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- Our Principal Investigators are Board Certified Dermatologists and Certified Clinical Research Investigators with many years of extensive experience. They are located onsite and are available full-time.
- Most subjects are recruited from the office of our PI's private practice, and/or FXM Research's extensive clinical database. We draw heavily from a Spanish speaking population, a group often under-represented in clinical trials. We also have continuing extensive experience with a pediatric population.
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Clinical Researcher™
The Authority in Ethical, Responsible Clinical Research

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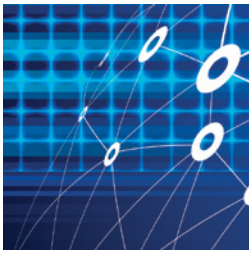

PEER REVIEWED

ACRP
FOR LEARNING FOR LISTENING FOR LIFE

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The October Surprise, Right on Schedule

MANAGING EDITOR'S MESSAGE
Gary W. Cramer

[DOI: 10.14524/CR-16-4045]

According to the poet W. H. Auden, "Routine, in an intelligent man, is a sign of ambition." On the other hand, "Routine and predictable days are the breeding grounds for complacency," warns Wayde Goodall in *"Why Great Men Fall: 15 Winning Strategies to Rise Above It All."*

So which is it? All I know is that anyone who works on a particular publication long enough can certainly fall into some comfortable routines that make the birth pangs of each issue easier to bear.

For example, up until a few years ago, it had long been our practice in putting together *Clinical Researcher* and its predecessor, *The Monitor,* to use at least one issue per year (often the October issue) as a bit of breathing space in between issues whose contents were geared mainly toward specific themes and solicited for us by guest editors who are experts in their specialty areas. This routine gave us the opportunity to "clear the pipeline" of miscellaneous articles that had come to us out of the blue (not intended for any particular themed issue) and passed muster with our Editorial Advisory Board reviewers, but then lingered in folders awaiting assignment to an issue—in some cases for nearly a year.

Still, rather than calling such issues our "Annual Grab Bag Special" or "Melting Pot o' Research," we did strive to find some sensible theme wording that would arise out of putting those pipeline articles together to identify any commonalities they might have. In case you ever wondered, this is how we arrived at such cover themes as "New Horizons in Clinical Research" (October 2011), "Strengthening the Clinical Trials Toolbox" (October 2012), "Beacons of Learning" (February 2013), "The Complexity of Clinical Trial Management" (February 2014), and "Human Subject Protections" (October 2014).

No Time Like the Present

As it turns out, from the December 2014 through August 2016 issues, we've had an uninterrupted string of enthusiastic guest editors who've brought in so many themed articles from their colleagues around the world that finding room for the pipeline articles—as high-quality contributions as they are—proved challenging. Thus, I breathed a small sigh of relief when it was evident that room on the publication schedule was opening up to make this issue one of our more, shall we say, eclectic ones in terms of content.

In "Monitoring of Clinical Trials—Are Remote Activities Helpful in Controlling Quality?", ACRP's 2016 Editorial Advisory Board Chair Michael R. Hamrell and colleagues highlight results from their survey of sites and sponsors regarding whether remote monitoring activities are viewed as beneficial or detrimental to an effective data quality program.

Next, Lindsay McNair, who guest-edited our February 2016 issue, returns with colleagues to address some of the complicating factors of "Getting the Right Signatures on Informed Consent Documents."

Rounding out the three articles forming the Home Study test for this issue is "Addressing Educational Gaps in Biomarker and Pharmacogenomics Research Knowledge Among IRB/IEC Members," brought to us by David J. Pulford and colleagues.

Elsewhere in these pages, Lorenz O. Lutherer and colleagues provide a first-hand overview of how clinical trials are run at Texas Tech University Health Sciences Center in "Academia, Investigator-Initiated Research, and a Unique Resource to Support Both."

Last, but not least, Shirley Trainor-Thomas and Manda Materne provide insights on the benefits of internal promotions about the conduct of clinical research to "Increase Awareness of Research in Your Organization by Using the Marketing Megaphone."

Five Articles in Search of a Theme

Sitting down and looking at these articles holistically, I couldn't help but feel that, although none of them were intended to feed off or bolster each other—arriving as they did separately across many months and from sources with quite different professional backgrounds—they nevertheless each touch upon one or more of the many barriers that exist to increased research efficiency at study sites. Hence, "Is Your Site Up to Speed?"

We hope the lessons you find in these pages are well worth learning, and that if the doldrums of sheer routine are keeping you or your organization from tackling barriers like those cited by our authors, you will heed the opinion of historian Arthur Helps, who said, "Routine is not organization, any more than paralysis is order."

I breathed a small sigh of relief when it was evident that room on the publication schedule was opening up to make this issue one of our more, shall we say, eclectic ones in terms of content.

Gary W. Cramer (gcramer@acrpnet.org) is managing editor for ACRP.

BY THE NUMBERS

A look at some of the facts and figures at play behind the scenes in the many moving parts of the clinical research enterprise.

A recent study reveals that **88%** of surveyed pharmaceutical companies do not complete commercial risk assessment activities until Phase III development, although **25%** of companies begin such activities during preclinical development.

Source: Marketwired, www.marketwired.com/press-release/-2151764.htm

In another new study, companies reported that site selection for new clinical trials took, on average, **3.2 months** and ranged from two weeks to six months. The reported average cycle time from site identification to site activation was **one year.**

Source: PR Newswire, www.prnewswire.com/news-releases/benchmark-study-assessing-study-startup-published-in-applied-clinical-trials-300314488.html

Is it acceptable for a doctor to attend a patient's funeral? Although the finding is not specific to principal investigators for clinical trials, **57%** of Australian doctors surveyed recently had attended at least one funeral of a patient; however, the number varied greatly depending on which medical specialization they had pursued.

Source: Newswise, www.newswise.com/articles/view/661304/?sc=mwhp

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Jim Kremidas

[DOI: 10.14524/CR-16-4036]

Learning, Listening, and Learning to Listen

For learning. For listening. For life. As I've said in earlier columns, we thought long and hard as we came up with a new slogan for our organization. We hoped to distill ACRP's mission down to a few words.

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

I've had the opportunity to do a lot of listening and learning in the past several months as I visited with ACRP chapters in Salt Lake City and Chicago. At press time, I was scheduled to meet chapter members in Nashville, Indianapolis, and North Carolina, as well. It's been an invaluable educational experience. I'm looking forward to meeting more and more ACRP members, even as I reflect on what I've learned so far in my first year with the Association.

Coming Through Loud and Clear

While each chapter contains members with unique concerns and ideas, I've been struck by how many shared ideas I've heard during my visits. Many of them echo what I heard at our Meeting & Expo in Atlanta last April, and in my other opportunities to interact with members.

The dominant message I heard is that you need and expect your professional association to help you keep up with changes in the rapidly evolving world of clinical trials. Whether it's explaining a new technology, shining a light on a trend in sponsor expectations, or simply helping "translate" some of those complicated guidance documents from the Food and Drug Administration and other regulatory authorities, I heard loud and clear that ACRP as an organization needs to be more proactive and nimble. We want to be there for you throughout the lifecycle of your career.

It's an exciting challenge, and we've already taken the first and second of what are planned to be many steps to help members continue to excel. I'd like to talk a little about those steps.

Focusing on Your Future

First, we are about to expand certification opportunities to better reflect the state of today's clinical research enterprise. These new opportunities will help to crystallize how roles in clinical trials have evolved. I'll talk more about that in a future column.

Second, we're working with you to develop eight clearly defined core competency domains for the clinical research professional. I'd like to briefly review them:

1. **Scientific Concepts and Research Design:** This encompasses knowledge of scientific concepts related to the design and analysis of clinical trials.
2. **Ethical and Participant Safety Considerations:** Encompasses care of patients, aspects of human subject protection, and safety in the conduct of a clinical trial.
3. **Medicines Development and Regulation:** Encompasses knowledge of how drugs, devices, and biologics are developed and regulated.
4. **Clinical Trials Operations:** Encompasses study management and Good Clinical Practice compliance, safety management to ensure adverse event identification and reporting, postmarketing surveillance, pharmacovigilance, and handling of investigational products.

> *The dominant message I heard is that you need and expect your organization to help you keep up with changes in the rapidly evolving world of clinical trials.*

5. **Study and Site Management:** Encompasses content required at the site level to run a study, including financial and personnel aspects. It also includes site and study operations.
6. **Data Management and Informatics:** Encompasses how data are acquired and managed during a clinical trial, including source data, data entry, queries, quality control and correction, and the concept of a locked database.
7. **Leadership and Professionalism:** Encompasses the principles and practice of leadership and professionalism in clinical research.
8. **Communication and Teamwork:** Encompasses all elements of communication within the site and between sites and sponsors, contract research organizations, and regulators, along with an understanding of the teamwork skills necessary for conducting a clinical trial.

Taking that final competency further, I must report that chapter members consistently told me they were frankly frustrated by what they perceive as the lack of communication they receive from sponsors. Sites don't always understand why or how a sponsor expects them to do something in a new way. Improving communication won't solve every problem or meet every challenge, but it will go a long way toward fostering important improvements across the board.

On the Road Again

Finally, I'd like to stress how inspiring it is to visit with the members who make ACRP Chapters such valuable resources for learning, networking, and spreading awareness of clinical research beyond our ranks. Over and over again I heard in your voices a rich passion and dedication to providing high-quality research. You are making a difference and you take that responsibility seriously. I'm looking forward to working with more of you in the future.

I have a final request. As we reach the end of 2016, the team at *Clinical Researcher* is reaching out in search of not just new scholarly articles for the peer-reviewed portions of this publication, but also for new columnists to reenergize columns whose traditional contributors have retired from such duties, or to bring us all-new ongoing columns on previously unexplored topics for 2017 and beyond. We welcome your input at editor@acrpnet.org.

Through the pages of this journal, and in everything else we do, your organization wants to help you share your best ideas and concerns with each other. I encourage you to share your ideas with us.

"I'm looking forward to meeting more and more ACRP members, even as I reflect on what I've learned so far in my first year with the Association."

[DOI: 10.14524/CR-16-4044]

The Lessons of Learning as You Go

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.

I started in clinical research 10 years ago, having left manufacturing and research and development to take a position as a research administrator. This move placed me into a role I knew little about, having not been engaged in clinical research beforehand. Adding to this was a lack of any formal training in the field.

What I did have, though, was a great staff, the members of which were not only knowledgeable about clinical research, but were able to show me what was involved.

I suppose the experience of having to learn the field of clinical research while working within it is not uncommon to many readers of *Clinical Researcher*. One can certainly learn a great deal from a colleague, but in the end it takes both the will of the individual to learn, and the organization to support that learning.

Learn, Learn, Then Learn Some More

A factor I learned early on in clinical research is that you never stop learning. Organizations that are involved in this field, whether they are sponsors of studies, contract research organizations, or study sites, need to understand this aspect of the enterprise in which we find ourselves.

On any given day, there may be new regulations to apply, a novel study to review, or a unique patient population to understand. What this all involves is a commitment to initial and ongoing education of stakeholders and personnel involved in clinical research.

You may think that I mean training, rather than education. True, training of personnel is a necessary factor in being successful. In this sense, training is a necessary component of being a clinical research professional. We start with learning about regulations, Good Clinical Practice, what a protocol is and how to manage a study, among other topics. These are parts of one's professional role and job function.

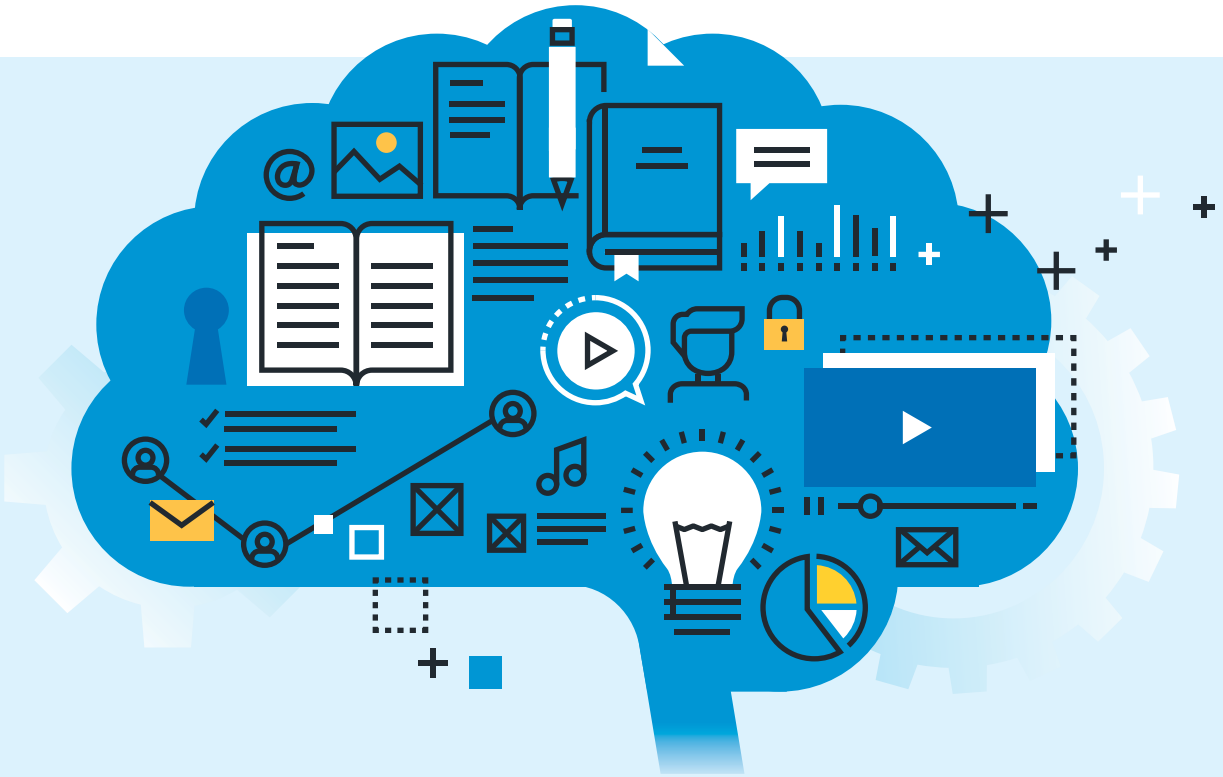
It is also true that training is part of education. However, education also means taking the initiative yourself. By so doing, you can further your own knowledge, and with it your career. This may entail pursuing professional certification, professional development opportunities, or even undergraduate and graduate degrees specializing in clinical research.

