose preparation, blinding procedures, dose administration, and drug storage. As appropriate, they can make recommendations regarding subject training when necessary.

Pharmacists also complete Abbreviated New Drug Application and FDA product information tables for the final study report. Given that the investigational drug is the very central core of the protocol, this information reviewed and commented on by the pharmacist is crucial.

Drug Accountability

After a protocol has been finalized and approved by an institutional review board (IRB), the pharmacy will initiate the creation of drug accountability forms. A database can be used to manage all aspects of drug accountability, as well as to manage study-related tasks and to track inventory. The database can provide protocol-specific summary reports and generate both standard and customized forms for drug accountability, dispensation, retention, inventory, and destruction tasks.

Tracking inventory is important, as all test articles must be accounted for not only throughout the life of the study conduct, but also possibly for long after the study is completed. As per 21 CFR 320.38 and 320.63 in the *Code of Federal Regulations,* retention samples for bioavailability/bioequivalence studies are to be retained by the CRU for at least five years following the approval of the application or supplemental application, or if not approved, at least five years following the completion of the study.[7,8]

Database use should be restricted to pharmacy personnel only, and an audit trail may be incorporated into the design. All forms should be reviewed and approved by the CRU's quality control department prior to use. Pharmacy staff can also interact with study monitors who are sent by the pharmaceutical sponsor of the study to periodically conduct quality (QC) on study records.

Manufacturing and Compounding

All pharmacy manufacturing in a CRU must adhere to Phase I cGMP guidelines and site standard operating procedures (SOPs). Ideally, the pharmacists can create a Pharmacy Manual in collaboration with the study sponsor for detailing the procedures to be used in any study that requires manufacturing or compounding.

A Master Batch Record (MBR) should be created to specify manufacturing procedures and demonstrate cGMP compliance. All manufactured products should be quarantined until the MBR is reviewed and product is released by the sponsor's quality assurance department. Any compounding, whether under sterile or nonsterile conditions, must adhere to FDA Compounding Guidelines (USP795 and 797, and State Board of Pharmacy regulations) as well as to the CRU's own SOPs.

To assure that the correct drugs are dispensed, the pharmacy should employ a system of double-checks throughout the dispensing process in order to ensure subject safety and compliance with the protocol.

Examples of compounding include filling of capsules, preparing oral solutions and suspensions, preparing intravenous (IV) admixtures, and compounding radio-labeled drugs used in specialized AME or microdose studies.

When the pharmacy needs to source study items or reagents that are not provided by the sponsor, a network of wholesalers, brokers, and specialty vendors can be utilized. For test articles originating from sources outside the U.S., pharmacists can also provide guidance and submit applications required to navigate test articles through import regulations as required by the FDA, U.S. Department of Agriculture, and Drug Enforcement Administration.

Investigational Drug Blinding

Many protocols in Phase I are conducted on a double-blind basis (both staff and subject/patient are blind as to whether they receive active medication or placebo). However, the pharmacist is often unblinded because he or she will prepare the study drugs (active product and matching placebo). A randomization schedule, generated either by the sponsor or by an independent statistical service, should be provided to the study pharmacist for review to ensure that it matches specifications written in the protocol.

The blinded randomization ideally should be secured in a locked cabinet that is only accessible to the unblinded pharmacist(s). For dispensing, two unblinded pharmacy staff (one being a pharmacist) should prepare the doses per the randomization. Placebo doses should be prepared first, and then active doses, in order to avoid any contamination from the active drug into the placebo. A member of the QC unit should witness all dispensing/dose preparation for blinded studies.

Once a staff member is unblinded, he or she is not able to participate in any other aspects of that study. Doses must only be administered by blinded staff members. Therefore, an unblinded pharmacist will not administer doses if he or she assisted in the preparation. Generally, pharmacy technicians, nurses, and/or physicians will administer blinded doses.

If blinding is required in a study in which the doses are not the same in appearance, quantity, volume, or taste, the following adjustments may be made to mask differences between active and placebo doses:

- **Difference in appearance (oral capsule/tablet):** Utilization of a dosing container that will conceal the appearance of the dose. For example, the dose may be directly administered and consumed from an opaque, narrow-mouth dosing bottle. The subject will be asked to not directly look into the container, but to consume the dose in a blinded manner.

- **Difference in appearance (IV):** Utilization of an amber bag to cover the IV bag and drip chamber. If the IV line needs to be concealed, amber tubing or amber plastic sleeves may be used to conceal all parts of the IV bag/line. Use of a small curtain may also be made to block the subject's view of the IV dose (doser and subject's arm on one side of the curtain, with the rest of the subject on the other side of the curtain).
- **Difference in taste:** Use of pharmaceutical-grade flavoring agents (cherry, bubblegum), juices (apple, orange), Bitrex, or artificial sweeteners (Orasweet).
- **Differences in quantity:** If a different number of capsules are being administered between treatments, additional placebo capsules/tablets may be used to ensure the number of pills are equal between treatments.

Subject Training

Phase I studies with investigational drugs often employ delivery systems that may be unfamiliar to subjects and/or patients. Such delivery systems include nasal sprays, inhalers, buccal and sublingual tablets and films, sublingual sprays, and orally disintegrating tablets. It is important that subjects be properly trained to administer these test items in order to assure that the study drug is properly administered and uniformly absorbed, so that the PK of the drug and its metabolites can be measured based on proper and consistent dose administration.

The inhalation route is particularly difficult, and subjects must be trained in advance on proper breathing technique and timing so that the drug is evenly distributed to the desired areas of the bronchi and lung for maximal effect. In effect, the subject must practice diaphragmatic movement both in the depth and speed of contracture.

Regardless of the delivery system being used, a pharmacy should have procedures in place for specialized dosing that have demonstrated high degrees of precision and consistency.

Dispensing and Dosing

There is no room for error when dealing with research medications. Given that such medications are often experimental and their safety is not yet established, they must be given exactly as described in the protocol.

To assure that the correct drugs are dispensed, the pharmacy should employ a system of double-checks throughout the dispensing process in order to ensure subject safety and compliance with the protocol. Ideally, the dose labels should be bar-coded and linked to the barcoded wrist labels on the subject; additionally, the process should often be overseen in complex studies by QC staff.

In order to ensure that there is no possibility for error, pharmacists and trained pharmacy technicians should dose the subject/patient in the CRU. Dosing should first involve verifying that the subject receives the proper dose according to the protocol's randomization sequence through a barcode system and a visual check. Then, the pharmacy staff should give the subject any needed reminders concerning earlier subject practice and training.

Following dosing, the pharmacist should check the subject's hands to ensure medication was taken, and perform a mouth check using a tongue depressor and small flashlight to explore the oral cavity, including under the tongue, the inside of the cheeks, and the back of the throat.

Post-dose instructions should be given and subjects reminded to notify staff if they feel in any way abnormal. Additional instructions may include staying seated upright for four hours after dosing and water restrictions. The pharmacist or pharmacy technician can record any observations noted during the dosing session.

Conclusion

This paper reviews an ideal, state-of-the-art suite of pharmacy services in a Phase I CRU tailored to the complex operations of early-phase clinical research. It will be appreciated that the services span a continuum of pharmacy practice, from compounding and drug preparation to the novel roles of protocol review and drug administration. Thus, the pharmacy both provides support and plays a crucial role in the early drug development process.

> When the pharmacy needs to source study items or reagents that are not provided by the sponsor, a network of wholesalers, brokers, and specialty vendors can be utilized.

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A Research Site's Guide to RANSOMWARE (and Other Attacks)

At a recent industry conference, representatives of a clinical trial site disclosed to a panel of expert mentors that their site had been attacked by ransomware. Needless to say, this created a litany of discussion on what happened and, like any good discussion with experts, this one ended up with more questions than answers:

Ransomware is usually introduced through phishing e-mails when the "bad guys" dupe a user into clicking on a malicious link or opening an attachment.

- Did third-party software create the pathway for the ransomware, or was this a general flaw in the site's system security? If the former, should the sponsor/contract research organization requesting use of the software in its written instructions be responsible, or is it the site's responsibility to assure the system is secure before installing such software?
- Was the sponsor's confidential information compromised? Is it subject to further compromise? If so, is the site responsible under the clinical data agreement/clinical trial agreement?
- Must the site be dropped from the study, or can it continue on paper or another computer system?
- If the site pays the ransom, is this invoiceable to the sponsor? [(Also jokingly) would the ransomist accept a quarterly payment and a 10% holdback from the sponsor to assure that the remaining files were actually restored?]
- What happens to active subjects? Was their identifiable protected health information on the computer? Should they be dropped due to the challenges (such as from missing information) raised by keeping them in the study?
- What paperwork needs to be recreated to support the electronic case report form data (i.e., reconsents and/or details gather from other sources)?

What is Ransomware?

Ransomware is a type of malware that encrypts a computer's data, rendering it useless. The ransomware sender offers the decryption key for a price. The choice is whether to pay the ransom in hopes you can recover your data, or to completely start over by re-imaging the device and using data back-ups to restore it. Oh, and yes…ransomware is migrating from desktops and laptops into mobile and medical devices.[1,2]

Ransomware can be propagated to the point of shutting down your information technology (IT) systems and medical devices, potentially causing major impacts to operations and patients, as well as making your source documents unavailable. Early-stage investigational devices are especially at risk, as they have yet to develop the necessary protections so soon in their development.

Ransomware in the healthcare ecosystem recently made headlines when someone attacked a major medical center in California and disabled its computer network for several days, until the hospital paid the ransom (in this case, for the low amount of 40 bitcoin, which is about $17,000 USD).[3] Before the hospital paid the ransom to get its systems working again, it had to transfer several patients, take many connected systems offline (e.g., pharmacy, lab), and rapidly move many processes back to paper, phone calls, and faxing.[4]

Many people believe that because this provider (as well as others) paid the ransom, criminal hackers have more reason to increase their attacks on healthcare facilities and users.[5] Quoting Stu Sjouwerman, CEO of the security firm KnowBe4, "If you have patients, you are going to panic way quicker than if you are selling sheet metal."[5]

Device manufacturers are challenged with this new need for security, as connected medical devices (even if only Bluetooth connected) have been shown to be easily hacked. *Popular Science* magazine believes that medical device–oriented ransomware (instead of telling Grandma that her pictures will be deleted from her computer, think of telling her that her insulin pump will be shut off if she doesn't pay $200) will be a significant issue in the upcoming years.[6]

How Do Ransomware Attacks Happen?

Most ransomware attacks come from the inside, which is to say that although employees, former employees, or visitors probably aren't sticking nefarious thumb drives into your systems (although this could happen), ransomware is usually introduced through phishing e-mails when the "bad guys" dupe a user into clicking on a malicious link or opening an attachment. This "spray and pray" technique is much cheaper (and apparently more effective) than attempting high-stakes, espionage-like hacking, especially when ransomware kits are available on the open, but illegal, market for only thousands of dollars to help people do it.

Most people are accustomed to phishing scams in terms of e-mails seemingly coming from a trusted external company/entity (e.g., your bank, the IRS, Microsoft), but ransomware artists are sophisticated enough to know the names of people in your company, especially senior officials, and to make the phishing e-mail appear as if it is coming from them. They may even track when the executives go on vacation, so as to send messages during that time with "do this for me quickly" instructions (see advice below in helping to avoid this).

Although phishing is the most common method of entry, ransomware can also be obtained by visiting specific untrusted websites through your browser, through social media links, by checking untrusted QR codes (those little black and white boxes with a bunch of dots that take you to websites), and/or by being installed without any effort on your part by a traditional hacker through a hole in your system. Rebooting the system usually does not work (as many pieces of ransomware attach to the boot process), and in some cases the ransomware notification tells you that rebooting will only accelerate the deletion of files or make the ransom price go up.

What Can You Do to Prevent an Attack?

Basically there are "silicon-based" defenses (software) as well as "carbon-based" defenses (people). Even many layers of strong silicon-based security defenses can't protect against every ransomware attack. The behavior of carbon-based people plays a huge role, as well.

The most important thing you can do is to raise awareness. Talk to your staff and colleagues about the dangers of phishing and the importance of security awareness—ransomware attacks really happen, and they have now happened in the clinical research industry! While silicon-based defenses are generally left to the IT professionals, below are some carbon-based protections you can utilize.

- **"Think before you click." Be certain that click is legitimate.** Do not open e-mails or attachments from unknown senders. Do not open e-mails or attachments from someone you know unless you are expecting it or know what it contains. Watch for suspicious attachments (e.g., "Revised Consent.pdf.exe" or "Protocol v2.docx.com"). Never click "unsubscribe" to unsolicited junk mail. Never click "Agree," "OK," or "I Accept" to get rid of a pop-up ad, unexpected warning, or even an offer to remove spyware. Instead, close the window by clicking the "X" or, even better, by pressing ALT+F4 on your keyboard, because that "X" might be a cleverly disguised hyperlink. If you are compelled to click the "X," hover over it first to see if it changes your mouse icon from the little arrow to a hyperlink icon (i.e., the little hand).
- **Don't use strange WiFi connections.** Assuming your company has this capability, always connect to the internet through VPN when working remotely. Connecting through your VPN gives you the silicon-based protections your company has to offer, as opposed to connecting to the web (even your home WiFi) without those protections. Hotel, coffee shop, and other public WiFi areas are popular hubs for dissemination of malware. Avoid alluring and/or unofficial SSID network names such as "Free_WiFi" or "Airport_WiFi."
- **Avoid untrustworthy websites and use bookmarks to access your favorite site.** As much as possible, only access websites that you need to perform your job. In particular, never access gambling sites, any sites related to computer hacking, or sites containing pornographic or hate-motivated material. Never download screensavers, games, music, or other executable files (such as files ending in .exe, .vbs, or .com) from the Internet or any other outside source unless your IT department has the chance to check it. Finally,

FIGURE 1: How Does Ransomware Work?

Phishing e-mail attachments or infected websites introduce the malware to a device

The software encrypts data on the device – and may attempt to spread to other systems

The encryption renders the device useless; a pop-up offers the decryption key for a price, typically to be paid in bitcoin

- Pay the ransom (and *hope* to get the data back); or
- Rebuild with back-up data
- Start over

Even many layers of strong silicon-based security defenses can't protect against every ransomware attack. The behavior of carbon-based people plays a huge role, as well.

FIGURE 2: Sample Ransomware Alerts

bookmarking frequently visited, trusted websites will prevent you from typing the wrong address, as an incorrect (but similar-looking) website could have downloadable ransomware on it.

- **Cautiously use "Out of Office" autoresponses.** While it is always nice to let your stakeholders know you may be delayed in your response (or a quicker response can be obtained through a colleague covering for you), autoresponses are similar to social media posts that put people at risk of home burglaries when announcing to the world they will be away on vacation.[7] Ransomware artists can send you junk mail, get an out-of-office response, and then make that phishing e-mail look like it came from you during your vacation time so that nobody can easily check with you before they "check this out" or "click on this link."
- **Regularly backup your important files.** Although backup is a best practice for recovery in case you are attacked, it is not a guarantee, as some ransomware is smart enough to encrypt before your scheduled backup and only asks for the ransom after your backups have been overwritten by the infected files.
- **Protect your USB ports from nefarious activity.** While most ransomware is introduced by Internet communications, physical introduction through USB and other connections is possible. Although your company may have protections from USB downloads (i.e., preventing downloads of protected health information or other company confidential information to a thumb drive), it may not have protections from uploads. This involves reassessing your electronic and/or physical security measures.
- **Keep antivirus protections, pop-up blockers, and software up to date.** Although common knowledge, this prevention activity is often not done or is delayed until it is too late.
- **White Hat hack your systems.** While you may not have the resources to hire hackers to expose your silicon-based securities, you likely could perform your own (or through a vendor) internal "phishing response" test to see if your workforce has understood the importance of maintaining security awareness. Many companies are surprised to find that, despite a plethora of training, posters, and reminders, employees will still click on things they should not. Case studies have shown that despite best efforts, human behavior is still hard to manage—such as the one by KnowBe4, which started out in a financial institution with a 39% phishing response rate and even after 12 months of training still had 1.2% response rate.[8]
- **Use strong and different passwords, as well as two-step verifications.** Yes, nobody likes the inconvenience of having to use a different username and password for each site (and sometimes

this is difficult, as the sites require you to use your e-mail address as your user ID). Know that every company out there is at risk of being hacked, and that using the same password gives the hackers your username and password to access other sites. Use two-step verification when offered, as having the company send you a text with a code each time you want to log in is an extra step that trades off about 15 seconds of delay in login time for significant enhanced security.

What to Do if You are Attacked (or Think You are Being Attacked)

- Don't panic!
- Remove the affected device from the network (i.e., unplug network cables, turn off Wifi, etc.).
- Report it immediately. Whether it is a suspicious e-mail or a possible infection on your workstation, the faster IT support responds, the better your chance of containing its spread. Also, let your manager know. Not reporting it in a timely manner can be detrimental.
- Document any facts you can remember as soon as you can (i.e., What were you doing when the message appeared? Had you been to any websites or opened any e-mails before the screen changed?).
  - »Sit and wait—Let the technical team members do what they do best! Don't turn off your computer and DO NOT initiate any contact with the "bad guys" or follow any on-screen instructions.
- Do I just pay the ransom? Many have, and you have to make your own business decisions, but the Federal Bureau of Investigation (FBI) does not recommend it. FBI Cyber Division Assistant Director James Trainor is quoted as saying: "Paying a ransom doesn't guarantee an organization that it will get its data back—we've seen cases where organizations never got a decryption key after having paid the ransom. Paying a ransom not only emboldens current cyber criminals to target more organizations, it also offers an incentive for other criminals to get involved in this type of illegal activity. And finally, by paying a ransom, an organization might inadvertently be funding other illicit activity associated with criminals."[9]
- Do I report a ransomware attack to the FBI? You have to make your own business decisions, but the FBI states, "If you think you or your organization have been the victim of ransomware, contact your local FBI field office and report the incident to the Bureau's Internet Crime Complaint Center."[9]

Conclusion

While the use of ransomware is growing, threats possibly leading to the destruction or inaccessibility of site records and risk for connectivity loss are nothing new to the research enterprise. Natural disasters such as hurricanes, tornados, and floods have caused damage despite warnings. Fires and water damage from leaks can cause such losses, as can general disorganization and clumsiness (lost or dropped laptop). Similar to the dangers from "acts of God" and simple human mistakes, there is never a guarantee that you will be 100% protected from ransomware at all times.

Just as you do with other risks of potential loss of records and/or connectivity, know that the best thing you can do to protect yourself against the growing threat of ransomware is to put in reasonable protections on the front end, and to have a backup plan to support your operations and protection of clinical trial subjects in the event you are attacked. More resources can be found at the FBI's website, which to my knowledge does not invade your system…but no warranties here.

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Paul Connelly is vice president of information privacy and security and chief information security officer for Hospital Corporation of America.

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James Michael Causey
[DOI: 10.14524/CR-16-4030]

CTTI Project Reveals Serious Flaws in Trial Recruitment Protocols

Failure to address clinical trial recruitment issues at the outset continues to plague sites, according to the findings of a new task force. Result? Nearly 40% of clinical trials fail to meet recruitment goals.

The biggest surprise is that after all these years—and all the data that demonstrate the large proportion of studies that fail to meet enrollment targets—we are still having discussions about how to get recruitment planning right.

It's time to change that, say members of the Clinical Trials Transformation Initiative (CTTI) Recruitment Project team. CTTI is a public-private partnership established by the U.S. Food and Drug Administration (FDA) and Duke University in 2007 to identify and promote practices that will increase the quality and efficiency of clinical trials. The team drew upon representatives covering the entire gamut of trials, including FDA officials, patient advocates, investigators, study coordinators, and others, to get a full picture of the state of the clinical trial industry. What the team members found is not always a pretty picture.

Beth Harper, president of Clinical Performance Partners, and Leslie Kelly, a clinical trials recruiting coordinator at Duke for more than 15 years, were active members of the team bringing their own perspectives to the process. *Clinical Researcher* Editor-in-Chief James Michael Causey spoke with them in June as they unveiled and disseminated their findings and recommendations.

Clinical Researcher: What were the biggest surprises or trends you saw as you collected input?

Beth Harper: To be frank, the biggest surprise is that after all these years—and all the data that demonstrate the large proportion of studies that fail to meet enrollment targets—we are still having discussions about how to get recruitment planning right!

Leslie Kelly: I was very surprised at how many studies are struggling. Some of the reasons for under enrollment include fear of research, procedures and appointments that require too much time, and strict inclusion and exclusion criteria.

CR: What have you learned along the way? Will the recommendations impact how you operate? How?

Harper: One of the most valuable aspects from the CTTI work is that we were able to systematically organize all of the planning activities into a simple strategic recruitment planning framework. While

For more information about CTTI projects and how to join in, visit www.ctti-clinicaltrials.org/.

many players in the recruitment planning space have done some of the activities to a greater or lesser degree, the framework helps all involved to think about the core elements that drive recruitment success. Having this all mapped out ensures that everyone is speaking the same language about what recruitment planning means. It provides a systematic approach to make sure that all of the factors are being addressed to set a study up for recruitment success.

Kelly: Coming from an academic setting, I have had the opportunity to work with CTTI team members who represent the FDA and pharmaceutical and device companies. I have learned that we share many of the same recruitment obstacles. Yes, as a recruitment coordinator I am always referring back to the recommendations, especially emphasizing recruitment planning from the study design phase. More planning up front will pay off in the long run.

CR: What do you think are some of the greatest opportunities you identified for recruitment improvement?

Harper: For me, the greatest opportunity is the recognition that successful recruitment planning cannot be done in a vacuum. The identification and involvement of key stakeholders, particularly the patients and sites, is a critical element that has historically been missed (with regard to industry-sponsored trials) when sponsors or contract research organizations do their recruitment planning. Further, understanding the interplay between patient recruitment, site selection, and site engagement reinforces that we can't simply focus on study awareness–building tactics, and that recruitment planning involves many more dimensions if we are to get it right.

Kelly: Presently only about 10% of the population participate in clinical trials. Hopefully, by reducing study burden and broadening inclusion criteria, the public will become more aware and interested in the opportunity to volunteer in a clinical trial. More efficient recruitment in clinical trials can lead to advancements in medicine, thus improving quality of life and survival rates.

CR: What kind of reaction are you getting from various sides of the clinical trial industry? Has that reaction been encouraging or discouraging?

Harper: We're still in the early days of rolling out the recommendations and all of the great work of the task force. That said, the reaction has been very positive. We've generated a lot of questions, interest, and enthusiasm. For some, they are interested in clarifying specific aspects of the process. For others, they are enlightened by the overall framework. In general, my sense is that folks really appreciate seeing all of the detailed and disparate elements pulled together in a well–thought out process with detailed recommendations.

Kelly: I think people are excited and agree with the "idea" of these recommendations. However, they are not quite sure how to implement them.

CR: How will you encourage industry to implement some of the recommendations?

Harper: At the risk of being blunt, I believe industry needs to be reminded that we often need to "slow down to speed up." Taking a few extra moments (days, weeks) to invest in the research, information gathering, and discussions outlined in the CTTI recommendations will pay huge dividends in the long run. We always seem to find the resources and time when things are in "rescue mode," but can't seem to pause up front to get all of the elements of recruitment planning right at the outset. The data on poor enrollment performance speak volumes and, frankly, haven't changed in more than 15 years. Doing the same thing over and over again will yield the same results, so advocating for the systematic process outlined in the CTTI recommendations should go a long way toward shifting the trend to a more predictive and successful result.

Kelly: CTTI is currently planning to disseminate the recommendations. Hopefully, as positive feedback spreads through the research community, these recommendations will become standard practice.

Hopefully, by reducing study burden and broadening inclusion criteria, the public will become more aware and interested in the opportunity to volunteer in a clinical trial.