Some individuals may be fortunate to work in an organization that supports one's pursuit of additional knowledge through providing funding and/or time, as well as at least the possibility of advancement afterward. Many individuals, however, do not have this luxury, especially in a challenging economy.

Not a Luxury, But a Necessity

Commitment to ongoing education goes beyond what one's employer is willing or able to provide. It becomes a personal responsibility. An individual who feels that a better job can be secured, either within his or her own organization or another, can facilitate that rise by looking for opportunities on a private basis.

Some options leading to advancement can be expensive, especially if going for a degree; rather than being seen as an expense, however, the associated cost should be seen as an investment in oneself. Obtaining education beyond the demands of one's



job role not only adds to one's own knowledge and experience, it can demonstrate to a current or future employer valuable traits in an employee. These can be one's commitment to the field, ongoing self-improvement, and a sense of initiative and motivation that may, in itself, be more valuable than the actual knowledge gained.

The Options Abound

With all of these positive attributes present, how does an individual decide what type of education to pursue? This can depend on several factors; resources, including time and money of course, are important to consider. An effort should be made, however, as expending these resources constitutes an investment. It also involves what one's personal learning style and interests are like.

A desire or need to learn a specific topic may make a webinar or short course of interest. If instead the wish is for more in-depth or broad-based learning, attending a conference or seminar series may be more appropriate. A more formal avenue is the pursuit of an associate, bachelor's, or master's degree in the field.

Many people are also self-learners, and do best from picking up materials and knowledge on their own. Achieving professional certification can be a motivating factor to do just that, or a means to demonstrate what has been learned along the way. It was one way I learned about clinical research, other than from my colleagues. I realized that setting a goal of certification was a way to make myself learn what I needed to know.

Conclusion

As I stated above, education is more than training—it involves a commitment to learning more than you need (or may think you need) at the present time, a sense of curiosity, and an investment in oneself and one's career. Utilize the resources and options of your organization in deciding what route is best for you. You'll see the results in more ways than one.

Commitment to ongoing education goes beyond what one's employer is willing or able to provide. It becomes a personal responsibility.

For all the latest details about ACRP's Training & Development opportunities and resources, visit www.acrpnet.org/MainMenuCategory/education.aspx

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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Talent Management Tools and Tactics for Today's Researchers

James Michael Causey

[DOI: 10.14524/CR-16-4043]

Barring robots automating all of our jobs anytime soon, human talent management will remain one of the top challenges for leaders at study sites, sponsors, and contract research organizations, and for others in managerial roles in the clinical trial lifecycle for the foreseeable future.

For **Julie Locke, MBA, CCRA,** a former clinical research associate (CRA) and winner of the *PharmaTimes* "Project Manager of the Year" award in 2016, talent management starts with recognizing outstanding performers while hoping to inspire others by example.

"It's very nice to know my company would support me when I applied for the award," Locke says. The company knew it would require a lot of out-of-office work, and encouraged her to pursue it regardless of the time requirement, she adds. She's currently director of program delivery at InVentiv Health Clinical in Philadelphia, Pa.

Winning the award has sparked a sense of increased creativity for Locke. Further, her company recognizes the importance of the award on any number of levels, she says. It's encouraging a wider swath of employees to explore applying. Winning, or even the application process itself, helps "breathe life into what can be a stagnant project manager" job, Locke adds.

A lack of professional development support is an oft-cited reason employees seek opportunities elsewhere. Successful organizations develop existing talent by providing opportunities for professional growth and development.

MANY SOURCES OF INSPIRATION

Another way to inspire talent to perform at its best is to offer new training options, including encouraging them to attend conferences and participate in online learning and webinar opportunities. (For a full run down of ACRP's latest offerings, visit www.acrpnet.org/MainMenuCategory/Education.aspx.)

A lack of professional development support is an oft-cited reason employees seek opportunities elsewhere. Successful organizations develop existing talent by providing opportunities for professional growth and development.

According to the Great Places to Work Institute, employees at the 100 best places to work are provided 66 hours per year of training, with 40% of those hours dedicated to employee growth.

That's today. What about tomorrow? If predictions hold true, the need to manage talent will become more and more important in the years ahead.

BOTH SIDES OF THE EQUATION

On the hiring side, identifying the true "rock stars" will become almost mandatory. On the operations side, CRAs and others have some justification if they feel like superstar college athletes nailing down big signing bonuses, and should enjoy it while they can—the job landscape of the future could be quite a bit different, says **Jeff Kasher,** president of Patients Can't Wait LLC. Thanks to risk-based monitoring (RBM) (see the October 2015 *Clinical Researcher*) and data collection technology such as the Apple's ResearchKit™ (see the June 2015 *Clinical Researcher*), the job market for CRAs could shrink in half over the next five to 10 years, he says.

However, the remaining jobs will be tougher and demand more experience. Kasher's advice to the talent of today? Seek out new skill sets, for instance by focusing on project management or specializing in a particular therapeutic area. Tomorrow's CRAs will be expected to understand the big picture "connectivity of actions" in a clinical trial, Kasher says. That includes resource management and being able to drill down to face tough questions from sponsors or physicians.

RBM also demands strong data analytics skills and the ability to spot red flags in data remotely when the monitoring style is further tied to centralized monitoring. There will be fewer onsite visits in the clinical trial landscape of the future, Kasher says. CRAs will need a deeper understanding of trial protocols, so they can identify study issues that cannot be addressed from afar and merit an onsite visit.

TOO NARROW A FOCUS?

It's easy for overwhelmed sites to get off track and overlook critical gaps in their quality training programs, says **David Morin**, director of research at The Holston Medical Group in Kingsport, Tenn. "We're all so busy and resources are so tight," he acknowledges. That said, high-quality, proactive training is key to better site management and bolstering quality assurance (QA) performance throughout a site.

Some sites look at QA in too narrow a manner, Morin adds. "Many use it to focus on a review of a single problem or a way to be proactive" about a specific task or situation, he says, and fail to recognize that QA should apply to operations across the board.

Adequate QA programs should include strong training, hiring, and ongoing competency verification methodologies, Morin says. He advocates using mentors to help clinical research coordinators (CRCs) and others perform their tasks adequately. He also strongly believes in establishing other ways to ensure that employees continue to grow in their jobs and learn new skills to address new challenges as their positions evolve (e.g, internal testing with clear explanations of roles and responsibilities).

Give employees a stake in site operations, too, Morin adds. Synchronize root cause analysis and corrective and preventive action responsibilities with clear job descriptions, he suggests. Since "errors tend to happen early" in the process, he says vigilant, well-designed site quality management programs can make all the difference.

MAKING THE MODEL MAKE SENSE

The leaders of institutions involved in the conduct of clinical research have the option of various models for managing their clinical research personnel. When considering a centralized or hybrid model for management of such professionals, experts advise that the organizational leaders must engage stakeholders early and often in the process, and build in flexibility to acknowledge there is never a one-size-fits-all approach.

According to **Mindy Muenich** and **Nirmala Thevathasan** from Huron Consulting Group, external economic and regulatory pressures continue to create challenges in the field of clinical research, including a changing research funding landscape and increasing regulatory and reporting requirements.

Elements of the internal dynamics of a research enterprise such as calls to centralize administrative service operations for research and to improve workflow, time to enrollment, and cost recovery are all challenging institutions to think strategically about how to manage their clinical research personnel and operations in an efficient and cost-effective manner.

Muenich, a director with Huron Consulting Group's research services practice area who previously served as the director of Clinical and Translational Research Office at the Cincinnati Children's Hospital Medical Center and UC Health, has first-hand experience with these challenges.

While flexibility is the key when considering a centralized approach, Thevathasan stressed a few bedrock ideas. "Regardless of your staffing model, standardized processes are critical to successfully conducting research," she says. Thevathasan is a manager with Huron Consulting Group and was previously the associate director of the Clinical Trials Office at The Children's Hospital of Philadelphia.

Muenich and Thevathasan advocate for institutional leaders taking an in-depth look at the strategic and financial goals for engaging in research, and aligning their staffing models accordingly.

WHERE DO THEY SEE THEMSELVES IN X YEARS?

Finally, it's important to remember that your best talent sometimes makes its decision at the outset regarding whether they're going to stick around or not. More than one-third of employees make their decision to stay or go within the first month of employment, studies show.

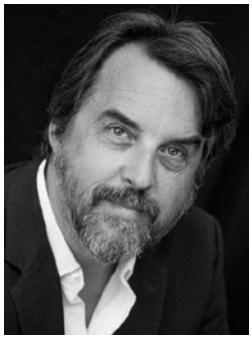
Given today's scramble for talent, now is the time to leverage any tool that can help retain top performers, says **Liz Wool, RN, BSN, CMT, CCRA,** global head of training with Barnett International.

Studies have also shown that a strong onboarding template, tailored to an individual employee, can cut retention by half and more than double that new employee's productivity almost from day one, she adds.

"The first day on the job is the most critical day in terms of the employee's lasting impression of his or her new employer," Wool notes. Managers should show enthusiasm for their new employee with an air of excitement ("I'm so glad I was able to get your talents for our organization") to an onboarding process that demonstrates the manager took the time to do it right.

There's nothing worse than appearing disorganized and making the new hire feel as though the manager threw something together haphazardly, Wool says.

More than one-third of employees make their decision to stay or go within the first month of employment, studies show.



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PI CORNER

Jeff Kingsley, DO, MBA, CPI

The Upside of Intervention in a World Full of Constraints

"Is Your Site Up to Speed?" and "Talent Management Tools and Tactics" are the running themes for this issue of *Clinical Researcher*—and good themes they are.

Let's talk about the talent in our organizations first. Do we always have a full complement of adequately trained talent on our research teams? I can guarantee you the answer is "no." I'm certain of this because contract research organizations continue to fly people to our offices, putting them up in hotel rooms for several days at a time so they can review our source documents.

Why do sponsors pay for all this? Because, despite our best efforts at the site, our source documents may harbor mistakes that these visiting clinical research associates (CRAs) help clean up. So is our internal talent adequate all the time, every time? Would an operating room (OR) at any hospital accept the error rates we accept

The simple act of establishing your desired result and measuring that which is associated with that result will improve your outcomes, even in the absence of a meaningful intervention.

in research? Would the National Aeronautics and Space Administration accept the error rates we accept in research? Would the Ritz Carlton hotel chain accept the error rates we accept in research? Of course, these are all rhetorical questions, because I know the answers.

Square Pegs in Round Holes?

This does not necessarily mean we have the wrong people on our teams. It more likely means we have inadequate talent development programs, inadequate resources, and inadequate processes.

The constraints are very real. I understand that no one is reimbursing us for adequate talent development or adequate process development, implementation, or maintenance; that does not mean it's acceptable for us to ever say "well, it is what it is." We would never have that attitude with error rates in the OR.

As for the "Is Your Site Up to Speed?" part of this issue's theme, it would include our quality assurance (QA) processes. In my experience, most sites really have no QA process at all—the data are collected and the CRA is the QA person. The errors caught are not collated in a way that would allow you and your team to learn from your mistakes and implement interventions capable of truly preventing future mistakes. Leading indicators (see my article in the August issue of *Clinical Researcher*) are not in place to catch errors before it's too late.

Whether or not you have a process you're proud of, if your error rate is above what is acceptable, then your process is in need of an upgrade. The problem is ours to fix—and we have the power to do so. It doesn't require a massive investment. No awe-inspiring training or lean six-sigma programs are necessary (although those would be nice).

The bottom line is that any intervention is better than nothing. Not much different from what we learned in medical school, right? Do *something*. Whether in your office, in a code situation, or receiving a trauma patient, we were taught that doing something is always better than doing nothing.

Further, we were all taught about the paralysis of analysis. If we allow a daunting, challenging, or confusing situation to slow our decision making or our intervention, then we have contributed to worsening a situation.

(It's Almost Always) Time for an Intervention

So here's my recommendation. Intervene. Everything you do will make a difference—I promise. Start having the conversation with your team; talk about your desired result and start measuring your current performance. The simple act of establishing your desired result and measuring that which is associated with that result will improve your outcomes, even in the absence of a meaningful intervention.

If you make a meaningful intervention and measure pre- and post-performance, all the better. Remember the "Hawthorne effect" (also known as the "observer effect"). In the late 1920s and early 1930s, Elton Mayo learned through a series of experiments that the mere act of measuring productivity with the desire of improving productivity produced the desired effect of improved productivity.[1]

For the experiments, Mayo and his colleagues increased the lighting in a factory and told factory workers that they were testing if it improved productivity. Productivity improved. They also changed rest breaks, and productivity improved. In all cases, productivity improved once a change was implemented, and then...drum roll, please... productivity even improved when the lights were again dimmed to where they started.