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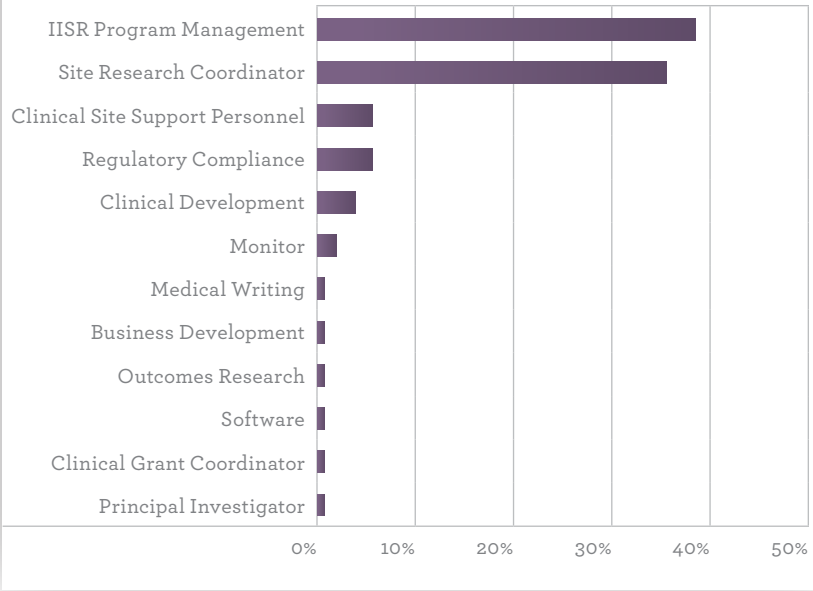
Current Practices Within Investigator-Initiated Sponsored Research

2015 ACRP SURVEY RESULTS

In 2015, the ACRP Investigator Research Interest Group conducted a survey to gain insights into how investigator-initiated sponsored research (IISR) is conducted, and to provide a valuable benchmark for how researchers and industry manage IISR studies. Through this survey, we hope to provide a way for both sites and industry to improve their communication about the research their efforts create.

PEER REVIEWED | Ashley N. Wills | Scott N. Cunningham, MS

FIGURE 1: Role at Organization



Background

IISR is a common tool used throughout the life sciences industry to generate evidence supporting therapies and associated products. IISR studies are independent projects in preclinical, clinical, or observational settings in which the investigator or institution serves as the sponsor.

Common sources of support for IISR studies are manufacturers within the life sciences industry, cooperative groups, nonprofit research organizations, and healthcare institutions. Support can come in the form of funding, provision of product, and/or other aid with study conduct.

There are five phases of the IISR lifecycle:

1. Sponsor-investigator submits an independent study proposal to potential supporters
2. A supporter's independent, cross-functional review committee reviews the scientific merit and feasibility of new proposals at regular intervals
3. Approvals and final documentation are granted and generated to support the trial start
4. Active study conduct and management is launched and maintained by the sponsor-investigator
5. The sponsor-investigator is responsible to adequately close out the study and report its results appropriately to regulatory bodies and through scholarly publication (supporters expect to review the results to be disclosed, the proof of study closeout, and the regulatory reporting before final milestone payments are made)

The intent of this survey is to better understand current practices in IISR studies and to identify any differences in their conduct in different situations.

Methods and Results

On February 6, 2015 a survey was posted to the ACRP website and distributed to ACRP's membership via an e-mail notification. The survey was open until April 30, 2015, and included 54 questions spanning eight categories (General Questions, Collaborations, Reviews, Support, Contracting, Compliance, System, and Metrics).[1]

The Investigator Initiated Sponsored Research Association (IISRA) conducted similar member surveys in 2007, 2008, and 2010. IISRA, which has since been incorporated into ACRP, has expanded the pool of responders to both industry and sites. This analysis does not compare the most recent survey's results to those of the previous surveys, although they are available for review on the ACRP website.

At the outset of the survey, there were 103 responses; 89% were from the U.S., 6% from the European Union and Canada, 3% from the Asia-Pacific region, and 1% from Latin America.

Respondents had a variety of roles, but were predominantly IISR program managers or site research coordinators (see Figure 1). Of the 34 industry respondents, 68% represented pharmaceutical companies, 21% represented medical device manufacturers, and 12% represented other companies such as those within nutrition or diagnostics.

There was a significant drop off of responses when comparing the first 10 (~103 responses) and last 10 questions (~40 responses) of the survey. As a learning point, future surveys should be shorter and more directed in scope to improve data capture quality.

Responses were categorized and classified by organization type to determine response variances. The classifications consisted of Research

93%
of industry respondents have formal review processes.

FIGURE 2: Organization Type

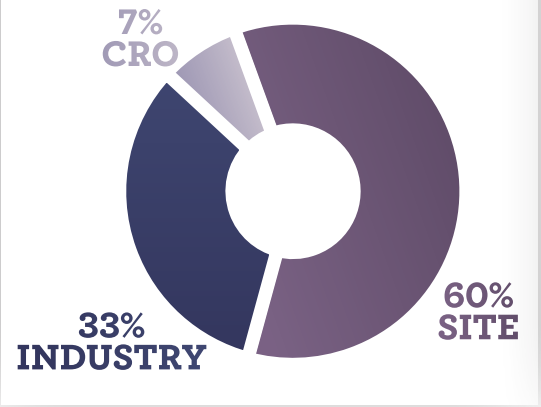
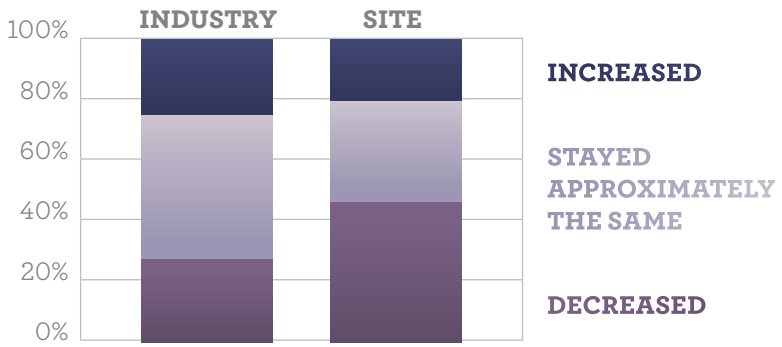


FIGURE 3: Program Vitality by Organization Type



Site, Industry, and Contract Research Organization (CRO) (see Figure 2). The limited responses from CROs and from other organizations not fitting into the final classifications were excluded from the analysis to focus on the viewpoints of sites and industry.

Year-over-year budget change is an indicator of the program vitality. Survey results indicate that IISR programs are relatively healthy, with respondents stating either that budgets increased (39%), remained approximately the same (40%), or decreased (20%) over the past two years (see Figure 3).

Upon further breakdown of the data by budget size (see Figure 4), programs with budgets smaller than $5 million tended to have neutral to decreasing budgets, and programs with budgets larger than $5 million tended to have neutral to increasing budgets. To these points, the overall health and outlook of IISR programs across the industry is positive.

Collaborations

Within the life science industry, a distinction may be made between IISR studies and collaborative studies. Two survey questions focused on whether respondents made a categorical distinction between these two study types, and under which policies a collaborative study would be evaluated. Nearly two-thirds of industry respondents (63%) made a distinction between IISR studies and collaborations, however very few (22%) reported having a separate policy for this research. Alternatively, only 29% of sites make a similar distinction, with 73% of sites responding that collaborations either have no existing policy or are treated as company-sponsored studies.

Among industry and site respondents, the defining factors for calling out collaborations separately from either IISR studies or company-sponsored studies were:

- Involvement in the study design, execution, or analysis (78%)
- Ownership of the data/study results (76%)
- Intellectual property ownership (62%)
- Sponsorship (56%)

Further, sites placed a greater weight on intellectual property ownership (70%) and industry placed a greater weight on sponsorship (65%) when defining collaborations.

Review Process

Proposal review varied greatly between sites and industry. With respect to sites, 64% had no review process, while 93% of industry respondents have formal review processes. If studies are global, it is common for industry to conduct local, regional, and/or global reviews.

There was a median of five reviewer types, with representatives from the following functional areas: regulatory/legal (20%), clinical development (16%), biostatistics (15%), IISR management (14%), safety (13%), and medical affairs (13%). A point to note is that in a few industry organizations, marketing is involved in the review process (2%). From a best practice standpoint, it is highly recommended to remove all commercial influence from the IISR review process.

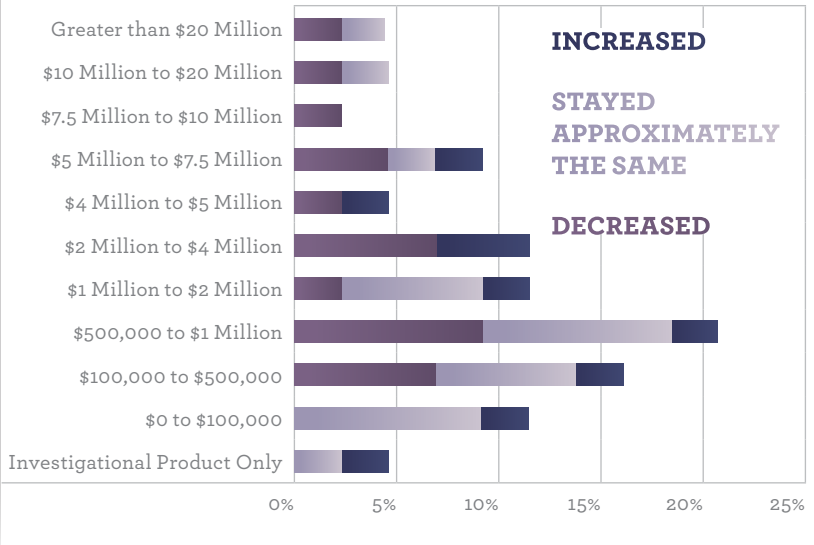
Established research areas of interest are common for industry (90%) and sites (56%). When applications are reviewed, the sponsor's publication plan followed by budget was common for both industry and sites; further, investigator eligibility and qualifications were important to industry. Reviews predominantly took between 46 and 90 days for both industry and sites.

Approval rates varied greatly, with nearly one-third of site respondents approving between 76% and 95% of proposed IISR studies and nearly one-fourth approving between 51% and 75%; and nearly one-third of industry respondents approving at a lower rate of between 26% and 50% and more than one-fourth at between 51% and 75%.

Upon review decision, communication style differed. Industry (46%) favors personal discussion followed by a formal written communication. Sites (41%) prefer formal or standard written communication only. Both industry and sites agree that system-generated notifications are inappropriate, with only 10% of industry and 9% of sites using this method of communication.

From a best practice standpoint, it is highly recommended to remove all commercial influence from the IISR review process.