"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," according to Mayo's report.[2]

Lessons Learned

Don't underestimate your ability to make a meaningful improvement in your talent, your processes, your quality, and your outcomes simply by showing the team you care about improved performance—and one step better, that you demand improved performance. Communicate this regularly. Start measuring this. It really doesn't take much. Implement just a single, new intervention this week. Small. Simple.

Then, next week or even a month from now, implement just a little more. Or add a new conversation about how committed you are toward dramatically improving the quality of research.

You will make a difference.

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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

PRAHEALTHSCIENCES

HOME STUDY

HS

Is Your Site Up to Speed?

HOME STUDY TEST

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This test expires on October 31, 2017

(original release date: 10/1/2016)

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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As an organization accredited by the Accreditation Council for Continuing Medical Education (ACCME®), the Association of Clinical Research Professionals (ACRP) requires everyone who is in a position to control the planning of content of an education activity to disclose all relevant financial relationships with any commercial interest. Financial relationships in any amount, occurring within the past 12 months of the activity, including financial relationships of a spouse or life partner, that could create a conflict of interest are requested for disclosure.

The intent of this policy is not to prevent individuals with relevant financial relationships from participating; it is intended that such relationships be identified openly so that the audience may form their own judgments about the presentation and the presence of commercial bias with full disclosure of the facts. It remains for the audience to determine whether an individual's outside interests may reflect a possible bias in either the exposition or the conclusions presented.

80% The pass rate for the Home Study Test is now 80% to be in alignment with ACRP professional development standards.

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The Association of Clinical Research Professionals (ACRP) is an approved provider of medical, nursing, and clinical research continuing education credits.

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The Association of Clinical Research Professionals (ACRP) provides 3.0 contact hours for the completion of this educational activity. These contact hours can be used to meet the certifications maintenance requirement. (ACRP-2016-HMS-010)

Continuing Nursing Education

The California Board of Registered Nursing (Provider Number 11147) approves the Association of Clinical Research Professionals (ACRP) as a provider of continuing nursing education. This activity provides 3.0 nursing education credits. (Program Number 11147-2016-HMS-010)

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Monitoring of Clinical Trials—Are Remote Activities Helpful in Controlling Quality?

PEER REVIEWED | Michael R. Hamrell, PhD, RAC, FRAPS, RQAP-GCP, CCRA | Kathleen Mostek, RN, CCRC | Lyn Goldsmith, BSN, RN, MA, CCRC

[DOI: 10.14524/CR-15-0049]

The implementation of risk-based monitoring has spawned many forms of remote monitoring activities. This development has the potential to significantly impact how monitoring is accomplished for clinical trials. One question raised is whether remote monitoring activities are beneficial or detrimental to an effective data quality program.

LEARNING OBJECTIVE
After reading this article, participants should be able to define remote monitoring and evaluate its impact on study conduct.

DISCLOSURES
Michael R. Hamrell, PhD, RAC, FRAPS, RQAP-GCP, CCRA;
Kathleen Mostek, RN, CCRC;
Lyn Goldsmith, BSN, RN, MA, CCRC:
Nothing to disclose

A survey was undertaken to assess the utilization and considerations related to remote monitoring activities and their impacts on clinical data quality. The results presented here provide what the authors hope are some useful observations on how remote monitoring is perceived.

Background on Guidance and Regulations

U.S. Food and Drug Administration (FDA) regulations require sponsors to monitor the conduct and progress of their clinical investigations.[1] Similarly, the International Conference on Harmonization's Guideline for Good Clinical Practice (ICH GCP) E6 also requires that a clinical trial be monitored by the sponsor.[2]

FDA regulations are not specific about how sponsors are to conduct such monitoring, and its 2013 "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring" is therefore compatible with a range of approaches to monitoring (see section III) that will vary depending on multiple factors (see section IV.C).[3] For example, increased use of electronic systems and records and improvements in statistical assessments present opportunities for alternative monitoring approaches (e.g., centralized monitoring) that can improve the quality and efficiency of sponsor oversight of clinical investigations.

The agency encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight, in part by taking advantage of the innovations in modern clinical trials.

Monitoring activities include communication with the principal investigator (PI) and study site staff; review of the study site's processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor. Initiatives undertaken by the members of TransCelerate Biopharma Inc. related to monitoring also support the use of remote monitoring and other alternatives to traditional onsite monitoring visits.[4]

The 2013 guidance makes it clear that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring PI conduct and performance in Investigational New Drug studies conducted under FDA's *Code of Federal Regulations* as described in 21 CFR Part 312, or Investigational Device Exemption studies conducted as described in 21 CFR part 812.[1] The guidance describes strategies for monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. For example, the guidance specifically encourages greater use of centralized and remote monitoring methods where appropriate.

Taking a Closer Look at Monitoring

Periodic, frequent visits to each clinical site to evaluate study conduct and review data for each enrolled subject remains the predominant mechanism by which pharmaceutical, biotechnology, and medical device companies monitor the progress of clinical investigations. However, FDA encourages sponsors to tailor monitoring plans to the needs of the trial.

Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than any of the sites at which the clinical investigation is being conducted. Remote monitoring processes can provide many of the capabilities of onsite monitoring as well as additional capabilities.

Currently, FDA encourages greater use of such centralized monitoring practices where appropriate than has been the case historically, with correspondingly less emphasis on onsite monitoring.

The types of monitoring activities and the extent to which centralized monitoring practices can be employed depend on various factors, including the sponsor's use of electronic systems; the sponsor's access to subjects' electronic records, if applicable; the timeliness of data entry from paper case report forms, if applicable; and communication tools available to the sponsor and the study site.

Sponsors who plan to use centralized monitoring processes should ensure that the processes and expectations for site record keeping, data entry, and reporting are well defined and ensure timely access to clinical trial data and supporting documentation.

Survey Overview

In response to the varied considerations on what role centralized or remote monitoring plays in impacting current quality oversight of clinical trials, we conducted a survey of Association of Clinical Research Professionals (ACRP) members on their experience with remote monitoring. The survey was created by the team of presenters for a session on this topic for the ACRP 2015 Global Conference in Salt Lake City, Utah.

The survey focused on gathering perceptions for gauging the use and acceptability among clinical research staff of remote monitoring practices as part of the new, risk-based approach to clinical monitoring. Based on these initial results, any future studies would delve deeper into the specifics of the concerns identified.

The survey consisted of 15 questions regarding remote monitoring, and was posted on Survey Gizmo for approximately one month. The availability of the survey was posted on the ACRP Online Community and on LinkedIn.

RESPONSES AND LIMITATIONS

A total of 199 responses to the survey were received; however, since its availability was posted for completion and not sent out to individuals, it is not possible to determine a response rate. About 88.9% of the responses were from individuals in the U.S., with most of the responses coming from ACRP members.

Of the respondents, 24% worked for study sponsors and 76% worked for clinical sites. We did not capture any further details on the job title of the responders relative to the specific questions.

No information was collected on the level of experience or exact role of respondents. Also, in most cases the responses were not captured in a manner allowing us to determine differences between the two types (sponsor-based vs. site-based) of respondents.

Finally, this article does not include responses for all questions in the survey. The survey questions not presented relate to additional items about monitoring, types of documents accessed, and country of origin of the responders, and were not considered essential for the present discussion.

Despite these limitations, the survey results describe some important perceptions regarding remote monitoring.

RESULTS

Almost 70% of the site respondents indicated that some of the data collected are monitored remotely, while 20% of the sponsor respondents indicate that they monitor some data remotely. Interestingly, 61% of the respondents indicated that they had experienced a change to a monitoring plan after study initiation by way of the addition of remote monitoring to the plan (see Figure 1).

70%
thought the relationship will be negatively impacted by remote monitoring

FIGURE 1: Have you had a change of monitoring plan that added remote monitoring after study initiation?

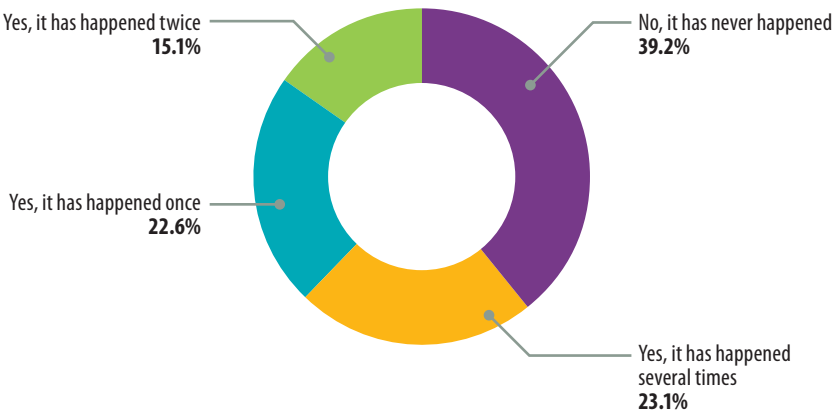


FIGURE 2: What documents are monitored remotely?

FIGURE 3: If source documents are reviewed remotely, how are they accessed?

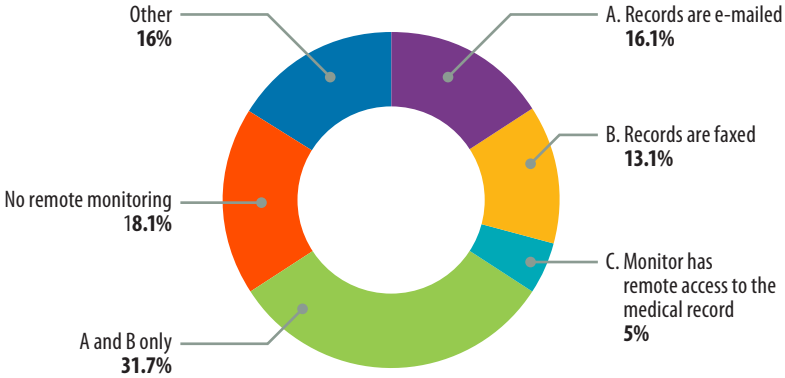
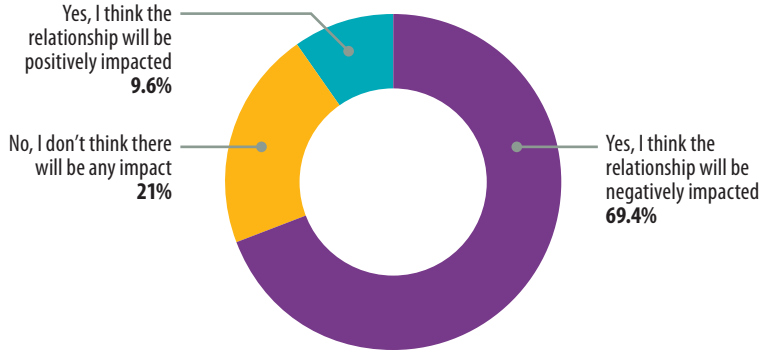


FIGURE 4: Do you believe that remote monitoring can have an impact on the quality of the relationship between site and sponsor?



The type of documents monitored remotely varied, with the largest type consisting of source documents and regulatory documents (see Figure 2).

As far as the method for remote access of source documents, the most common method was either e-mailing (26%) or faxing of the records (13%) for access (see Figure 3).

One of the most important results was the perception of the impact of remote monitoring on quality of the relationship between the site and sponsor. Almost 70% of the respondents indicated that they thought the relationship will be negatively impacted by remote monitoring (see Figure 4). In parallel to this, 62% of the respondents also felt that remote monitoring will have a negative impact on the quality of the data collected for a clinical trial (see Figure 5).

Along with this change in focus on remote monitoring, the change in monitoring approach has the potential for a significant impact on the budget for a study. Site staff are now expected to assume the work of gathering data on items that were previously reviewed by an onsite visit, such as drug/device accountability, and send it to the monitor for remote review.

There can also be costs associated with remote monitoring, including time allocated for repeated telephone calls, copying, maintaining encryption on e-mail correspondence, repeated requests, faxing, scanning to a pdf format, and/or e-mailing documents to the monitor. There are also the costs of maintaining fax, scanner, and copier machines, including paper, ink, phone line charges, and time spent sending and resending documents (see Figure 6).

Although the intent of remote monitoring is to lessen the time monitors spend at sites, it appears to have had a negative effect on the site staff. More than 65% of the site respondents indicated that remote monitoring has added to the time spent on monitoring activities (see Figure 7). From a monitor's perspective, the responses were about equal as to whether it added or lessened the time to monitor a site. This highlights one of the problems in the implementation and success of remote monitoring—the time involved is not even perceived the same by site and sponsor personnel.

Conclusions

The goal of monitoring a study is to assure regulatory compliance, human subject protection, and data integrity. The use of approaches that include remote monitoring in addition to traditional monitoring techniques has the potential to impact the relationship between the site and monitor, and to impact the quality of the data collected. In this survey, more than 69% of the respondents indicated that they think the relationship between the site and sponsor will be negatively impacted, with a correspondingly high potential to impact the quality of the data collected.

This survey, although limited in scope, does provide some interesting perspectives on how clinical research professionals view remote monitoring

FIGURE 5: Do you believe that remote monitoring can have an impact on the quality of data collected for a clinical trial?