FIGURE 4: IISR Vitality by Program Budget Size



Support Provided

The purpose of IISR programs is to provide access to funding and/or product so that qualified researchers are able to conduct and publish independently generated evidence. Respondents stated that their organizations provide the following types of support for studies:

- Products with marketing authorization approval (89%)
- Products with unapproved product indications (61%)
- Investigational products requiring additional regulatory approval (i.e., through Investigational New Drug or Investigational Device Exemption [IND/IDE] applications) (57%)
- Observational studies (66%)
- Outcomes research on patient outcomes only (68%)
- *In vitro* and *in vivo* studies (48%)
- Outcomes research studies on patient outcomes or pharmacoeconomics (45%)
- Other (12%)

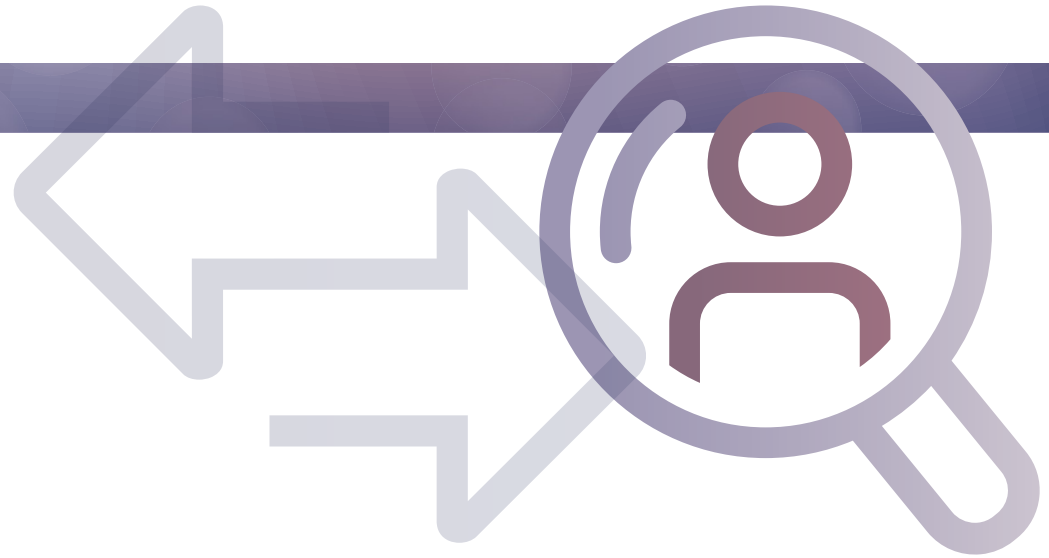
Meanwhile, there are some differences between the two types of studies in terms of the typical support received and other considerations:

- **Study Support:** Industry (77%) predominantly provides product and/or funding, whereas sites (35%) provide protocol development, case report form (CRF) development, statistical analysis, and monitoring support, and this difference is often the source of misunderstanding. Legal and regulatory constraints often limit industry's involvement with study development and conduct, in order to maintain the integrity of the research and the impartiality of the study sponsor. Interestingly, a small portion of industry respondents to the survey (4%) will provide support for protocol, CRF development, statistical analysis, and monitoring. With respect to best practice,[2] it is highly recommended that any "sponsor" activities (i.e., protocol development, data analysis, monitoring) are not conducted by the study supporter.
- **Study Costs:** Assuring that study costs are aligned to fair market value (FMV) is a well-recognized and required step for most of the industry (90%), while only some sites (42%) evaluate FMV. Use of commercially available datasets to establish FMV is preferred by industry (50%) to establish impartiality, whereas sites (26%) predominantly use internal data to assess costs.
- **Institutional Overhead:** Overhead charges are common and are often included in an IISR study budget. Industry (46%) caps these charges at 21% to 30% for clinical research. Sites (45%) have an expanded overhead range of 21% to 40%. Both industry (33%) and sites (31%) lack established limits for preclinical overhead.

According to survey respondents, upon final approval of the study, the following documents are most commonly collected prior to distribution of any funding:

- Institutional review board/ethics committee (IRB/EC) approval (84%)
- Final protocol (74%)
- Executed agreement (73%)
- Local regulatory approval (68%)
- IND/IDE and/or U.S. Food and Drug Administration letter if required (64%)
- Investigator's curriculum vitae (63%)
- Final budget (61%)
- Certification/qualification statement (27%)

It is possible to note within the slight variances mentioned above that industry is focused on the study's regulatory and legal requirements, whereas sites focus on IRB/EC, protocol, and budget support.



Contracting

A frequently cited concern related to the initiation of IISR studies is the length of time to negotiate the study agreement. The majority of survey respondents (94%) indicated that agreements typically take one to six months to negotiate, with sites estimating slightly shorter timeframes than industry respondents.

When compared to other timeframes within the survey, these results suggest that contracting does not take significantly longer than other steps. The perception that contracting takes too long may be related to contracts being negotiated late and becoming a rate-limiting factor for the study start. Given this, our recommendation is to draft the agreement as soon as studies have a high likelihood of starting, so that the contract is not a rate-limiting step.

Survey respondents reported that IISR agreements were made with both the institution and the investigator (50%), directly with the institution (42%), or directly with the principal investigator (8%).

Posting of trial information on a publicly accessible website, as defined by International Committee of Medical Journal Editors (ICMJE) guidelines,[3] is frequently included in IISR agreements (69%). Site respondents included this in their agreements 50% of the time, while industry respondents were much more likely (76%) to include this within the contract.

Milestones included in the study agreement varied widely across the study respondents. The majority of respondents included milestones related to critical deliverables or process steps (75%), study results (65%), finances (58%), or periodic status updates (52%). Industry respondents were more likely to include financial milestones, while only site respondents stated that they were party to agreements that included upfront payments with no contracted milestones.

The approach to indemnification varied widely across survey respondents when they were given the options of no indemnification clause (33%), explicitly stating that indemnification will not be provided by the respondent (29%), indemnification provided (21%), or indemnification only provided when required by local law (17%). Industry respondents made up the bulk of the respondents who would not provide indemnification for the research (86%). Interestingly, a significant minority of the site respondents favored not including an indemnification clause in the agreement at all (five of 12, 42%).

Lastly, respondents were asked if specific clauses giving reasons for terminating a study were routinely included in agreements (see Table 1). While the response of "without cause" was not included in the original survey options, a number of respondents indicated that this was common practice at their organization. We recommend that future surveys explore the situations in which studies may be terminated.

The purpose of IISR programs is to provide access to funding and/or product so that qualified researchers are able to conduct and publish independently generated evidence.

TABLE 1: Use of Clauses Regarding Termination of Study in Trial Agreements

Response	N (of 48)	Percent
Preliminary Safety Data Indicating Undue Harm or Risk to Subjects	27	56%
Lack of Study Progress	26	54%
Protocol Amendments or Changes that are Not Agreed Upon	18	38%
Study is no Longer Medically or Scientifically Relevant	15	31%
Without Cause	10	21%
No Termination Clause	2	4%
Other—Breach in Good Clinical Practice	1	2%

Compliance

The Foreign Corrupt Practices Act (FCPA)[4] is a U.S. federal law that is jointly enforced by the Securities and Exchange Commission and the Department of Justice. The FCPA makes it illegal for U.S. companies to influence anyone with personal rewards, or bribes, for business. About half of the survey's industry respondents (52%) and a third of site respondents (33%) self-reported that their organizations had an established policy for IISR studies in

relation to the FCPA. Of those with a policy, the vast majority (88%) indicated that the policy applied to all IISR studies, with a handful carving out exceptions for studies that involved funding below a minimum threshold value.

Further, some governments recently have created transparency reporting laws for the "transfers of value" made from manufacturers to healthcare providers. In the United States, transparency laws have been formalized under the "Open Payments" portion of the Patient Protection and Affordable Care Act,[5] while in the United Kingdom they are within the Association of the British Pharmaceutical Industry's (ABPI's) *Code of Practice for the Pharmaceutical Industry 2015*.[6] Other guidelines are under way in a number of other countries.

The purpose of these laws is to limit the influence of industry on prescribers. Nearly all of industry and site respondents (91%) from the United States and United Kingdom have an established process by which IISR studies are included in their reporting obligations. Respondents outside the U.S. and U.K. infrequently had established processes, indicating that caution should be used when there are "transfers of value" outside one's home country.

Meanwhile, one of the key risk areas for IISR compliance is the delineation of roles and responsibilities between the investigator-sponsor and the industry supporter. Industry respondents reported that they had little to limited involvement with the development of the research protocol (see Figure 5).

In addition to protocol development, industry's involvement in the writing of publications based on IISR studies is another well-known risk area. Table 2 outlines industry and site responses on existing policies tied to IISR-related publications.

When it comes to safety reporting, the investigator-sponsor is responsible for collecting and reporting all applicable adverse events (AEs) to the relevant regulatory authority within the appropriate timeframe. Additionally, the industry supporter has a vested interest in understanding the safety profile of their product, and may have additional reporting obligations in other countries where the company seeks product approval.

FIGURE 5: IISR Study Roles and Responsibilities by Organization

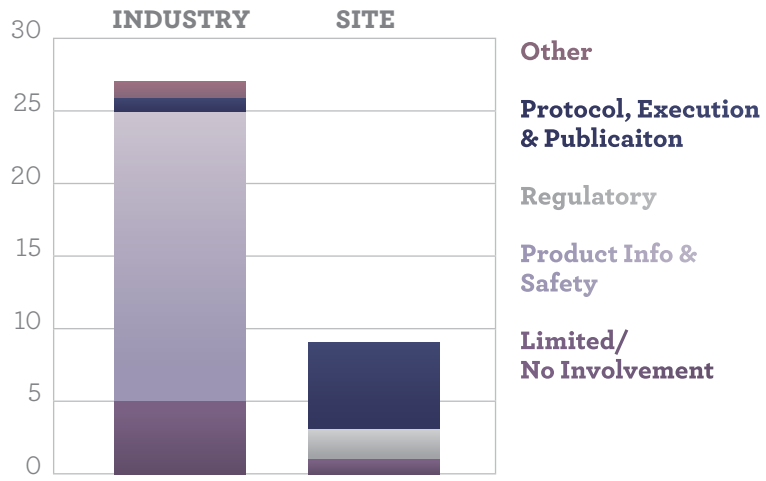


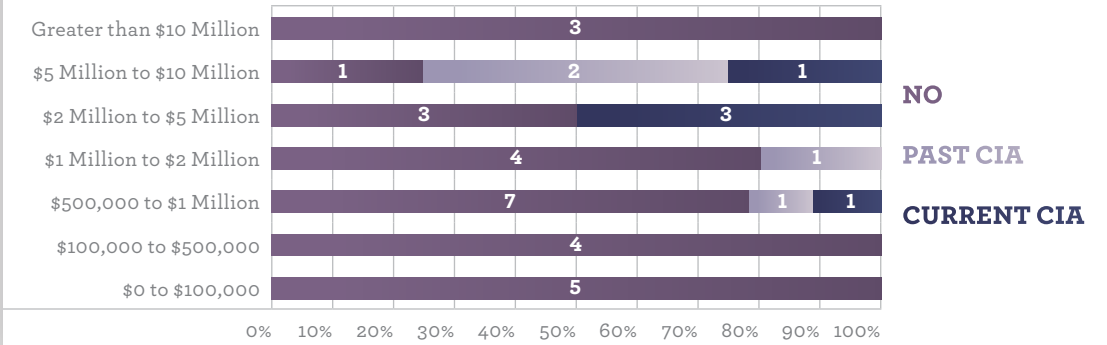
TABLE 2: Industry and Site Responses on Existing Policies Tied to IISR-Related Publications

IISR Policy Points on Publications	Industry	Site	Overall
Industry review prior to disclosure	27 (100%)	1 (11%)	28 (78%)
Disclosure of the company's support	15 (56%)	7 (78%)	22 (61%)
Compliance with ICMJE guidelines	13 (48%)	6 (67%)	19 (53%)
Confidential information redacted upon request	12 (44%)	4 (44%)	16 (44%)
No policy	0 (0%)	1 (11%)	1 (3%)
Total	27	9	36

Of industry respondents, 46% required investigator-sponsors to provide only serious AEs within a given timeframe of awareness of the event, 27% required all AEs within a given timeframe, and 27% required all AEs without a timeframe specified. Further surveys are needed to determine the periodicity of AEs that are not collected within a given timeframe of awareness of the event.

Taking a look at compliance enforcement actions, 75% of industry and site survey respondents have not been under a government Corporate Integrity Agreement (CIA), 11% had previously been under one (all industry), and 13% were currently under a CIA (four industry respondents, one site respondent).

Figure 6: Size of the IISR Program Based on the Annual Support Provided as it Relates to CIA Enforcement



As one would expect, enforcement action closely correlates to the overall budget of an IISR program; higher volume means higher scrutiny (see Figure 6).

Systems, Metrics, Approvals, and Durations

Industry respondents were more likely to utilize a commercial IISR system (65%) either alone or in combination with other systems to track study progress, while site respondents were more likely to record all details in hardcopy format or to store them in a clinical trial management system (CTMS) (50%). Only four respondents from industry and one from a site (15%) strictly utilized an in-house system that had been tailored for IISR tracking.

Respondents felt that IISR personnel were sufficiently trained to set up metrics within their current system and conducted metrics that met (38%) or partially met (35%) their needs for improvement. We also found a strong correlation between the overall IISR budget and satisfaction with metrics; organizations with less than $500,000 annual investment were generally dissatisfied, while organizations with more than $2 million annual investment were satisfied with their current metrics.

As Figure 7 demonstrates, when systems were called out separately, 26% were satisfied, 56% saw a need for greater efficiency, and 18% were dissatisfied with their current systems. Nearly 73% of industry respondents receive IISR submissions via a webportal, with 27% receiving hard-copy submissions.

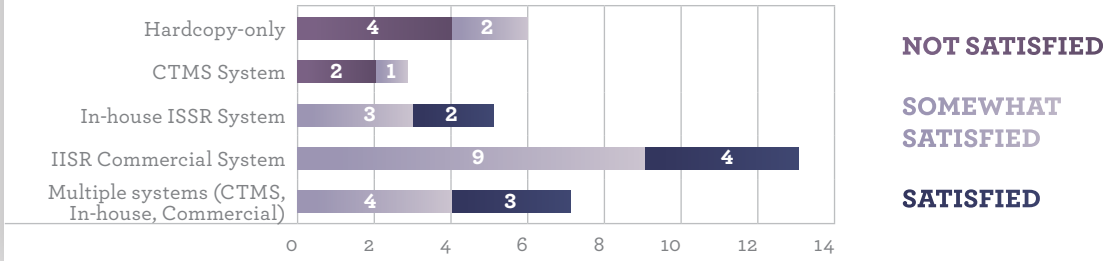
There was a bell curve distribution of time from submission to decision with a median of nearly three months. Sites responded that the majority of IISR studies were approved, while industry stated that a little less than half were approved. Combining these two elements, organizations with high approval rates normally responded in less than two months, while organizations who approved 26% to 50% of submissions took between two and four months to reach a decision, substantiating the idea of the "slow no."

The majority of respondents indicated that the median duration of IISR studies was two to three years (74%). The median time from study closure to receipt of clinical study report was one year, however, a significant minority (26%) reported that the median time to publication was more than two years.

When looking at IISR completion rates, the median response across all survey respondents was 75%, however site respondents generally reported a lower rate than industry respondents. This may reflect a difference in how "completion" was interpreted—as either complete enrollment, the achievement of the primary objective, or the disclosure of study results through a conference presentation or publication in a journal.

One of the key risk areas for IISR compliance is the delineation of roles and responsibilities between the investigator-sponsor and the industry supporter. Industry respondents reported that they had little to limited involvement with the development of the research protocol.

Figure 7: Satisfaction with System by System



Conclusions and Next Steps

Results from the 2015 ACRP Investigator Research Interest Group survey provide insight into how sites and industry handle different aspects of IISR studies. Our recommendation is that future surveys should include both shared and separate questions for site and industry respondents, in order to prevent survey fatigue. In particular, smaller, targeted surveys are recommended to evaluate perceptions of site/industry partners, contracting, safety reporting, metrics assessments, and training needs.

These survey results support the view that sites and industry continue to view investigator-sponsored research very differently. IISR studies are considered important for evidence generation, and programs are growing in spite of increased regulations and legal enforcement actions.

Where IISR studies are concerned, industry aims to comply with regulations, support new research, and maintain its budgetary commitments; sites are focused on the development and dissemination of evidence. Investigators can more effectively target study support opportunities by understanding the needs of industry and communicating their own needs, thereby improving the chance that their research requests will be approved and will positively impact the community as a whole.

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These survey results support the view that sites and industry continue to view investigator-sponsored research very differently.

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Insights On the Talent Shortage Situation

Both sides of the career equation—employers and employees—are in great flux these days. As talent levels ebb and flow, employers and clinical research professionals must also navigate ever-changing demands brought on by new technologies and best practices. Taking a hard look at this environment, financial analyst Douglas Bryant III, an assistant vice president with the Cate Bryant Houser Group and member of the ACRP Board of Trustees, shared his thoughts with *Clinical Researcher* in a recent interview conducted by Editor-in-Chief James Michael Causey.

Q: Imagine I'm speaking as an employer, saying I know there is a shortage of talent out there. How do I get the best employees in that kind of environment?

The by-products of a low barrier to entry and the mindset that there is a talent shortage are poor hiring decisions and short careers.

A: Hire hard up front. As leaders, we have made the barrier to entry into any good company too easy. I believe this is a direct result of the perception that there is a talent shortage. The by-products of a low barrier to entry and the mindset that there is a talent shortage are poor hiring decisions and short careers.

If you make the mountain of getting into a good company higher, the employee begins to really buy into a few concepts that will be win-win for the employee and the company, including:

- The employee feels a sense of accomplishment by gaining entry into the company. A grateful employee yields a good work culture that promotes loyalty and dedication.
- The employee looks at the position as a career, as opposed to a job. People job hop. In fact, the modern odds of a person staying with one company more than 10 years are very low, simply because the employee and the company look at the position like a job. When you develop the environment and the mentality that the position is a career, all of a sudden, the employee does not see limitations or ceilings and has less incentive to look around for other opportunities. The employee commitment is stronger.

Q: Speaking as an employee now, I'm in the driver seat today, but that could change. What's the best way to position myself now to help me grow in the future?

A: Lose the mentality that you are in the driver's seat. You have to keep your competitive edge. A small dose of fear can help you maintain that edge. It can also prepare you in advance for the always-present risks associated with growth, including competition, regulatory hurdles, and innovation.

With that in mind, the best way to position yourself now to help with growth in the future is to always be recruiting. Human capital is your most valuable resource, and therefore recruiting before the need arises is the best way to win the talent you need to support future growth.

For instance, my investment advising practice is in a serious growth mode, and likely will be for the next 10 years. My strategic plan calls for aggressive growth. At this precise moment, though, I don't have room nor can I support a new client associate. However, I anticipate the capacity to do so in the next eight to 12 months. Therefore I am looking "softly" for talent to fill that position. The typical job description is not what I am using to find this talent. Whether it is a junior advisor or a client associate, I am, of course always looking for the basic position requirements. However, I am also looking for someone who can see himself

or herself as a partner. If the talent can't envision partnership, then they don't have the extra qualities I need to sustain growth and overcome risks.

The best way to position yourself for future growth is to recognize that human capital is your most valuable resource. You must always be seeking new talent; talent with the ambition and vision to see being a partner/owner in his or her future.

Q: What are the most common characteristics you see with a good boss? A bad boss?

A: First, a good leader doesn't see him or herself as a boss. Leadership doesn't recognize the title; but for the sake of answering this question, I will use the word boss. A good boss is unselfish and always seeking to grow people. A good boss recognizes human capital and does not place the customer first. If you place the employee first and that employee reflects the leadership of the good boss, the customer will always be taken care of.

Other characteristics I like to see in leadership include being a visionary, a change agent, purposeful, and passionate.

In regards to a bad boss, I would have to state that this person thinks of himself as a boss. He or she doesn't develop people and is very selfish.

Q: On the employee side, how can I make sure to get credit for something important at work without looking like I'm selfish or a grandstander?

A: This can be a thin line, but I've always lived by this motto: "Let your success make all the noise." Your efforts may go unnoticed for a short period of time, but eventually, your success will be so loud that everyone around you, including your peers and leadership, will have to cover their ears.

You don't have to seek the spotlight when your success becomes loud. My advice is simply not to seek credit. Include others in your success. The spotlight and credit will find you.

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Culture-Driven Patient Recruitment and Retention

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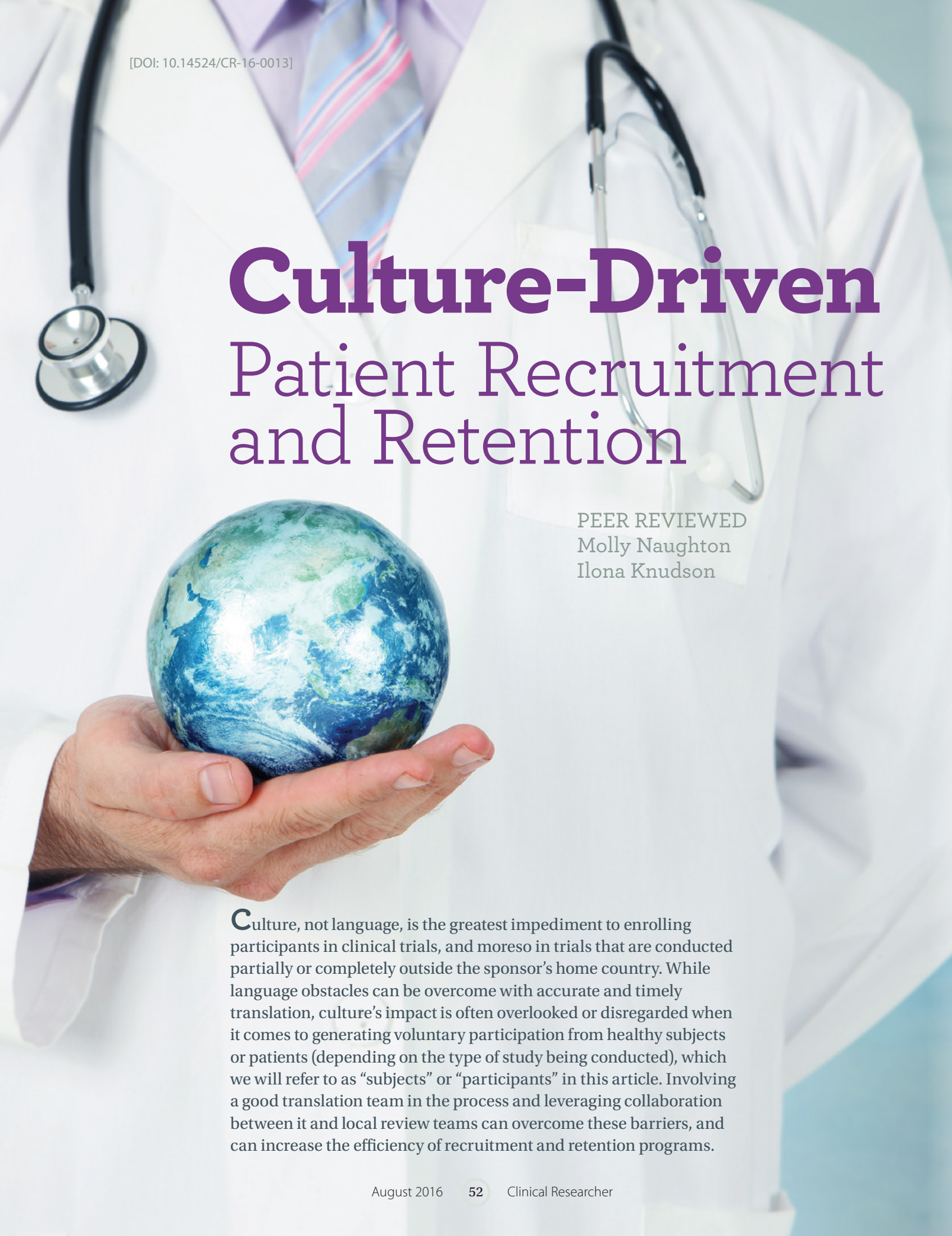

Culture, not language, is the greatest impediment to enrolling participants in clinical trials, and moreso in trials that are conducted partially or completely outside the sponsor's home country. While language obstacles can be overcome with accurate and timely translation, culture's impact is often overlooked or disregarded when it comes to generating voluntary participation from healthy subjects or patients (depending on the type of study being conducted), which we will refer to as "subjects" or "participants" in this article. Involving a good translation team in the process and leveraging collaboration between it and local review teams can overcome these barriers, and can increase the efficiency of recruitment and retention programs.