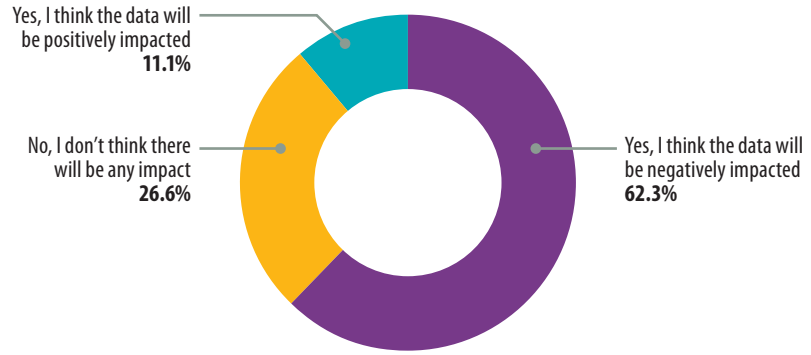


FIGURE 6: Have you added (or, as a sponsor, been asked to pay for) faxing/copying/scanning/redacting as a line item to a study budget?

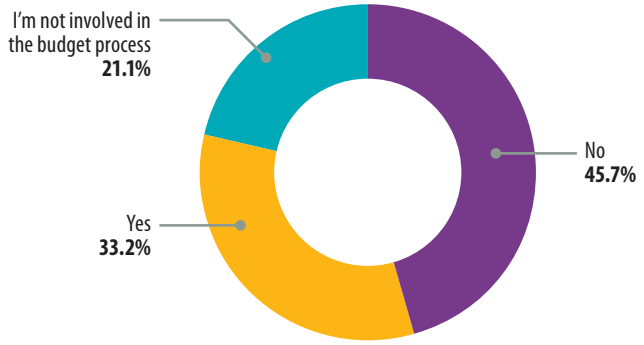
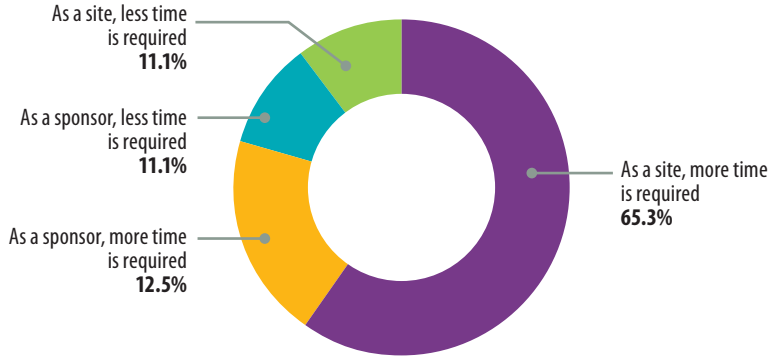


FIGURE 7: Has remote monitoring added to or lessened the time of monitoring by you or your employer?



activities. It is likely that this will change over time as sponsors, contract research organizations, and site personnel become more experienced with remote monitoring and, more importantly, with further advances in technology for remote access.

However, at the present time, not everyone is convinced that remote monitoring aids in efficient use of time or aids in overall data quality. One approach is to further educate sites (and clinical research associates) at the beginning of the study on expectations for data availability and access, in order to avoid the kinds of changes after the study is up and running that lead to some of the concerns raised. The more of these items that are identified and negotiated before the study starts, the better the results and interactions between the staff involved.

Site staff are very busy and focused on completing projects per protocol and on time, but constant change can also negatively impact data quality and sponsor-site relations. The risk-based monitoring guidance suggests that onsite visits can be lessened in favor of remote and central monitoring activities, but it does not appear that industry believes this can happen at the present time.

Risk-based approaches to monitoring, including the use of remote access to documents and data, need to be integrated within a dynamic process. Further changes need to be made to facilitate continuous improvements to the process over time, as the industry gains more experience and expertise with this approach to monitoring.

Electronic solutions for remote data access, such as cloud-based storage, secure websites, fax machines, webportals, or even direct access to site files, provide the potential to facilitate this type of data and information exchange. Concerns over privacy and security weigh heavily into the considerations of any solution.

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Getting the Right Signatures on Informed Consent Documents

PEER REVIEWED | Lindsay McNair, MD, MPH, MSB | Patience Stevens, MD, MPH, CIP | Glenn Veit, JD, CIP

[DOI: 10.14524/CR-16-0010]

LEARNING OBJECTIVE
After reading this article, participants should be able to define "impartial witness" and "legally authorized representative" (LAR) as they would be used in the informed consent process; demonstrate understanding of the roles of the impartial witness and the LAR, and in what situations they would participate in the informed consent process; and develop informed consent documents that appropriately specify which persons should sign the informed consent form, consistent with the protocol and the intended study population.

DISCLOSURES
Lindsay McNair, MD, MPH, MSB;
Patience Stevens, MD, MPH, CIP;
Glenn Veit, JD, CIP:
Nothing to disclose

The process of informed consent to participate in clinical research, and documentation of that conversation, is usually straightforward; the study population includes adults who are capable and competent to make their own decisions, who speak the same language as the investigator and study team, and who can participate fully in the consent discussion and can document their agreement to participate in the study by signing an informed consent document written in the language they speak. Sometimes, though, either the consent process or the documentation of informed consent is more complex.

Complicating Consent

In some settings, the informed consent process may require the involvement of other persons. One example of another involved person is termed a "legally authorized representative" (LAR). Some guidelines use the term "legally acceptable representative,"[1] but the meaning is essentially the same.

An LAR is a person who is "authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."[2] Increasingly, many protocols consider LARs as including parents and legal guardians of children who have not reached the age of majority to provide consent themselves. This practice can be confusing in studies that enroll both children and adults.

For the purposes of this article, the authors use LAR only in reference to situations in which potential adult study participants lack the capacity to consent.

A second example of an involved person is an impartial witness to the consent process. An impartial witness is defined by the International Conference on Harmonization (ICH) as "a person who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's [LAR] cannot read, and who reads the informed consent form and any other written information supplied to the subject."[3]

However, there are also regulatory references to witnesses found in U.S. Food and Drug Administration (FDA) and Department of Health and Human Services (HHS) regulations, various state-specific laws (e.g., as found in Virginia) requiring a witness signature in some human subject research, and local uses of a witness signature based on standard procedures. These uses may be very different from ICH, and the U.S. federal regulatory application of witness signatures does not define, nor do consent documents usually define, the purpose of the witness signature.

This article will focus on the ICH and U.S. federal regulatory application of the witness role. Examined in addition will be the fact that informed consent documents might request the signature of someone who is not involved in the consent process. For example, informed consent documents often have a space for the signature of the study's investigator, in addition to the signature of the person who actually conducted the consent discussion.

Whose Line is it, Anyway?

In the process of institutional review board (IRB) review, questions frequently arise when the informed consent document has signature lines for persons who would not be expected to participate in the consent process, based on the protocol information. Delays in IRB review may occur when the protocol and the consent document are apparently inconsistent in their respective intentions regarding the intended informed consent process or the study population. While this may sometimes seem to study sponsors to be a minor clarification, the implications of the potential enrollment of vulnerable subjects in research are significant in the IRB review process.

Ahead, we will take a closer look at the parties who may be involved in the consent process, including those who may be asked to sign the informed consent document, and at the specific settings in which consent should occur. We will also describe the need for careful review of the protocol's description of the intended subject population, the considerations of the IRB for vulnerability, and the informed consent document as part of the development of study-specific consent forms.

When Should LARs Provide Consent?

The inclusion of LARs in the informed consent process implies that potential study participants are expected to be incapable of providing consent on their own behalf. The corollary to this is that someone who would be the LAR (if the subject were not competent) cannot provide a valid consent on behalf of someone who is capable of providing consent for themselves. That is, though a wife would be the LAR for her husband should he become incapacitated, she cannot provide valid consent for her husband to participate in a research study if he is currently capable of making his own decisions about participation.

State laws determine who may serve as an LAR if there is no pre-existing documentation naming an LAR, and in what hierarchy persons should be considered (parent, spouse, adult children, etc.).

As noted previously, it is not uncommon for the signature spaces of a consent document to imply a consent process that is different from that which is described in the study protocol. For example, the eligibility criteria may state that "subjects must be able to agree with the requirements of the study and provide informed consent for participation," but the informed consent document submitted from the sponsor to the IRB with the protocol includes a signature space for an LAR, indicating the expectation that subjects may be enrolled who in fact cannot provide their own informed consent.

In many cases, it is probable that the LAR signature line was present on the template form used to draft the consent, and was never deleted when the consent was made study-specific. In other cases, the protocol eligibility criteria as described in the above example may conflict with other sections of the protocol describing overall quality and compliance standards for the study conduct, which states that "the subject or their Legally Authorized Representative" will sign the consent document. This type of conflict within the protocol must be resolved by the IRB before approving the research and the study documents supporting the consent process.

What Types of Studies Usually Need LARs?

The ICH Guideline for Good Clinical Practice and federal regulations in the United States recognize that decisionally impaired persons are a vulnerable population for whom additional protections are required.[4] As FDA regulations state in the criteria for IRB approval of research, "When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects."[5]

Inclusion of such subjects must be made thoughtfully and with specific consideration of the implications for issues pertaining to justice, respect for persons, and the potential benefits of the research. In addition, the IRB is expected to consider "… inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects…" as part of the review of research involving vulnerable persons.[6] Thus,

In some settings, the informed consent process may require the involvement of other persons. One example of another involved person is termed a "legally authorized representative" (LAR).

The inclusion of LARs in the informed consent process implies that potential study participants are expected to be incapable of providing consent on their own behalf.

consideration of issues pertaining to vulnerable populations requires experience by the IRB reviewing the protocol and attention to the "additional safeguards" that make the research ethical.

Many study protocols refer to the enrollment of decisionally impaired subjects, either intentionally or by implication, by referring to consent by the subject or LAR or by including the LAR signature space on the consent form. IRBs consider the implications of enrolling subjects who do not have the capacity to provide consent themselves very seriously. It is rare to encounter a research proposal that explicitly makes a case for enrolling subjects who lack capacity for consent, unless the disease or condition that causes that lack of capacity is the focus of the study (for example, a new investigational agent for the treatment of acute stroke).

A significant complicating factor in the potential enrollment of decisionally impaired study participants is the wide variety of presentations and etiology of lack of capacity. Conditions such as schizophrenia, brain injury, loss of consciousness due to acute trauma, and dementia such as found in Alzheimer's disease represent very different considerations regarding the prospect for regaining decisional capacity; however, all persons with such conditions deserve the same protections and additional safeguards afforded by the regulations and ethical considerations. IRBs must then consider two core principles that are generally recognized in the ethical literature as supporting the inclusion of this vulnerable population: scientific need and the prospect for direct benefit to those participating in the research.

The concept of *scientific need* asks the question whether the study objectives can reasonably be satisfied by enrolling the less vulnerable population that includes only those who are capable of providing consent. The applicable standard for the IRB's consideration for inclusion can be stated as enrolling those persons with the least degree of impairment that is compatible with the study goals. If there are adequate numbers of competent individuals available, there is little to be gained by including those who lack the ability to consent for themselves, unless the research is specifically intended to treat cognitive impairment.

Consider a large Phase III trial in diabetes comparing add-on therapy with standard of care to standard of care plus placebo. Studies have suggested that type 2 diabetes can increase the risks of Alzheimer's disease, vascular dementia, and other forms of dementia.[7,8] However, there is no scientific need to include those who actually have dementia in the typical diabetes trial—where the endpoints are better glucose control—given the widespread nature of the disease and availability of potential participants. However, if the study drug is intended to treat dementia, the narrative with respect to scientific need would be altered in a positive direction, due to the potential need to try the drug in the population in which it is intended to be used.

The concept of *direct benefit* is an aspect of additional protection for vulnerable populations in that there is justification for the prospect of risk associated with a study that is offset by the potential for direct benefit by participating in the research. The higher the potential risks of the research, the greater the anticipated benefit must be to justify inclusion of vulnerable persons. Thus, a drug with relatively few risks of a transitory nature can be justified by rather modest symptomatic relief. However, a drug with potentially serious and permanent risks must likely meet a higher standard for benefit that might include disease modification rather than mere relief of symptoms.

As an example of how to apply the above concept, a product aimed at treating moderate to severe Alzheimer's disease would likely first be tested in normal, healthy adults for safety, and then in those with less profound loss of mental acuity for reasonable signs of efficacy before being given to more severely ill participants.

What if the Capacity to Provide Consent May Change During the Study?

Some conditions involving mental capacity are expected to deteriorate over time. If a study is anticipated to run for several years or more in a population including mild-to-moderate Alzheimer's disease, best practices often dictate that individuals asked to take part in such research *identify* an LAR at the beginning of the consenting process in order to reduce unnecessary

withdrawal from the research and the loss of important data. Failure to identify this individual may leave investigators in a position of having to navigate arcane state laws and tricky family dynamics in order to identify an appropriate surrogate for consent. Although the identified LAR would not provide the consent for initial enrollment in the study—when the subject is still competent to make that decision—informed consent is an ongoing process, and the LAR would be asked to provide continuing agreement for participation should the subject become incapable later.

Conversely, some forms of diminished capacity can improve over time. An LAR may be needed for someone to be enrolled in research who may be temporarily incapacitated—for example, in studies involving patients with acute traumatic loss of consciousness or in a medically induced coma. In trials where the intended population may be in this situation, consent by an LAR is appropriate for enrollment, but such subjects must be re-consented in the event that they regain consciousness and the ability to consent.

When Should a Witness be Involved in the Consent Process?

If used, a witness is expected to ensure that the prospective subject was provided sufficient opportunity to consider study participation, that the possibility of coercion or undue influence was minimized, and that the subject or the subject's LAR understood the information provided to them. There are two situations defined in the regulations in which an impartial witness may be required in the informed consent process.