Subject Recruitment is Key

Human clinical trials would not exist without the participation of volunteer subjects. Obtaining speedy enrollment lowers overall study cost and improves feasibility. The integrity of a trial's outcome lies in retrieving reliable data from enough participants. The capture of clean, high-quality data relies on communications with participants that are clear, concise, and culturally appropriate.

It's a fact: subject recruitment can make or break a clinical drug trial. Most pharmaceutical industry studies indicate as much as 80% to 90% of clinical trials fail to close on time, and at least 72% overrun their projected schedules by at least one month.[1] With the average cost of running a Phase III trial of approximately $35,000 per day, time is indeed money. Although other factors contribute, the "usual" culprit causing trials to run over is a lack of consistent enrollment at the study sites.

Simply recruiting large numbers of people for a study is not enough. To be viable, participants must remain in the study for its duration to provide tangible results. For this reason, selecting the right subjects from the outset increases the rate of long-term retention.

With this in mind, many study sponsors spend hundreds of thousands of dollars to hire a firm to develop a recruitment and retention strategy. Using demographics, psychological profiling, and statistical research, the firm's staff (or possibly outsourced consultants) will take the subject criteria for the protocol, crunch the numbers, and determine potential populations for the study. They figure out who the target subjects are, where they are, and the modes for communicating with them to elicit participation.

From the depths of this market research, a recruitment and retention program is initiated, featuring tools developed to attract the right kind of subjects and keep them involved. Participants are provided with important information about inclusion and exclusion criteria and visit schedules. Physicians are provided with succinct data to explain the study. Subjects feel their participation is important and relevant through newsletters and educational materials.

However, what happens when a study site is located outside the sponsor's home country? Do trial sponsors consider what makes people feel involved in research in, for instance, Thailand? Or how health information is delivered in Costa Rica? It is important to understand that recruitment is not enhanced by translation alone. Changing English into Hindi does not create a culturally sensitive Indian document.

In such transnational situations, should the recruitment strategy change to produce successful and consistent patient enrollment? The answer is an overwhelming "Yes!" Patient recruitment programs are not "one size fits all," and need to change to fit the cultural norms of the study's target population. Cultural issues like credibility and autonomy play a large role in whether or not an individual will participate in a clinical trial. Let's explore.

Credibility

Consider a scenario that begins in the United States, with a sponsor running radio ads encouraging people with a specific ailment and whose situations satisfy certain criteria to inquire about participating in a clinical study. Next, the study sites are expanded to South Korea. Documents are sent to the translation agency—radio spots included. Translations are completed, with a Korean voice talent providing the audio. It sounds great; unfortunately, no one back in the U.S. contemplated that Koreans consider radio ads an untrustworthy source for health information, preferring to place their trust in doctors as information resources. The investment is lost.

In many countries, doctors, empowered with knowledge not shared by a majority of the population, are considered to be omnipotent. In the U.S., approximately 66% of study participants are enrolled independently of their physicians, while in Latin America, studies suggest 80% were enrolled because of their doctor[2]; from this, we can see that a decrease in recruitment initiatives outside the doctor's office, along with a reinvestment and refocusing of initiatives directed at the physician, makes sense in parts of Latin America.

Many agencies make the mistake of trying to recruit within a community context in other countries, for example by placing posters in houses of worship and neighborhood centers. While this makes sense for nonmedical purposes, the average Latin American (or citizen of many other countries, for that matter) does not expect to find promotions about participation in medical research in a church or other types of social settings instead of at a doctor's office.

In the U.S.,

66%

of study participants are enrolled independently of their physicians.

In Latin America

80%

were enrolled because of their doctor.

Autonomy

Global studies recruiting geriatric or pediatric populations suffer from additional cultural barriers. Similar to U.S.-based trials, whether or not to participate is not generally an individual decision in these populations. Aiming recruitment and retention tools at the individual is ineffective because characteristics of the culture surrounding that group or family need to be considered. Caregivers will be involved in the decision-making process, but how does culture affect the role of caregivers in different nations and regions of the world? What motivates and influences decisions made by a patient's caregiver?

There are many factors influencing a caregiver's support of a clinical trial that need to be considered in recruitment and retention tools. For some cultures, simply helping to advance science and medicine is reward enough. The fact that the clinical trial will help cure a disease will be motivation enough. In the United States, on the other hand, convenience is a major motivating factor for participation in caregiver-led studies, so having few trial sites in remote locations will not yield good results.

For the residents of emerging settings for clinical trials in Eastern Europe, Asia, and South America, an opportunity to obtain access to treatment is the biggest incentive for participation.[3] In South African culture, as an example, familial responsibility and improved access to quality healthcare are equally important, and sponsors find providing additional basic healthcare services at sites keeps patients and their caregivers both involved and healthy.

What about studies targeted at women in patriarchal societies like India? Sponsors or contract research organizations (CROs) translate their newsletter and patient study information documents (targeted for women) into Hindi and put the drug name on pens and bags and other free giveaways, but if the Indian woman targeted for recruitment sees participation as something that requires her husband's consent, will she take part?

Indeed, the recruitment strategy for women in many target populations needs to be reshaped, independent of language. Resources need to be redirected and expanded to provide the potential participant with the tools she needs to involve and inform her spouse—and to obtain his support. For example, included in the recruitment documents could be a standard letter written to the spouse, explaining the process and requesting support for involvement. The cost is minimal but the benefit is tremendous.

While language obstacles can be overcome with accurate and timely translation, culture's impact is often overlooked or disregarded when it comes to generating voluntary participation from healthy subjects or patients.

Pediatrics: A Cross-Cultural Perspective on Recruitment

No matter the country setting, as contrasted with studies involving adults, pediatric trials are another issue altogether. The entire framework of the parents' emotional response, an important indicator in their consent for a child's participation, is altered depending on culture. The nature of parental anxiety accompanying the participation of a child in a clinical study can become quite complex when analyzed in a cross-cultural perspective. To assume this can be addressed as it is in the U.S. is to miss many cultural distinctions.

Further, recruitment strategies for pediatric trials normally take into account the risk/reward ratio even more than in adult trials. Again, as part of the emotional response, parents hesitate to put their children through a process where the benefits do not outweigh risks. The challenge becomes defining risk and reward in the various countries from which patients are recruited.

What About Local Review?

Sponsors hosting studies in a foreign country surely benefit from having offices and personnel in and from that country able to review recruitment and retention materials at the local level for cultural applicability, but onsite review boards can only review the translated materials that actually reach them. For example, in one case, proposed materials for an obesity drug trial were translated at the local level for use in 28 countries, including counselor guides, patient participation guides, and other pamphlets, and all finished products were sent to sponsor/CRO personnel in the U.S. for review. Several tools were rejected at face value and never seen by the target countries' local review boards for evaluation of impact and recruitment utility. Thus, money was wasted upfront translating materials that never saw the light of day.

Source tools cannot be evaluated by a target country's local review board for cultural appropriateness because they are in English. If they are translated first, then sent for local review, money and time are wasted if they were off course from the start. If they need additional adjustments, more money is spent having them translated a second or third time. The overwhelming solution is to allow an experienced translator to culturally adapt the tools from the start, prior to receipt at the local sites. This improves efficiency, saves time and money, reduces workload at local sites, and increases the number of available and useful tools in the recruiting country.

Also, local review boards generally only localize content—the language of the document—rather than also adapting for culture. So, for instance, the generic Spanish word for "physical therapist" is "terapeuta físico," but in Colombia, the local institutional review board might switch this to "fisioterapeuta" without ever stopping to consider that a Latina woman considering participation has not been given tools to convince her husband to let her see a physical therapist in the first place.

Local investigators at review sites are not linguists, and they have specific jobs that do not focus on language. They can be valuable assets, however, and are part of the solution to developing culturally relevant patient recruitment campaigns. With appropriate time, a good translation partner can gather solid input from local sites while filtering out difficulties arising from a low level of English comprehension. Supporting a relationship where these two groups openly interact with each other to develop the most appropriate retention tools makes sense.

Tips for Creating Culture-Driven Recruitment

1. Determine the culture's primary source of health information. Is it the Internet? A doctor? A religious leader?
2. Determine the health decision maker in a family unit. Is it the mother? The father? The grandfather? The village elder?
3. Determine the literacy rates of decision makers and calculate the reach of printed documents versus seminars or radio ads.
4. Allow local country study coordinators to have a voice in cultural decisions.
5. Work with a specialized translation vendor who can ensure that cultural adaptations are made during the translation process.

Translators are Assets

Global clinical trials rely on translation. To obtain the most value from their translations, sponsors and CROs must ask more of their translation partners. Within this process lies an asset able to reduce expenditure on inappropriate tools and increase the effectiveness of tools that are culturally adapted.

Translators specializing in clinical trials understand the purpose and the goals of the studies. They understand the sponsor's need to enroll quickly, obtain valid consents, have ready access to their data, and be able to retain participants for the life of the study. They also understand that culture drives willingness or lack of willingness to consent—not language. Subtle changes can be made, within the translation process itself, to address any cultural issues that arise. Adapting recruitment and retention materials can be easily done, and can have a great impact across cultures.

To make the most of a global patient recruitment and retention program that allows for differences in culture, translation agencies need to be provided with a mandate allowing for excellence. This excellence comes from an increased focus on content and purpose. Translators need to be involved in the planning and implementation of the strategy for a trial, as well as to know when content is open for discussion and adaptation. Leveraging the translation process as an asset is crucial when translated documents and tools will ultimately be responsible for communicating across languages…and cultures.

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Industry Embraces Precision Clinical Trials

Adoption of precision clinical trials and the pursuit of personalized medicines are ascendant and inextricably linked, and neither show any signs of losing altitude any time soon, say a number of experts dotting the clinical research landscape.

In Pursuit of Precision

Institutions such as the Harvard Business School (HBS) are taking tangible steps designed to encourage precision clinical trials and the benefits of personalized medicine to help sponsors target individualized therapies.

HBS was recently part of a project that awarded $100,000 in prizes to the winner and two runners-up in its HBS/Kraft Precision Trials Challenge (PTC). "The objective of the challenge is to highlight innovations or ideas that show promise in either reducing costs or increasing the speed in which these go through the trial process," says Robert S. Huckman, faculty chair for the Health Care Initiative with HBS. The PTC was the first research pilot for new HBS/Kraft Precision Medicine Accelerator, propelled by a $20 million gift from the Kraft Family Foundation.

"Across topics ranging from identifying patients for targeted enrollment and matching biomarkers with off-label uses of drugs to conducting 'N-of-1' trials and sharing data, it was clear from the entries that precision medicine holds promise for reinventing the clinical trials process," Huckman says.

First place winner MatchMiner is an open computational platform developed at the Dana-Farber Cancer Institute (DFCI) for matching patient-specific genomic profiles to precision cancer medicine clinical trials.

Want to learn more about precision medicine, personalized trials, and other cutting-edge trends in the clinical research? Visit the ACRP Online Conference Library at www.prolibraries.com/acrp/?select=session&sessionID=1720 for details on "An Aerial View of Forces Reshaping the Global Clinical Research Enterprise," a keynote presentation by Ken Getz of the Tufts Center for the Study of Drug Development at the ACRP 2016 Meeting & Expo, and www.prolibraries.com/acrp/?select=session&sessionID=1511 for details on "The New World of Molecular Diagnostics in Cancer Clinical Trials—How Sponsors and IRBs Must Adapt," a regular session presented at the ACRP 2015 Global Conference & Exhibition.

The award "gives us a platform to make it open source," says Ethan Cerami, PhD, director of the Knowledge Systems Group in the Department of Biostatistics and Computational Biology with DFCI. The long-term goal is to accelerate the patient accrual rate and "help every patient maximize trials available to them," Cerami adds.

Others Weigh In

Supporters of the personalized concept are easy to find. "I recognize I have a bias, but I believe this is the absolute future of cancer research," says Dr. Maurie Markman, a physician and president of medicine and science at Cancer Treatment Centers of America. "This is exactly where we need to be moving forward."