In the first situation, use of an impartial witness is necessary when either the subject or the subject's LAR speaks and understands English, but either cannot read and write, or is visually impaired such that changes to the consent document, such as increasing font size, are insufficient to allow the subject (or LAR) to read the document(s). In this case, the witness is expected to listen to the verbal presentation of the informed consent discussion, which must include all the required regulatory elements of informed consent. The witness is present to ensure that the potential subject appears to understand the information provided to him or her and has the opportunity to ask questions, and that the potential subject is freely consenting to participation in the research. The witness will then sign the consent form on the "witness" line, to document his or her confirmation of these facts.

> In the process of institutional review board review, questions frequently arise when the informed consent document has signature lines for persons who would not be expected to participate in the consent process, based on the protocol information.

In the second situation, a witness is necessary when the informed consent process uses a "short form" informed consent document (a brief document containing the basic statements about the rights of research participants in a language that is understandable to the potential subject).[9] While short form documents are not frequently used in clinical research, they are permissible in situations in which the potential subject does not speak English (or the language in which the study is being conducted, if it is not English) and a full and complete translated informed consent document is not available.

As defined in the regulations,[10] a short form written consent document requires that there is a witness to the oral presentation. The IRB must approve a written summary of what is to be said to the subject or the LAR. Only the short form itself is to be signed by the subject or the LAR; however, the witness will sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary should be provided to the subject or the LAR in addition to a copy of the short form.

Neither FDA regulations nor HHS regulations define "witness" per se. FDA Guidance (FDA Information Sheets, A Guide to Informed Consent, "Illiterate English Speaking Subjects") indicates the expectation that the witness be an "impartial third party," but does not provide guidance on what constitutes impartiality. It is useful for any institution at which research is conducted to have a written definition or standard operating procedure that covers who may serve as a witness to an informed consent process.

Note that, since the witness should be independent of the trial, the witness cannot be another member of the study team, and should ideally not be someone who works closely with the study team (e.g., office staff). In larger institutions, a person of presumed neutrality, such as a chaplain or someone from another department, would be an appropriate choice.

In many cases, it is probable that the LAR signature line was present on the template form used to draft the consent, and was never deleted when the consent was made study-specific.

Although not prohibited, best practice often dictates that the witness not be a member of the potential subject's family, as it is may be difficult for them to be impartial about the decision regarding study participation. It is also not generally recommended that a family member act as translator when oral translation of informed consent information is needed, since they may not fully understand the medical information and may mistranslate information, and because they may incorporate their own thoughts into the discussion as the information is translated.

Thus, sites should be prepared to have staff who can serve as translators, especially if the need is frequently encountered, or to have a reliable translator service available. This is important as dialogue will continue *after* the initial consent process, or if the subject or LAR has questions that may require site contact outside planned visits.

Having a pre-defined policy will help minimize situations in which a witness has to be chosen quickly, or in which study-related site personnel are pulled in unprepared, or inappropriately, to serve as witnesses.

Further, many protocol inclusion criteria begin with a statement mentioning the "subject who has signed the consent form," or something similar to this. An illiterate or visually impaired subject can usually provide a "signature" (their "mark"—be it an X or thumbprint), and consent forms would also contain impartial witness lines to accommodate these subjects. However, many studies have diaries, dosing instructions, and questionnaires for subjects to complete. Sometimes these documents must be completed by the subject directly, but sometimes completion by someone on behalf of the subject is acceptable.

When no impartial witness lines are present on the consent form, the IRB may anticipate only literate or sighted readers are to be included, even though that is not the sponsor's intent. Therefore, the protocol eligibility criteria should address whether or not nonreaders will be enrolled, to facilitate the IRB's review.

When Should an Investigator's Signature Appear on the Consent Form?

According to the ICH Guideline for Good Clinical Practice, "Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's [LAR], and by the person who conducted the informed consent discussion."[11] The person who conducts the discussion is either the investigator for the study or a study staff member delegated by the investigator to conduct the consent process.

Sometimes, in addition to the space for the signature of the delegated person who conducted the informed consent process, there is also a space for the signature of the investigator. Presumably, a principal investigator is expected to sign the consent form in this space to indicate his or her awareness of the enrollment of the participant in circumstances when he or she was not the person who conducted the consent discussion.

There is no regulatory or best practice requirement for an investigator to sign the informed consent document, unless the investigator was the person who conducted the consent discussion—in which case, he/she would sign the form in that space. Although less frequently seen now, this practice seemed to be a trend for several years, and presumably was intended to document the oversight of the investigators and their knowledge of participants being enrolled in the study. However, asking investigators to provide a signature as verification of a discussion for which they were not present is not good evidence of oversight.

This practice also creates an additional potential issue of noncompliance; what if the study coordinator who conducted the discussion has signed the form but the investigator has not? What if the investigator signature is dated days, weeks, or even months after the consent discussion occurred, and well after the subject's study participation has begun? The routine addition of an investigator signature line seems to add nothing of value to the consenting process. The recommendation, therefore, is that investigators not be asked or required to sign a consent form, unless they were the person who conducted the consent discussion, in which case they would sign in that capacity.

Conclusion

Documentation of informed consent can involve many layers of complexity and is fraught with the potential for errors and confusion. The persons creating the protocol and documents for informed consent should ensure clear descriptions of the eligible population sought for the research, and should carefully review protocol and consent template language to ensure that it is appropriate in that specific setting and that documents are concordant. This requires evaluation of the research proposal's legitimate need to enroll persons who lack capacity to consent for themselves, and when it is neither necessary nor appropriate, to remove protocol language and consent signature lines for LARs.

Of course, in protocols where the intervention is intended to treat the cause of the incapacity to consent, or where there is a robust expectation of benefit for participants, inclusion of those incapable of consent is ethical and just. The issue of allowance of nonreaders is very different, in that these subjects have the capacity to consent for themselves. One can make the case that it is unethical to exclude this population, barring considerations of the necessity for reading to safely administer a study drug or satisfy study endpoints such as self-administered survey instruments.

When these decisions have been reached and the protocol language is clear, the IRB can easily find the correct documentation and the information required to make approval determinations. Adding signature lines that have no regulatory or ethical relevance to the research is an invitation for noncompliance. The result of this careful review is a more ethically sound study, with reduced timelines to initiation.

If used, a witness is expected to ensure that the prospective subject was provided sufficient opportunity to consider study participation, that the possibility of coercion or undue influence was minimized, and that the subject or the subject's LAR understood the information provided to them.

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Addressing Educational Gaps in Biomarker and Pharmacogenomics Research Knowledge Among IRB/IEC Members

PEER REVIEWED
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What is the distinction between biomarker and pharmacogenomic (PGx) research? How are studies conducted in this arena, and what value do they have for patient care? These are just some of the questions that members of institutional review boards and independent ethics committees (IRBs/IECs) may ask themselves when encountering PGx or biomarker research in a clinical protocol.

LEARNING OBJECTIVE
After reading this article, participants should be able to briefly describe biomarker and pharmacogenomic (PGx) research, identify some of the areas of concern for ethics committees and institutional review boards, and locate educational resources available through the I-PWG on biomarker and PGx research.

DISCLOSURES
David J. Pulford, PhD; Linda M. Coleman, JD, CIP, CHC, CHRC, CCEP-I; Kathleen M. Smith, PhD; Jennifer Ribeiro, MBA; Sandra K. Prucka, MS: *Nothing to disclose*

Seeking clarity on how best to help IRB/IEC members, the Industry Pharmacogenomics Working Group (I-PWG), a voluntary collaboration of nearly 20 pharmaceutical companies, conducted a 25-question, global survey, the results of which highlight the educational needs of IRB/IEC members. In particular, the survey's results point to a need to better define biomarker and PGx research and provide tangible examples of its clinical utility. The survey aided in the development of a one-page information sheet to address these educational needs in a format that recognizes the time constraints under which many IRB/IEC members operate.

Understanding Biomarker and (PGx) Research

Biomarker and PGx research as a whole aims to improve the medical field's understanding of drug response (see Sidebar 1) and is an integral part of modern clinical trials. Researchers are required to understand how study participants respond to a drug during the various phases of clinical development, and to evaluate both PGx and non-PGx biomarkers in parallel to enable a better understanding of diseases and responses to medicines (e.g., in terms of safety and efficacy).

There have been numerous successes in biomarker research, a summary of which can be found in the U.S. Food and Drug Administration's (FDA's) Table of Pharmacogenomic Biomarkers in Drug Labeling.[1] For example, research demonstrated that only those patients with metastatic colorectal cancer whose tumors express the EGFR protein and are also negative for a mutation in the K-Ras gene receive a benefit from taking cetuximab.[2] Thus, the FDA has approved a companion diagnostic test for K-Ras to identify colorectal cancer patients best suited to receive cetuximab.[3]

As this example illustrates, the process of research leading to companion diagnostics allows physicians to have individualized information available as they consider the most appropriate treatment recommendations for their patients. PGx and biomarker research can also help streamline drug development through the use of biomarkers as "surrogate" safety/efficacy endpoints, and through lessening the incidence and healthcare burden of adverse drug reactions.

Feedback from IRB/IEC Members

Despite the potential benefits from this research, there have been few, if any, studies examining the comfort of IRB/IEC members in reviewing the ever-growing number of protocols with a PGx and/or biomarker research component. The I-PWG queried IRB/IEC members across 147 countries in an effort to better understand their knowledge of this research, and to aid in developing educational resources that could fill any knowledge gaps identified.

The survey aimed to assess IRB/IEC members':

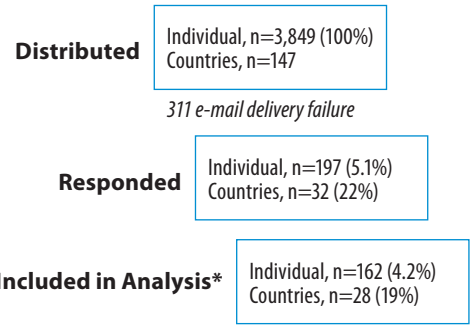
- understanding of the I-PWG;
- use of the current I-PWG educational resources;
- interest in a shortened resource to explain biomarker/PGx research;
- recommended focus areas for educational resources; and
- demographic makeup.

The full survey and other supplemental material related to this article can be found in the Good Clinical Practice & Ethics Interest Group area of the Association of Clinical Research Professionals website at www.acrpnet.org/Interest-Groups/Good-Clinical-Practice-Ethics/Shared-Resources.aspx.

SURVEY RESPONDENT DEMOGRAPHICS

The list of IRB/IEC members used in the present survey was originally compiled for an earlier I-PWG survey conducted in 2011.[5] The current survey was distributed to 3,849 IRB/IEC members, of which 197 (5.1%) responded. (E-mail response rates to surveys of the general public can vary, with some sources reporting 10% to 15% responding [Survey Gizmo][6] and others showing rates as high as 25% [Fluid Surveys].[7])

FIGURE 1: Number and percentage of IRBs/ECs that completed the survey



*Answered at least one survey question which was informative in developing the I-PWG single-page educational brochure.

Sidebar 1: What does biomarker and PGx research involve?

Biomarker and pharmacogenomic (PGx) research aims to provide an understanding of factors that contribute to disease and response to medicines. This research may enable the assignment of patients to specific treatments and may involve, for example, examining DNA, RNA, proteins, or cellular responses (e.g., changes in lipids and metabolites) between patients. Furthermore:

- Biomarker research can involve examining biomolecules (e.g., proteins, changes in lipid/metabolites, hormones) or other measurements (e.g., blood pressure or brain images) to see what the relationship may be between these characteristics and variations in clinical response.
- PGx research is a type of biomarker research that is focused on understanding genetic/genomic contributions to drug response. Pharmacogenetics (PGt) is a subset of PGx research that is specifically focused on the study of DNA sequence variation as it relates to drug response.[4]
- Companion diagnostic tests may be developed for validated PGx and biomarkers with clinical utility. These tests allow for the safe and effective use of the drug when it is available to patients.

Figure 1 and Table 1 show the number of responses received and the breakdown by country for the current survey. While responses were received from IRB/IECs globally—as approximately two-thirds of the responses were from the United States (Table 1)—perspectives of U.S. IRB/IECs are over-represented. The low response rate and overrepresentation of U.S. sites are clear limitations of the current survey; thus, our results may not be representative or generalizable to the global IRB/IEC community.

Of the 91 respondents who answered demographic questions, 85% had participated in an IRB/IEC for at least five years, and 52% had previous experience reviewing protocols that included PGx or biomarker research. Since respondents were predominantly from the U.S., we evaluated whether the U.S. respondents' level of experience differed from those of respondents from other regions of the world. Approximately 56% of U.S. respondents had experience reviewing protocols with biomarker and/or PGx research, which was greater than the 44% observed in non-U.S.

TABLE 1: Distribution of the 162 informative survey responses by country

Country	Number of IRBs/ECs Surveyed	Percentage of Responses
United States	112	69%
Australia	5	3%
Nigeria, Canada	4 each	5%
Brazil, India	3 each	4%
Argentina, China, Germany, Israel, Mexico, Peru, Philippines, Puerto Rico, Thailand	2 each	11%
Belgium, Bulgaria, Egypt, El Salvador, France, Georgia, Ireland, Italy, Namibia, New Zealand, Palestine, Poland, United Kingdom	1 each	8%

Despite the potential benefits from this research, there have been few, if any, studies examining the comfort of IRB/IEC members in reviewing the ever-growing number of protocols with a PGx and/or biomarker research component.

countries. Thus, while the reasons for the low response rate to this survey are unclear, possible contributing factors include the low number of IRB/IEC members with experience in this area of research and limited time to devote to completing this survey.

SURVEY RESPONDENT FEEDBACK

One of the main goals of the survey was to better understand how to create a shortened resource that would have utility for IRB/IEC members. We received helpful feedback to written responses for two questions that asked what information IRB/IEC members felt was most important to communicate about biomarker and PGx research.

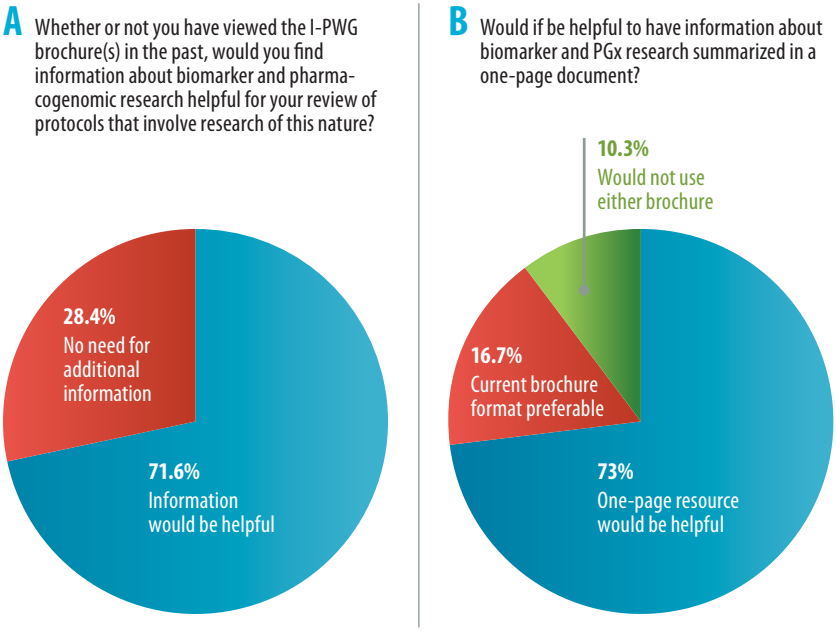
Although the response rate was not robust, there were recurring themes. In particular, multiple survey respondents wrote that they had limited time to commit to further education given life and work demands. The majority of respondents noted that they had not read either of the existing I-PWG brochures, and cited a lack of time as a major contributor.

These data underscore the very real constraints experienced by IRB/IEC members, and served as a motivator for the I-PWG to create a shorter brochure, which may be more accessible to IRB/IECs and healthcare professionals conducting clinical trials. Furthermore, the responses received helped us conceptualize how the information from our more lengthy resources could be condensed into a one-page resource focused on the areas felt to be the most important to those responding.

Although this feedback was helpful, we also wanted to be certain this type of resource is needed before taking this project on as a group. To that end, survey participants were first asked a series of three questions about the availability and usefulness of the current I-PWG educational brochures. Results from two of the questions demonstrated that the majority of IRB/IEC members felt that information about biomarker and PGx research would be helpful as they review protocols (see Figure 2).

The majority (66%) indicated that the current length of the brochures is sufficient, with 11% of respondents feeling more detail could be added and 22.2% saying the current brochures are too long to be useful. Regardless, when asked directly if it would be helpful to have a shorter brochure to complement existing resources, the majority (73%) said yes.

FIGURE 2: Interest in I-PWG educational resources



Translating Feedback to the Development of a One-Page Resource

To create a concise, educational brochure, we used survey responses to focus on what our target audience found to be the most helpful information. This was primarily driven by the responses to seven survey questions that allowed for open-ended answers.

INFORMATION OF MOST INTEREST TO IRB/IEC MEMBERS

As described above, the two open-ended questions leading to the most numerous and informative responses were: "What information do you think would be most important and helpful to communicate regarding biomarker research?" and "What information do you think would be most important and helpful to communicate regarding pharmacogenomic research?" We categorized responses as displayed in Figure 3.

To ensure all feedback from each IRB/IEC member was represented, we assigned a category to each concept. Thus, a single respondent could provide information that was scored into more than one category. For example, if a respondent indicated he or she felt both clinical utility and privacy were important to communicate when discussing PGx research, the answer was counted in both categories. A total of 48 respondents answered the question regarding biomarker research, and 47 responded to the question regarding PGx research. A total of 66 biomarker and 55 PGx topics were tabulated.

As we analyzed responses to these two questions, two areas emerged as most important to include in our resource: better scientific explanations of biomarker and PGx research, and explanations and examples of its clinical utility. The majority of those expressing a desire for "better scientific explanation" articulated a basic need for "definition of terms—biomarker, etc." and "basic definitions, functions, and examples of use."

NEED FOR INCREASED GENETICS EDUCATION

This desire for better understanding of basic definitions highlights the disparity between the knowledge base of ethics communities who review protocols containing this research and the expectations of regulators (such as the FDA and the European Medicines Agency [EMA]). These regulatory bodies have increased expectations for integrating biomarker research in general, and PGx research specifically, into drug discovery and development.

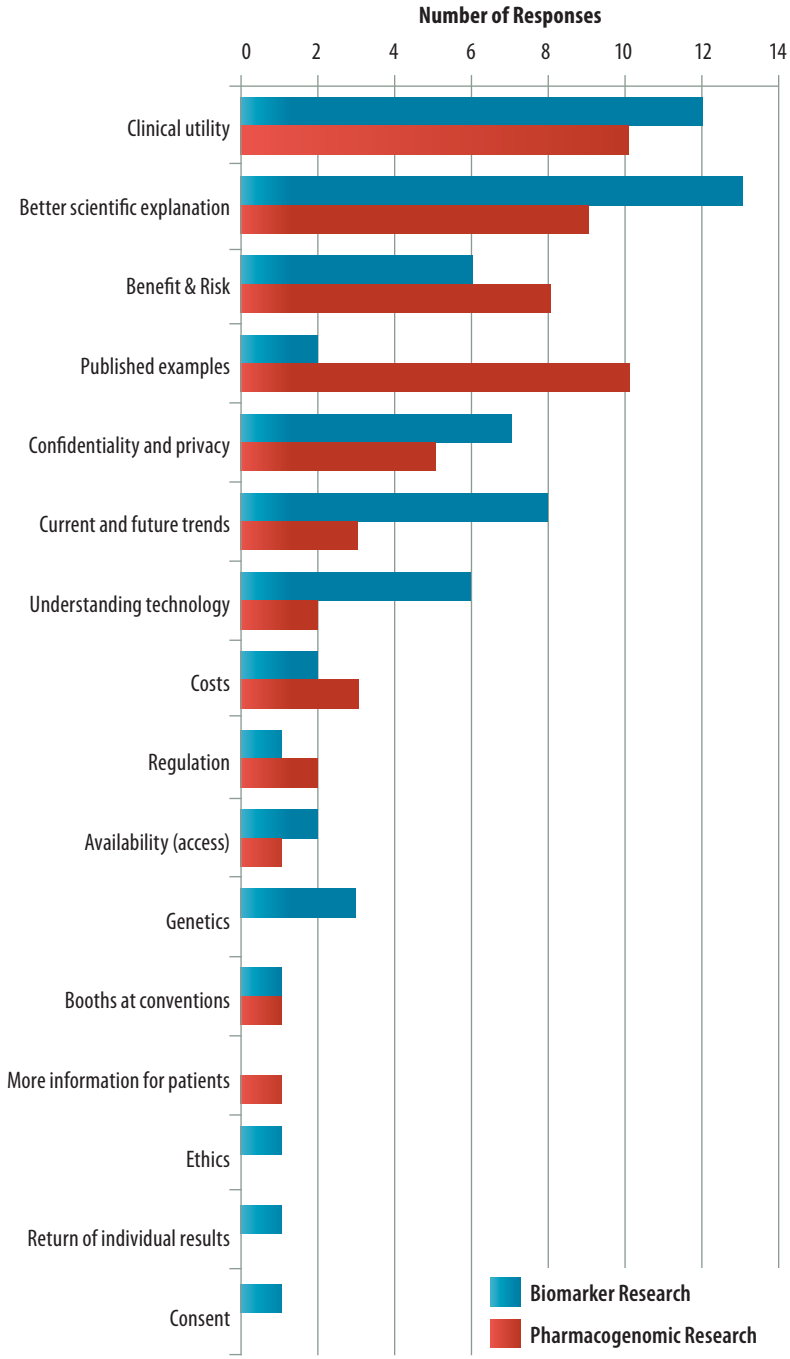
There have been multiple position papers and guidance documents published that support PGx and biomarker sample collection and research. A FDA report entitled "Paving the Way for Personalized Medicine" states that "[a]dvances in PGx have opened new possibilities in drug discovery and development. PGx has allowed for more tailored treatment of a wide range of health problems, including cardiovascular disease, cancer and HIV/AIDS."[8] Quotations from additional guidance documents are listed in Sidebar 2.

Thus, the pharmaceutical industry, through the I-PWG and other consortia, is working to bridge the gap between regulator expectations and the ethics community's obligation to stay apprised of the current science relevant to human subject research.

Despite a growing focus on genomics in biomedical research, genetic education for healthcare professionals is lagging. The need for more genetic education is not an entirely new concept; a 2008 Canadian study involving family medicine residents found that "medical school educational experiences may not be preparing future primary care physicians to address genetic issues with patients. A change and a broadening of the teaching of genetics are required to fulfill this need."[12] In addition, a 2013–14 study examining trends in genetics curricula in U.S. and Canadian medical schools similarly found that most respondents felt that the amount of time spent on genetics was insufficient to prepare them for clinical practice.[13]

The need for more genetic education for the general public was noted in a 2004 study that found many adults lacked a basic understanding

FIGURE 3: Most important information for a resource to include



Sidebar 2: PGx Sample Collection Recommendations from Regulatory Bodies and ICH

- EMA 2011: Prospective DNA sampling and banking for pharmacogenomic/pharmacogenetics-related genotyping analysis are highly recommended.[9]
- FDA 2013: Ideally, baseline DNA samples should be collected from all patients in all arms of clinical trials in all phases of drug development.[10]
- ICH 2014: Genomic sample collection for future use...to enable retrospective analysis when new scientific evidence emerges or when additional analyses of genomic samples become necessary.[11]

Despite a growing focus on genomics in biomedical research, genetic education for healthcare professionals is lagging.

of genetic terms. This lack of understanding impacts genetic literacy, public health practices, and routine healthcare, and can be problematic when individuals are asked to take more responsibility for the management of their own health.[14] Furthermore, lack of genetic education amongst physicians and subjects in clinical trials may negatively impact participation in biomarker and PGx research, thus limiting research opportunities.

It is difficult to predict what the experiences of IRB/IEC members may be, since IRBs/IECs typically are composed of a diverse group of individuals (including nonscientific members) who collectively have expertise and experience to review research from a scientific, ethical, and community perspective.[15,16] Therefore, in order to effectively translate genomics into the promise of personalized medicine, more education and practical training opportunities are essential for the general public, healthcare professionals, and IRB/IEC members.[17]

INTEREST IN CLINICAL UTILITY

The second most commonly expressed need was for examples demonstrating the utility and application of biomarker/PGx research in clinical practice, and a better understanding of how this research contributes to developing tests for routine medical practice.

Despite numerous examples (nearly 166 drug labels in the U.S., or about 10% of all FDA-approved drugs since 1938, include genomic information), there is an understandable frustration that more clinically actionable biomarkers have not been identified to date.[18] This frustration was articulated by one respondent, who noted: "There is a critical lack of specific, reliable, quantifiable, and easily measured biomarkers that correlate well with early disease progression."

While regulators, such as the FDA, are advising pharmaceutical companies to take a more objective stance toward PGx research, there is still considerable effort needed to make these tests applicable to clinical practice.[19] In addition, there is a pressing need for the research community to better communicate the complexities of achieving actionable results from biomarker/PGx research.

Increased communication, which could be achieved in part through the sharing of published examples, would provide better education of the research process, successes to date, challenges ahead, and expectations for the future.

BENEFITS AND RISKS

One of the complexities requiring increased communication is an understanding of the research process and the difficulties in reporting individual results. In the "benefit/risk" category, one respondent asked: "What is the impact on an individual human subject? What is the impact of this research on communities from which the subject is drawn?" Utility in this category was articulated not only as a need for information on individual benefits, but also on societal benefits.

Before clinical utility is established, scientific hypotheses must be replicated in additional patient cohorts, and an association between the marker(s) and outcome of interest must be validated. This research is often done in parallel to development of therapeutics, or analyzed retrospectively on samples banked from previous clinical trials. Therefore, it can take years before the clinical utility of an individual biomarker is established and is ready to be used in medical decision making.[20] Any direct benefits of research to individuals enrolled in such studies are thus limited, though eventual benefits may be experienced by future patients.

The survey results suggest a strong need for researchers to demonstrate the value of biomarker and PGx research through successful examples of such work, and to ensure that these are provided to the members of IRB/IECs, so that they can determine the added benefit of the research for potential study participants and the public at large. Clearly providing examples from the literature and drug labels also provides evidence of the benefits of this research to society as a whole.

PATIENT PRIVACY CONCERNS

As would be expected, another area of great interest was a need for information regarding patient protections, as evidenced by the categories on "benefit/risk," "confidentiality/privacy," "consent," and "ethics." Concerns over patient privacy pointed

specifically to concerns regarding "whole genome sequencing or analysis of many alleles." Due to the sensitivity and personal nature of these data and expressed concerns over privacy, we chose to make this one of the focal points of the I-PWG one-page information resource.

It is worth noting that privacy concerns with this research are often directed specifically at germline PGx/genetic research (genetic changes that are passed from one generation to the next), as release of this information may have consequences for individuals and their families. In contrast, oncology research that focuses on understanding genetic variation in the tumor (somatic genetics) does not provide information that is passed down generationally.