Positive benefits to one side, no one is pretending adoption of these kind of trials won't present clinical research coordinators (CRC) with a wide array of new challenges. "It's harder because, quite frankly, we're talking about a new paradigm," Markman explains. As precision/personalization is not about focusing on a particular disease, CRCs might struggle with acceptance because that's not how they were trained to do their jobs, Markman adds.

The approach demands revising the standard operation procedure for connecting with potential patients, Markman says, adding that the treatment might be more difficult than with more traditional types of trials. For example, if a genome identifies that a patient's tumor contains a particular target that appears to match with the drug being tested, that requires explaining to the patient whether the target has proven its value yet.

"Maybe it hasn't, and you have to take the time to explain that properly," Markman elaborates.

"Patients will ask how they will benefit from this, and if the CRC is not well versed and able to clearly explain the potential benefits, that patient will feel like a guinea pig," says Christopher R. Cogle, MD, a professor of medicine at the University of Florida and scholar in clinical research with the Leukemia & Lymphoma Society. "We have many clinical trials, but if patients don't fit the [exact] eligibility criteria, we [currently] don't have a lot to offer them." That's the bad news.

The good news? While precision clinical trials require some new effort, they also promise vastly improved outcomes.

An investigator-initiated study would allow 100% of patients to be involved by capturing genomic data and drug sensitivities and matching that with specific patients, Cogle says. His organization was one of the PTC runners-up, cited for its "iCare for Cancer" project using patient-specific avatars for predicting drug response, discovering new indications for older drugs, and forecasting new drugs.

The other PTC runner-up is the Clinical Trials Co-Operative's "No Patient Left Behind" initiative, which set up patient-centric, biomarker-driven clinical trials cooperatives where companies participate and "buy in" with biomarker/drug pairs.

Looking for Brave CRCs

Cogle also believes that this brave new world demands some brave CRCs.

"A CRC has to be well versed in this technology and its ramifications," Cogle says. He works closely with his CRCs to help modify protocols as needed and educate them on the most appropriate way to collect specimens.

While the stereotype is that older employees tend resist change—especially new technologies—more than millennials, that's not been Cogle's experience. "Maybe I've been lucky, but the CRCs I've worked with embrace new ideas and new technologies," he says. "That's why they are CRCs. It's the 'R' in the job."

It's also important to remember not to be too dazzled by all the shiny new technologies and bright new ideas, Cogle and others emphasize. "Without fantastic CRCs, we wouldn't be as successful," Cogle notes. The work of CRCs to recruit patients and capture clinical outcomes is "absolutely critical" to the entire process, he says.

Sometimes it comes down to personality. "The gung ho CRCs get it," Cogle says. They relish learning something new, they are excited by new technology, and appreciate that this can offer some new opportunity for a patient stricken with, for example, certain blood-related or pancreatic cancers. "CRCs want to help to offer patients a new opportunity to fight back," Cogle concludes.

Across topics ranging from identifying patients for targeted enrollment and matching biomarkers with off-label uses of drugs to conducting 'N-of-1' trials and sharing data, it was clear from the entries that precision medicine holds promise for reinventing the clinical trials process.

James Michael Causey
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ADVANCES IN CLINICAL RESEARCH TOWARD THE Data-Driven Economy

PEER REVIEWED

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Clinical research encompasses gathering information to benchmark and define improvements on the last leg of translating innovative diagnostics, therapeutics, and strategies from discovery research into routine patient care. Such research has traditionally relied heavily on paper-based operations; however, the current data exploration era has introduced increasingly capable clinical trial management systems (CTMSs) and electronic data capture solutions that have replaced paper workflows to a large extent.

Despite these disruptive advancements, the clinical research enterprise still has to bridge tremendous gaps when it comes to interoperability, affordability, data quality, and patient recruitment. New technologies are now being leveraged not just to address these problems, but also to empower patients in a much more active role in clinical trials.

This article highlights how cutting-edge, ubiquitous, participatory, and rapidly expanding technology trends impact clinical research. Mobile devices, social networks, new computing paradigms, and interoperability standards help to democratize the field, thus enabling high-quality data collection and participant recruitment. The innovative developments demand multidimensional data analytics and secure computing infrastructures that are capable of scaling up to new requirements, and the availability of unprecedented amounts of diverse trial data.

The following six sections highlight some select technological advancement opportunities and their adoption by the research enterprise.

Mobile Technologies

Unprecedented adoption of mobile devices by nearly 90% of the U.S. population (and nearly 70% globally) presents itself as a low-cost technological opportunity to guide and monitor consumers regarding healthy lifestyle choices, nutrition intake, treatment adherence, biomedical tests (through wearable devices), and access to medical information. Due to the manner in which mobile technology may be integrated into one's daily life, it presents an unobtrusive way of collecting data at sampling frequencies that were previously unavailable.

In the U.S., around 64% of the population owns a smartphone and more than 93% of mobile device owners use the texting function, which makes texting an affordable dissemination mechanism.[1] Furthermore, with the increasing availability of interoperable and secure data-sharing platforms, some consumers have started to store their genomic and medical records (e.g., with Apple's ResearchKit and CareKit apps) in their devices to share them at their discretion during provider visits or to make them available for clinical studies.

Clinical research that engages in behavioral intervention studies, remote data collection, disease screening, and patient-reported outcome (PRO) collection could embrace mobile technologies to increasingly replace current methods with virtual interviews and online consenting.

The major challenges with mobile health include ensuring that information shared via the technology is based on the accepted medical evidence, especially during the dissemination of medical knowledge and/or interventions; and compliance with the privacy requirements of the Health Information Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health (HITECH) Act.

Social Networks

Social networks provide prospective and omnipresent opportunity to reinforce cultural norms by means of the dissemination of ideas and practices. Hence the unprecedented and inclusive growth of social network channels holds promise for those conducting evidence-based public health research, PRO research, disease surveillance, and pharmacovigilance.[2–4]

Patient-centric social networks both democratize access to clinical research information and positively influence subject recruitment by reaching out to wider populations than may often be the case in traditional recruitment efforts by study sites. For example, in 2013 the U.S.-based patient network and real-time research platform PatientsLikeMe® unveiled a global clinical trial tool that draws on "open data" to match patients from around the globe with clinical trials. Also, several studies have focused on how the Twitter platform can facilitate smoking cessation or timely adverse event capture through the "mining" of tweets.[4,5]

Based on a network of trusted relationships, Facebook offers people an opportunity to seek and find relevant medical information. Relying on this trend, the clinical research community has begun to publish dedicated pages on Facebook to inform visitors about conditions of interest, advertise related clinical trials, post alerts about new research opportunities, and maintain active relationships with enrolled trial participants.

Studies analyzing the online behavior of social media platforms have fueled some controversies among the clinical research community, privacy advocates, and the general population. This could be attributed to a gap between technological means, regulatory oversight, and cultural readiness considering established norms within the research enterprise. Nonetheless, as the members of new generations enter the ranks of both participants and researchers, these norms will shift and enable new social media practices that are both ethical and novel.

Improved Information Flow between EMR and Research Systems

The Institute of Medicine concluded that interconnected and interoperable data infrastructures would allow researchers to identify the interventions in practice that were the most cost effective and generated the best patient outcomes.[6] While the reuse of clinical data is hampered by the still prevailing disconnect between the data standards used in patient care and the ones used in clinical research, some efforts to bridge this gap are finally starting to take place.

An organization known as Integrating the Healthcare Enterprise (IHE) has been developing specific solutions to integration problems (called "profiles") to enhance interoperability between electronic medical records (EMRs) and CTMSs.[7] The profile designs aim to bridge the gap between clinical care and clinical research systems to greatly improve operational efficiency of study execution by reducing duplicate data entry and redundant workflows. Although IHE profiles have been in existence for some time, support by EMR and CTMS vendors has gained momentum only recently.

The Retrieve Process for Execution (RPE) profile orchestrates the transfer of data in a set of workflows with defined roles and operations. Clinical Research Process Content (CRPC) is an RPE-dependent content profile defining messages and processes relevant for transmission of new and updated study summary, subject enrollment, and patient study calendar data from the CTMS to the EMR. Clinical study initiation and budgeting are meticulous processes that depend on a detailed study calendar and pricing (which may differ from case to case based on study type and sponsor) via institutional charge master codes and associated fees. For each study, a schedule of events, procedure cost and price, and administrative fees (e.g., for institutional review board [IRB] services, staff, training) are entered into the CTMS in which Medicare Coverage Analysis (if appropriate), institutional approvals, and sponsor negotiations are performed.

Studies performed under an Investigational Device Exemption from the U.S. Food and Drug Administration (FDA) have additional budget constraints, including a medical device excise tax. Prior to the study initiation, the approved budget and calendar should be transferred to the EMR system intact, so that as medical staff follow and patients are subjected to the procedures defined by the protocol, any related billing/invoicing will occur in an accurate, complete, and timely manner.[8]

Some studies involve so many procedures, visits, and treatment arms that manual transfer of data from the CTMS to the EMR system becomes a cumbersome process that is prone to error. However, the RPE and CRPC profiles are quite instrumental in supporting transmission of the approved budget (billing grid), calendar, and study and subject synchronization details through which protocol compliance and proper reimbursements can be achieved. Unfortunately, making the transmission work in the other direction (i.e., notifying the CTMS on completed procedures from the EMR) is not within the scope of the protocol.

To address data collection challenges, IHE has created the Retrieve Form for Data (RFD) profile, which allows the electronic case report forms (eCRFs) to be filled within the EMRs. This profile supports initial extraction of some clinical information from the EMR by means of the consolidated Clinical Document Architecture (CDA) documents (part of the care coordination–centric rules introduced by stage 2 of the Meaningful Use certification). RFD also supports form management and data aggregation in dedicated clinical research systems supporting a many-to-many eCRF distribution and data collection model.

Just like RPE, RFD defines interoperability workflow orchestration and has content-specific subprofiles:

- Clinical Research Data (CRD) for HL7 Continuity of Care Document (CCD)
- Redaction Service Profile (RSP)
- Drug Safety Content (DSC)
- Structured Data Capture (SDC)

These profiles are responsible for converting EMR data from HL7 to standards typically used in clinical research.

Further, the Clinical Data Interchange Standards Consortium (CDISC) has coined Operational Data Model (ODM) for eCRFs and Study Data Tabulation Model (SDTM) to support data interchange and archive. These two models were developed in order to allow submission of clinical study data to the FDA.

An item of significance in this context is that RFD implementations can support FDA guidance on electronic source (eSource) data, and can be aligned with the efforts of CDISC's eSource Data Interchange Group to encourage the research community's use of eSource data and available data standards.[9] Streamlining clinical research execution and data capture with the implementation of these profiles will, in all probability, have the biggest impact on addressing prevalent quality issues within clinical research.

Data Warehouses Become Data Lakes

The betterment of evidence-based translational medicine requires researchers to adapt to new information systems (e.g., the "cloud") and approaches (e.g., "big data" analytics) that can process and analyze data for multiple clinical research stakeholders in a cost- and time-effective manner globally.[10] Many experts suggest that the research community needs to collect, organize, analyze, and comprehend heterogeneous, hierarchical information at a vast scale due to the variety of data standards that exist at different levels of time, space, and organizational complexity.

The clinical research enterprise still has to bridge tremendous gaps when it comes to interoperability, affordability, data quality, and patient recruitment.

Relational database management systems and star/snowflake schemas are proven traditional models for use in business intelligence and analytic processing of structured clinical research data. NoSQL data store systems do not require data transformation into a physical schema, and thus are much better suited to tackle the unstructured, semistructured data prevalent in clinical documentation with highly scalable query and data access mechanisms.

Currently, many organizations utilize one of various commercially available data warehouse systems or the National Institutes for Health–funded Informatics for Integrating Biology & the Bedside (i2b2) software to house patients' clinical, study, and genomic data as a framework for researchers to query for study feasibility. With more widely available high-performance computing architectures, the traditional structured data warehouses will be substituted for so-called "data lake" and "Lambda" storage and processing architectures, which provide generic, scalable, fault-tolerant, and flexible platforms to accommodate diverse datasets and changing requirements.