Researchers must be aware of legal and regulatory requirements that are in place to provide data protection, and should communicate steps taken to protect research subject confidentiality.

Conclusions

The I-PWG undertook a survey of IRB/IEC members that provided feedback for the generation of additional education materials that meet the needs of this global community. Despite the recognized limitations of the survey, there was an underlying theme that more information is required by IRB/IEC members on biomarker and PGx research. As a result, we created a concise educational resource to better prepare IRB/IEC members and investigators and their site staff for reviewing and implementing protocols with biomarker and PGx research (see the online supplemental materials in the ACRP interest group referred to earlier). Survey results highlighted the need for increased education and communication to keep these individuals and the general public aware of the progress being made toward making personalized medicine a reality.

Resources

The I-PWG aims to promote better understanding of PGx and biomarker research by providing educational materials for use by ethics review boards, healthcare professionals, scientists, and the public. It engages regulators to identify noncompetitive issues about which the group can provide information or support. The I-PWG has produced several informational brochures to explain biomarker and PGx research targeted toward IRBs/IECs and investigational site staff (available at www.i-pwg.org), and continues to examine ways to increase education and communication about this research.

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HOME STUDY HS

Is Your Site Up to Speed?

OPEN BOOK TEST

This test expires on October 31, 2017

(original release date: 10/1/2016)

Monitoring of Clinical Trials—Are Remote Activities Helpful in Controlling Quality?

1. **Monitoring of clinical trials can involve a number of techniques described in which source(s)?**

- **A.** Only in U.S. Food and Drug Administration (FDA) regulations
- **B.** In regulations and guidelines from multiple sources
- **C.** Only in the protocol for a specific clinical trial
- **D.** Only in the official Good Clinical Practice (GCP) guideline

2. **Which of the following is true of the FDA's risk-based monitoring guidance on "Oversight of Clinical Investigations"?**

- **A.** It is in conflict with all advice from the International Conference on Harmonization (ICH)
- **B.** It is only of value to principal investigators (PIs) as a reference during monitoring visits
- **C.** It allows for many different approaches to monitoring to be followed according to different circumstances
- **D.** It advises against the use of electronic systems and records in support of centralized monitoring

3. **Monitoring activities include which of the following?**

1. Verification of study-related data
2. Surveys of patients' health status
3. Review of study-related activities at the site
4. Communication with site study team members

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

4. **Centralized monitoring involves which of the following practices?**

- **A.** Remote evaluation of how a site is conducting a study
- **B.** Asking the site staff to review their own documents
- **C.** Reviewing databases without verifying the contents against the sources
- **D.** Only reviewing key documents that are submitted to the sponsor

5. **Use of centralized monitoring may depend on which one of the following factors?**

- **A.** State laws limiting access to sites by monitors for out-of-state sponsors
- **B.** Conflicts of interest between PIs and contract research organizations
- **C.** Demands for records to retained at the site for years following study completion
- **D.** The timely sharing of data from paper case report forms with sponsors

6. **What percentage of survey respondents indicated some data collected at their sites are being monitored remotely?**

- **A.** 30%
- **B.** 50%
- **C.** 70%
- **D.** 90%

7. **What documents did the largest percentage of survey respondents indicate are monitored remotely?**

- **A.** Source and Regulatory only
- **B.** Source, Regulatory, and Drug/Device Accountability
- **C.** Source and Drug/Device Accountability only
- **D.** Regulatory and Drug/Device Accountability only

8. **What percentage of survey respondents felt that remote monitoring would negatively impact the relationship between sites and sponsors?**

- **A.** Almost 10%
- **B.** Almost 30%
- **C.** Almost 50%
- **D.** Almost 70%

9. **How did the largest percentage of respondents feel that remote monitoring had affected workload time devoted to monitoring?**

- **A.** Less time required for sites
- **B.** More time required for sites
- **C.** Less time required for sponsors
- **D.** More time required for sponsors

10. **The authors suggest which of the following approaches to avoid changes in monitoring after a study has started?**

- **A.** Educate site staff about expectations regarding data availability and access
- **B.** Establish legally binding contracts regarding data availability and access
- **C.** Withhold payments to sites until all data availability and access expectations are met
- **D.** Terminate studies before completion if data availability and access expectations are not being met

Getting the Right Signatures on Informed Consent Documents

11. **Which of the following additional persons may, in certain circumstances, be needed to participate in an informed consent process?**

1. Impartial witness
2. Legally authorized representative
3. Participant's primary care physician
4. Site's regulatory compliance officer

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

12. **Why do signature blanks on an informed consent document frequently cause delays in the process of institutional review board (IRB) review?**

- **A.** Because the labels are misspelled
- **B.** Because the signature blanks are inconsistent with the protocol information regarding the study population
- **C.** Because the only signature blank should be one for the study participant
- **D.** Because the only signature blank should be one for the principal investigator (PI)

13. **The term "legally authorized representative" should be used in which of the following settings?**

- **A.** When referring to the parent or guardian of a child who is being asked to participate in a clinical study
- **B.** When referring to the person who is legally empowered to make healthcare decisions for someone who does not have the capacity to make these decisions for themselves
- **C.** When referring to someone who is visually impaired
- **D.** When referring to someone who is a prisoner

14. **Which of the following are qualifications of an impartial witness per the Good Clinical Practice guideline of the International Conference on Harmonization?**

1. That they are independent of and cannot be influenced by people involved in the trial
2. That they can pass a quiz about the goals of the study
3. That they attend the informed consent process
4. That they can read

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

15. **If there is signed documentation that makes Person A the legally authorized representative for Person B, Person A can do which of the following?**

- **A.** Give consent on behalf of Person B, even if Person B currently has the capacity to make his or her own decisions
- **B.** Give consent on behalf of Person B, only when Person B does not have the capacity to make his or her own decisions
- **C.** Appoint a different person to make decisions for Person B
- **D.** Veto any medical decisions made by Person B, even if Person B has the capacity to make his or her own decisions at the time

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

16. **Decisionally impaired persons are considered to be a vulnerable population; therefore, which of the following is not true?**

A. The IRB must consider whether inclusion of these participants requires additional protections for them.

B. The protocol should provide a rationale for why the study cannot be conducted by only including a less vulnerable population, such as persons who can provide consent themselves.

C. The sample size should be increased to allow for additional attrition.

D. The IRB will consider the prospect of direct benefit to potential participants in relationship to the risks of participation.

17. **If the capacity of a participant to provide consent may be lost over the course of the study, and the study anticipates this and allows continued participation, which of the following is a best practice?**

A. Have the person who would be the legally authorized representative give consent at the start of the study, even if the potential subject has the capacity to give consent at that time

B. Do not enroll that potential subject in the study

C. Have an impartial witness participate in the informed consent process

D. Identify the participant's legally authorized representative at the start of the study, as he or she may need to provide continuing consent as the study progresses

18. **Which of the following situations may require an impartial witness to participate in the informed consent process?**

1. The participant (or his or her legally authorized representative) is able to read and understand English but unable to write

2. The participant (or his or her legally authorized representative) is visually impaired to the degree of being unable to read consent documents

3. A "short form" consent document is being used

4. An IRB member is present to observe the consent process

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

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

19. **An impartial witness should be which of the following?**

A. The study coordinator

B. A family member of the potential study participant

C. A person of neutrality, such as someone from another department

D. The PI for the study

20. **Why should the PI not sign the informed consent document if he or she was not the person who conducted the informed consent discussion?**

1. If not present, he or she cannot attest by signature that the consent discussion occurred.

2. Compliance issues are likely if the date or time of signature is after the study participation began.

3. There is no requirement for them to do so.

4. The study coordinator can sign the PI's name if he or she was not present.

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

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

Addressing Educational Gaps in Biomarker and Pharmacogenomics Research Knowledge Among IRB/IEC Members

21. **The Industry Pharmacogenomics Working Group (I-PWG) is a voluntary organization that does which of the following?**

1. Promotes a better understanding of biomarker and pharmacogenomic (PGx) research

2. Engages in information sharing with regulators to identify noncompetitive issues that the group can provide support and information on

3. Provides educational materials to healthcare professionals, ethics review boards, scientists, and the public regarding relevant ethical, legal, and regulatory issues on biomarker and PGx research

4. Funds potential breakthrough biomarker and PGx research at startup pharmaceutical companies internationally

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

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

22. **Biomarker research examines characteristics that are which of the following?**

1. Indicators of normal biological processes

2. Pathological processes

3. Evidence of patients' noncompliance

4. Pharmacological responses to medication

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. **PGx research is focused on which of the following?**

A. Examining protein biomarkers to understand pathogenic processes

B. Understanding protein and cellular responses between patients

C. Understanding genetic and genomic contributions to drug response

D. Identifying and validating novel molecular targets for the treatment of disease

24. **The I-PWG survey revealed what key consideration as most important to respondents?**

A. The need for better explanations of biomarker and PGx research and examples of clinical utility

B. The need for more geneticists to sit on ethics committees

C. The need for more regulation in biomarker and PGx research

D. The fact that there are already sufficient educational tools and resources for ethics committees, clinicians, and patients in biomarker and PGx research

25. **Which of the following is true about how the members of ethics committees (ECs) feel regarding having adequate information about biomarker and PGx research to understand it?**

A. ECs have all the information they need to evaluate protocols

B. Only U.S. ECs need education on pharmacogenomics

C. Educational materials would help the majority of ECs

D. Biomarker and particularly PGx research is irrelevant

26. **Why do pharmaceutical companies want to bank samples for future biomarker and PGx research?**

1. They have unlimited money to spend.

2. It supports retrospective analysis when new scientific evidence emerges.

3. Research on these samples facilitates personalized medicine.

4. International regulatory bodies recommend it.

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. **Which of the following agencies have increased expectations for integrating biomarker research in general, and PGx research specifically, into drug discovery and development?**

1. U.S. Food and Drug Administration

2. Office for Human Research Protections

3. Centers for Medicare & Medicaid Services

4. European Medicines Agency

A. 1 and 3 only **C.** 2 and 3 only

B. 1 and 4 only **D.** 2 and 4 only

28. **Which of the following best describe the benefits of biomarker and PGx research?**

1. There are limited direct benefits to individual study participants.

2. Individual study participants should expect immediate return of research results.

3. It can take many years before the clinical utility of a biomarker is established.

4. The benefits to this research are mainly in terms of cutting study costs.

A. 1 and 2 only **C.** 2 and 4 only

B. 1 and 3 only **D.** 3 and 4 only

29. **Which of the following were presented in the article as being true of establishing clinical utility of an individual biomarker?**

1. Scientific hypotheses must be replicated in additional patient cohorts.

2. An association between the marker and outcome of interest must be validated.

3. The research is often done in parallel to the development of a therapeutic, which in and of itself can take years.

4. Establishing clinical utility is only a secondary or tertiary goal in the majority of studies.

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. **What did the survey reveal was related to the greatest privacy concern in biomarker research?**

A. The wide variation in coding practices across the industry

B. Whole genome sequencing or analysis of many alleles

C. Cyber security is particularly lax in this kind of research

D. Insecure storage of paper case report forms with study results

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[DOI: 10.14524/CR-16-4038]

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At a study site, it is important to demonstrate to sponsors that you are on the cutting edge and are willing to learn and make changes to improve your site's performance.

Q: Can you tell us how you first became interested in clinical research, and describe a little bit about the path you took to get involved with your career?

A: I graduated from nursing school in Toronto in the late 1970s, and went to work in the Intensive Care Unit at the University of Texas Medical Branch in Galveston. It was a teaching- and research-focused facility. I was fascinated by all the research they were doing there, but it wasn't until I transferred to the University of Texas Health Center at Tyler (UTHCT) that I had the opportunity to start my career in research. I became the hospital's first nursing research coordinator for a National Cancer Institute–sponsored monoclonal antibody study. I went on to help other departments start their research projects and eventually assisted with the creation of the Center for Clinical Research at UTHCT.

I later joined the nursing facility at The University of Texas at Tyler and fulfilled a dream I had to conduct my own research. My co-worker and I were able to obtain a large Health Resources and Service Administration grant and established a school-based health clinic in rural Texas, where I live. Since then, I have started three other research offices and have maintained several positions as the Director of Research.

Q: How about your involvement in ACRP? When did you first get involved, and what type of benefits have you enjoyed from being a member?

A: I became involved in ACRP in the late 1980s, and was a founding member of the North Texas Chapter. I remember meeting with a small group of fellow Canadians at one of the ACRP annual meetings and discussing forming a Canadian chapter. I didn't have the opportunity to assist my fellow countrymen in that endeavor, but it was formed, and I continue to be a member of the Canada Chapter to this day. I am very proud of what they have accomplished. I am currently helping to establish an East Texas Chapter.

I have enjoyed attending more than 20 ACRP annual meetings (I've stopped counting), and have had the privilege of presenting several times on topics involving study site performance, pharmacology, and ethical issues.

I have definitely benefited from being a member of ACRP for the last 30-plus years (I've stopped counting). I took the first Certified Clinical Research Coordinator (CCRC) exam in 1992, back when no course or study books were available. I'm glad I took it, because the designation told sponsors that our site had staff with the knowledge to properly manage their studies. I believe certification also helped me to be appointed to serve on several national boards of directors, such as the Medical and Scientific Advisory Board for the Alpha-1 Foundation.

Q: Since your career has spanned several years and you have no doubt seen many changes, what advice do you have for others about using technology to advance their careers?