The most widespread implementation of the data lake technology is the highly scalable Apache Hadoop–based processing platforms, which can exploit, for instance, the Greenplum Database, Hadoop File System (HDFS) storage, and Hadoop with Query (HAWQ), a parallel SQL query engine on Hadoop for unstructured data. Additionally, Hadoop is very cost effective, with some companies suggesting that it retains up to 10% of the traditional SQL solutions, considering yearly hardware and software costs.[11]

High-Performance Computing and Cloud Platforms

In our ever-changing world of connected devices, hardware is becoming a commodity. Cloud computing fosters transformation of software into a more attractive service utility (i.e., Software as a Service [SaaS]) or manageable platforms (i.e., Platform as a Service [PaaS]). Therefore, cloud solutions can easily scale due to highly elastic nature. Furthermore, many researchers have studied cloud security and data privacy.[12–15] Accordingly, some cloud vendors market their services as being in compliance with the Federal Information Security Management Act (FISMA) and HIPAA, which is a necessity for U.S. agencies.

In addition, traditional biomedical research analysis models rely heavily on a local/desktop computing paradigm, in which researchers download data for processing by running algorithms on local hardware. The sheer amount of available biomedical data (e.g., molecular, imaging, clinical, patient reporting) creates pressure for a paradigm shift toward elastic infrastructures allowing translational researchers to integrate and process complex data for generating actionable insights in large team settings.

For instance, the National Cancer Institute (NCI) has invested in the Genomic Data Commons (GDC) and the NCI Genomics Cloud Pilots program to address the aforementioned challenges. GDC serves as data repository to house data from The Cancer Genome Atlas (TCGA) and other cancer initiatives, while the Cloud Pilots demonstrate how cloud-based technologies allow researchers to analyze large-scale datasets and perform experiments from one location. Additionally, the Global Alliance for Genomics and Health (GA4GH) has defined open application program interfaces for researchers to access TCGA data and, more importantly, to analyze these data with computational tools embedded in a cloud infrastructure.[16]

National Data Networks and Data Exchange

Numerous federated distributed networks (i.e., ones in which users are able to send messages from one network to the other) have been established among organizations to allow researchers to access data via single search requests to the federation's search engines in a privacy-compliant manner. Federated data network technologies such as POPMEDNET and Shared Health Research Information Network (SHRINE) allow software governance by only returning aggregate patient count for hypothesis testing and cohort discovery based on an agreed-upon data model (e.g., the Patient-Centered Clinical Research Network [PCORnet] developed the Common Data Model). These networks are particularly critical for rare disease or geographically distributed large cohort studies.

Since 2013, the FDA's OpenFDA program has provided easy access to public data, creating a new level of openness and ensuring the privacy and security of public data. The availability of online information about such matters as medical devices, drug side effects, and food recall notices is remarkable, as it can now be integrated into clinical research and analytics pipelines. OpenFDA also drives interoperability by pioneering new modes of data exchange between the FDA, contract research organizations, and other clinical research stakeholders.

Discussion and Challenges

Engaged digital consumers generate an incomparable amount of personal, lifestyle, environmental, dietary, and biomedical data; however, low data quality continues to present a significant hurdle for clinical research.[17–20] The problem is partly due to the complex nature of the biomedical domain, but also related to insufficient data governance, user training, best practices, and user-friendly system designs.[21,22]

Regardless of high demand from users, the interoperability and utilization of available standards are usually restricted to settings within institutions, rather than across them, due to the unwillingness of competitive vendors to share

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information, nonstandard/incompatible system implementations, and privacy concerns. This disconnect can cause up to 56% of data to be unusable in a network,[23] and may require more resources than ideal to be utilized for training staff about studies at separate sites instead of across multiple sites at once.

We also acknowledge that, despite the availability of central IRBs and other potentially shared services, the vast number of systems and processes involved makes for a burdensome environment in which to navigate for relatively smaller organizations.

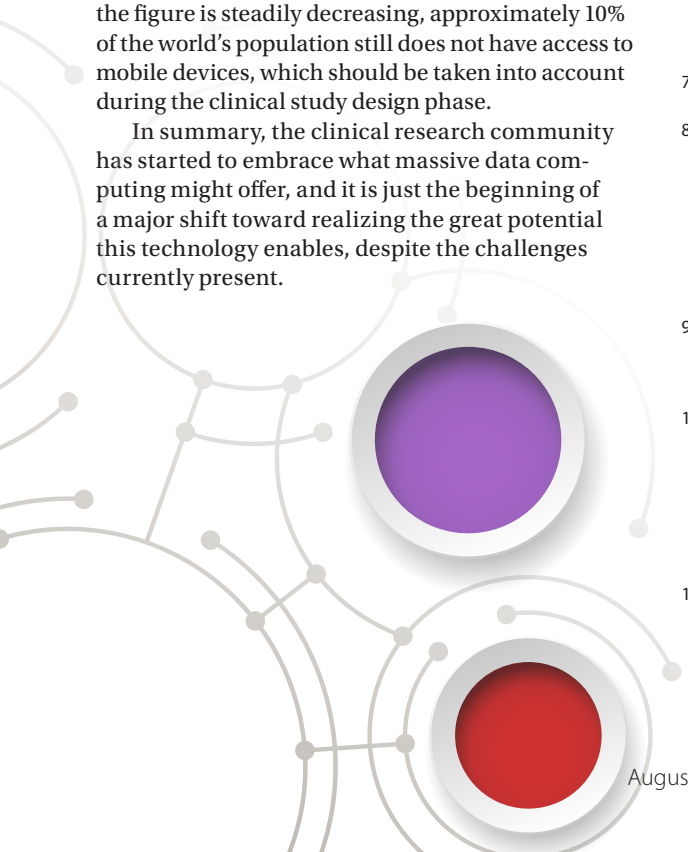
New parallel elastic architectures are capable of processing multidimensional data with lower costs. Hence, the cloud offers an alternative pricing model (pay-per-use) for organizations of any size to utilize instead of making major local investments in storage and processing technology.

Meanwhile, despite advancements in network technologies, it remains a challenging and time-consuming task to transfer large amounts of data. However, as "in-memory"/"in storage" computing (which relies on the idea of computing where the data are held) becomes more widely feasible and achieves the greatest possible performance for analytical processing, it alleviates computation and network bandwidth burdens on distributed data.[24,25]

While such technological advances as these enable scopes of research that were previously unthinkable, trained personnel with versatile skills across cognitive, computational, and biomedical sciences are in high demand.

Lastly, many global issues related to health disparities and the "digital divide" are complex and intertwined, with contributing factors that include low socioeconomic status, lack of access to care, and unhealthy lifestyles in various populations. While the figure is steadily decreasing, approximately 10% of the world's population still does not have access to mobile devices, which should be taken into account during the clinical study design phase.

In summary, the clinical research community has started to embrace what massive data computing might offer, and it is just the beginning of a major shift toward realizing the great potential this technology enables, despite the challenges currently present.



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QUICK TAKES:

Facebook-Based Trials, Communication Breakdowns, Wasteful Data Reporting

The ACRP Blog provides real-time news reporting and expert analysis on a wide range of issues impacting clinical researchers today. Here's a quick recap of a few recent posts. For the full versions, and to view other posts, go to https://acrpblog.org/.

Facebook-Fueled Trials: Opportunity or Threat?

A Phase IV clinical trial deemed "successful" by the firm that provided patient outreach technology for it is the type of new trial that will make the job of a clinical researcher coordinator (CRC) more "meaningful," according to Kai Langel, director of patient research and cofounder of eClinicalHealth Limited. The diabetes trial recruited all of its patients using only Facebook.

Far from being any kind of threat to CRCs, who often are tasked with patient recruitment, this kind of technology will spare them from some of the tedious administrative work that takes away time more productively spent looking at patient data and helping keep trials on track, Langel says. "CRCs shouldn't go looking for a new career," he stresses. "Their jobs won't go away no matter how good the tool."

Seventy-four individuals registered interest in the study through Facebook, and 60 were ultimately enrolled, for an 81% conversion ratio. That's a much better result than what is seen in typical online patient recruitment studies, according to eClinicalHealth. In addition, the study site estimated spending about two-thirds less of the investigator and study nurse's time on recruitment versus the usual situation in a trial that did not use online recruitment.

Flawed Nurse, Researcher Communication Can Create Trouble

Imagine you are a research nurse/clinical research coordinator (CRC) for an in-patient randomized, double-blind study that aims to lower "bad" cholesterol. One of your subjects is seen by a resident who is not on the study team, and who orders a lipid panel, the positive results of which are then shared with your subject by a non-team nurse before you realize what's going on. Whoops. So much for blinding the patient from knowing if she was receiving the active treatment or a placebo.

Shannon Huffaker, RN, MSN, CCRC, doesn't have to imagine this frustrating scenario. As a clinical research supervisor at Lehigh Valley Health Network in Allentown, Pa., she has witnessed this and similar circumstances, and now uses the anecdote as an example of the importance of effective

communication between researchers and the nurses who are providing the standard care for trial participants who are also hospitalized patients.

"The complexity of studies that makes communication so challenging in hospital settings includes such factors as study procedures that may seem 'tacked on' to standard of care to staff who are not directly involved in the study; the fact that several medical disciplines are often involved in any given study; and the likelihood that there are differences in local nursing practices from one hospital to another in multisite studies," she says.

Expert: Chronic Over-Reporting Wastes Valuable Time and Money

When it comes to reporting ongoing data updates in clinical trials, less is sometimes more, according to Lynn Meyer, CCRP, president of IntegReview IRB in Austin, Texas. "There's a lot of wasted energy spent on over-reporting ongoing trial results," she says. Unnecessary reporting to institutional review boards (IRBs) can cost an extra $5,000 per site, adds Meyer, offering some case study math showing how the situation can get out of hand:

- Coordinator spends 5 minutes submitting the Investigational New Drug (IND) safety report to an IRB and 5 minutes to get the principal investigator's signature and file everything in the site file
- 10 minutes x 10 reports/month = 100 minutes, or about 1.5 hours per month
- One protocol = 2 IND safety reports per month
- 2 x $25 (report) = $50 per site
- If 100 sites: $5,000 per month

It's a common and costly problem, Meyer says. It takes an experienced investigator to understand the nuances of the situation. While it is mandatory to report an unanticipated problem in a trial, inexperienced investigators sometimes feel that they are "safer" if they report on every little thing. "It's a lack of confidence" as much as it is a true understanding of what's required and what isn't, Meyer explains.

Help "Outsiders" Appreciate Value of Clinical Research

Site staff and sponsor-based personnel, and even some of the professionals operating in other parts of your hospital or physician practice, don't always understand how a strong research program can elevate your organization's public profile, lure the best job candidates, and contribute to the bottom line in a very real way, says Manda Materne, a former nurse in a big city emergency room and now Clinical Trials Pipeline Manager at GuideStar. She makes the case that research can:

- Increase ancillary services
- Minimize patient outmigration and attract new patients
- Create institutional donor opportunities
- Bolster the recruitment efforts to lure the right candidates and retain your stars
- Improve community health

Strong, proven research capabilities can provide a "halo effect" for the entire hospital or physician practice. Done right, a research unit enhances the image and reputation of your organization.

IN MEMORIAM

Christopher P. Allen, MB BS, 52, of Solebury Township, Pa., died at his home on July 2, 2016.

Allen was associate vice president for Global Medical Affairs at Merck in the Greater Philadelphia area and a former member of the Association Board of Trustees for ACRP. He had also served at various times as a president of the Academy of Physicians in Clinical Research (APCR) during its affiliation with ACRP, as vice president of international affairs for the Academy of Pharmaceutical Physicians and Investigators (APCR's predecessor), and as president of the International Federation of Associations of Pharmaceutical Physicians.

He was born and raised in Bristol, United Kingdom. He is survived by his wife Janet, son Jack, parents Philip and Mary, sister Gillian, and cat Yoda. Donations in his memory may be made to the Rescue Mission of Trenton, PO Box 790, Trenton, NJ 08605-0790 (rescuemissionoftrenton.org).

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