A: It's imperative to keep up with the "latest and greatest" in technology. At a study site, it is important to demonstrate to sponsors that you are on the cutting edge and are willing to learn and make changes to improve your site's performance. A lot of the programs available now actually help you streamline activities and make your job easier, so you can spend more time on important things, like attending to your study subjects.

Q: What about your personal goals? Where do you see your career path heading?

A: I see my path as a "mentor," and I want to share my knowledge in a "pay it forward" fashion. I have been a mentor for junior high school girls by introducing them to the world of research at our annual "Expanding Your Horizons" symposium. I developed a program called "Gummy Bears versus Jelly Beans: Research in Action." The girls sign a "Candyland Informed Consent Form," and then they are randomized into two groups. We perform a statistical analysis to see which candy tastes better. We'd offer the program three times during the symposium day and it was always full. The girls were so pumped up about research after the presentation that they all wanted to be study coordinators, pharmacists, or to work for a pharmaceutical company. I believe that giving this presentation and others I have done (for patient groups, nurses, and investigators) was the reason I received the "Advancing Public Awareness in Clinical Research" award from ACRP in 2013, which was such a great honor for me.

Another way I am paying it forward is by working at Azalea Orthopedics. I am so excited about the opportunity to introduce many of the physicians and surgeons to device and clinical drug trials.

In the future, I see myself continuing to work as a consultant to assist other sites in developing their research programs, and I will continue to be an adjunct nursing professor. I love to teach students, and I get to interact with patients at the same time. In my mind, helping with research and having the opportunity to be a nursing instructor means having the best of both worlds.

Q: As you think about the future generation of clinical research professionals, what three "lessons learned" would you like to share?

A: As a preface to my three lessons, I'd say that to be successful, you have to have a great team. We all know the roles of the sites and sponsors, and of the clinical research coordinators and associates, but there are others on this team who are often not given the credit they deserve. An excellent team embraces everyone at their facility.

First, I would say recognize and properly train individuals involved at your site so that they can perform optimally. Our research team members start at the front end with the check-in clerks who greet our research patients, and go all the way to those who handle the back end processes, including the billing clerks and other critical staff.

Second, not only do we need to recognize all the players on our team, but we also need to say "thank you" to them. Yes, their duties may be a part of their job description, but everybody likes to feel valuable and appreciated.

Third, share your knowledge. If staff have been adequately trained, their confidence levels and self-esteem will increase, as will their productivity. I have never agreed with the "micromanager" type of approach, and I encourage people to work more independently.

Q: Do you have any closing thoughts you would like to share?

A: Having the opportunity to play a part in delivering "tomorrow's medicine today" has been an awesome career for me. My advice would be to never stop learning and to embrace change. Don't doubt yourself; if you want something bad enough, you can make it happen and achieve your goals.

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I love to teach students, and I get to interact with patients at the same time. In my mind, helping with research and having the opportunity to be a nursing instructor means having the best of both worlds.

ACADEMIA, Investigator-Initiated Research, and a Unique Resource to Support Both

PEER REVIEWED

Lorenz O. Lutherer, MD, PhD
Catherine J. Lovett, MSN, RN, CCRC, CCRP

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The reputation of an academic institution depends to a large degree on the scholarly activity performed by its members. There is general agreement that the components of scholarly activity are those defined by Boyer[1]:

- **Discovery** (advancing knowledge)
- **Application** (applying existing knowledge)
- **Integration** (synthesizing knowledge)
- **Teaching** (disseminating current knowledge)

Research, as embodied in the discovery component, is the major component by which an institution's scholarly level or reputation is judged, and it ties in with the others in many ways. Factors contributing to this reputation include the number, quality, and impact of publications produced by the institution's faculty and trainees; the amount of grant support they have received; and the accomplishments of its graduates, reflecting the quality of the training they received. Thus, encouragement and support for doing research is valuable for faculty members, trainees, and the institution.

The Drivers of Research Activity

Although tenure and promotion policies may differ across academic institutions, scholarly activity (i.e., research) is usually a requirement to receive either one. In most medical schools, there is a need for faculty members to do research in order to obtain credit for scholarly activity; however, industry-sponsored research does not generally count as scholarly activity, because the work of asking the question, designing the study, analyzing the data, and writing the manuscript may be done largely, if not entirely, by the industry sponsor, not

Investigator-initiated research at an academic institution provides the opportunity for faculty members, fellows, residents, and students to work together as mentors and trainees. This interaction expands the learning that will be obtained, especially if more than one faculty member is involved.

48%
of completed studies were published in peer-reviewed journals

the faculty member. Conversely, in investigator-initiated research, all of those activities are performed by the faculty member and qualify as scholarly activity. Thus, in academia, the emphasis must be on investigator-initiated research.

Clinical faculty must be proficient not only in teaching and clinical practice, but also in research. Each one of these pursuits, in its own right, is extremely time demanding, and the major emphasis tends to be placed on clinical practice and teaching. Thus, it is difficult for clinical faculty to do research unless they have "protected time" or substantial assistance provided toward the effort by their institution. Protected time has become increasingly rare, but providing substantial assistance is possible and becoming more important.

The requirement for faculty and trainees to have a greater exposure to research is being mandated by a relatively recent standard (IS-14) from the American Association of Medical Colleges.[2] It reads: "An institution that offers a medical education program should make available sufficient opportunities for medical students to participate in research and other scholarly activities of its faculty and encourage and support medical student participation." This has meant that faculty involvement in research must be sufficient to offer this experience to students and to serve as effective mentors for the research.

A Closer Look at Investigator-Initiated Research

Investigator-initiated research at an academic institution provides the opportunity for faculty members, fellows, residents, and students to work together as mentors and trainees. This interaction expands the learning that will be obtained, especially if more than one faculty member is involved. This original research also increases the opportunity for the investigators to acquire external funding to support follow-up studies. Above all, this type of research provides investigators with the ultimate satisfaction that comes from completing a study that answers the question that they themselves asked.

Given this background, special programs and support systems—technical and monetary—must be developed in order to meet the challenge of being a successful, research-based, educational institution. The following is a description of how one institution addressed this challenge.

On a Mission

The West Texas town of Lubbock is in the center of a large area that is medically underserved. Before the establishment of the Texas Tech University School of Medicine in 1971, the closest advanced healthcare

for persons in this region was 350 miles away. The mission of the School of Medicine originally was to provide much-needed healthcare in the region and to train physicians and residents who might develop their practices in the area.

Today, the School of Medicine is only one of the five schools in the Texas Tech University Health Sciences Center (TTUHSC); the other schools are Allied Health, Nursing, Pharmacy, and the Graduate School of Biomedical Sciences. TTUHSC has three major campuses (Lubbock, Midland/Odessa, and Amarillo) as well as several satellite campuses in other West Texas cities.

In 1998, clinical research at TTUHSC, as in many institutions, focused mainly on industry-sponsored research. Various departments were doing this type of research using their own coordinators, but were unable to keep up with the expanding workload. In 2001, institutional leadership centralized the contracting services for clinical trial resources into one unit, the Division of Clinical Research (DCR), and provided a number of highly trained clinical research coordinators to help conduct studies, which continued mainly to be sponsored by industry. The DCR was a fee-for-service unit, and departments using its services were charged a fee, even though the departments were still allowed to hire their own coordinators.

In 2009, scholarly activity (i.e., investigator-initiated research) became the primary clinical research focus of the institution. The dean of the School of Medicine transitioned the DCR into this new role, renamed it the Clinical Research Center, and relocated it to operate within the school. A faculty member with an MD and PhD who had experience performing both basic and clinical research was appointed as the center's executive/medical director. The existing DCR personnel transitioned into the center to provide the leadership and coordinator support needed; meanwhile, the contracting portion of the former DCR did not transition, but stayed centralized at the institutional level in a separate office.

In its first year, the Clinical Research Center almost doubled the number of new studies being done, increased the number of investigators by 38%, and increased the number of departments producing research by 44%.

Because of the center's success in stimulating investigator-initiated research, the president of TTUHSC in 2010 broadened its functions to cover research at the institutional level in order to facilitate clinical research for all TTUHSC schools on all campuses. Renamed as the Clinical Research Institute (CRI), the unit was first found solely on the Lubbock TTUHSC campus, but its presence subsequently was expanded to the Permian Basin Campus in Odessa.

The mission of the CRI is to facilitate the conduct of investigator-initiated clinical research in the TTUHSC and affiliated institutions; to provide training in the conduct of investigator-initiated clinical research; and to promote development of a clinical research culture. Specific functions are to:

- Incentivize and facilitate faculty members, residents, and students to conduct investigator-initiated research
- Provide support for the conduct of clinical research (thereby decreasing the need for "protected time")
- Facilitate interactions between clinical and basic science faculty to conduct translational research
- Build a network across departments, schools, campuses, and other institutes and centers
- Provide clinical research education

Lending Structure to Growth and Change

The transition from industry-sponsored to investigator-initiated research at TTUHSC required a culture change; it required focusing on generating new knowledge instead of generating revenue. The culture change meant that clinicians originate new, innovative ideas and author protocols instead of simply receiving a completed document from industry that is ready for implementation after institutional review board (IRB) approval.

The overall goals of the CRI are to increase research activity, to support faculty development for tenure and promotion, and to play an important role in the development of trainees. Although the mission of the CRI is to facilitate investigator-initiated projects, it does continue to conduct some industry-sponsored projects, provided the time commitment does not a) interfere significantly with the conduct of investigator-initiated projects; b) the study is well designed; c) sufficient subjects can be recruited; and d) it is an innovative opportunity to offer to the institution's patients.

Departments wishing to conduct many industry-sponsored studies usually choose to hire their own research coordinators at their own expense. Use of the CRI is voluntary, but all CRI services are provided at no cost to faculty and trainees doing investigator-initiated studies.

The CRI is governed by the TTUHSC provost and president, and has an advisory board composed of representatives from each school and each campus it serves. The leadership consists of an executive director, two co-directors, and a managing director, all of whom who have had extensive experience with basic and clinical research. Critically, there are nine nurse coordinators—five for Lubbock and four for the clinics in Midland and Odessa. Additionally, a full-time biostatistician, a regulatory specialist for IRB submissions, a monitor, a section manager, and an administrative assistant are on staff.

Investigator-initiated research at an academic institution provides the opportunity for faculty members, fellows, residents, and students to work together as mentors and trainees. This interaction expands the learning that will be obtained, especially if more than one faculty member is involved.

63%
increase in the number of PIs conducting research

How it All Works

To access the CRI's services, the principal investigator (PI) submits a short route sheet defining what services will be needed, followed by a draft protocol and data collection sheet. If faculty members or trainees are unfamiliar with protocol development, templates are available on the CRI website for their use. CRI directors and a biostatistician will review the protocol and data collection form, inserting comments/suggestions as necessary. These comments are then returned to the investigator and a meeting scheduled to discuss the study and finalize development.

Suggestions from the CRI go only to the PI, and are based on an understanding of the system, extensive research experience, input from the biostatistician, and knowledge of what the IRB will require. Complex proposals may be referred to other faculty with peer review experience for additional comments.

Once the protocol and study documents are final, they are given to the CRI regulatory specialist who prepares the appropriate IRB application, including the informed consent form, the case report form, and any special study advertisements, subsequent IRB amendments, and responses to any questions or stipulations raised by the IRB. Next, a study coordinator is assigned and study start-up activities are initiated. When IRB approval is received, the study coordinator will schedule the site initiation meeting, after which the study begins.

These are critical areas of support for those with little experience doing research, and serve to ensure the validity of the study. They are also part of the educational process, and often result in the time required for IRB approval being markedly decreased.

Thus, working through the CRI, the PI, while still maintaining full responsibility for any study he/she undertakes, has markedly diminished time expenditure, which is a major factor in being able to pursue research.

The CRI also plays a major role in study conduct. Representative services provided by the CRI coordinators are consenting and enrolling subjects, scheduling study visits, collecting data, obtaining samples, and attending to other study procedures, many of which are unique to the particular study.

Finally, the CRI provides study monitoring when applicable, statistical assistance for study design and data analysis, regulatory and grant application review, and support in preparing presentations and writing manuscripts.

Painting the Big Picture

Part of the CRI's mission is to provide education related to clinical research. For those faculty members and trainees who have had only limited exposure to research, the education is directed toward increasing their understanding of study design elements, outcome measures, and how they relate to data collection and analysis and the ability to develop a protocol.

An additional objective is to explain why there are regulations, what they are, and the role they play in study conduct and IRB review.

The ultimate goals are for faculty members and trainees to obtain meaningful results from their studies and to publish them in a well-read journal. Meeting these goals is believed to mean that the faculty are competent and successful researchers, are comfortable conducting clinical research, and are enthusiastic about maintaining their research activities.

To these ends, the CRI educational programs consist of formal courses, lecture series, and, perhaps most importantly, on-the-job training with one-on-one conferences. The formal courses include a 12-week faculty development course covering study design and grant writing, a one-week course for training study coordinators (approved for continuing nursing education hours by the Texas Nurses Association), an approved elective in the School of Medicine, and a course for graduate students offered through the Graduate School of Biomedical Science.

It is expected that the CRI's educational component will continue to grow in order to comply with the new Accreditation Council for Graduate Medical Education's requirements for increased scholarly activity in residency programs.[3]

Economic and Reputational Considerations

As previously indicated, the CRI's services are provided at no cost for investigator-initiated projects. Financial support comes from the TTUHSC Offices of the President and Provost, and from a tax on clinical departments in the School of Medicine. Additional funding comes from the TTUHSC School of Pharmacy and the affiliated teaching hospital.

Investigators are responsible, however, for all other costs their studies might entail, such as laboratory tests, X-rays, and drugs. Without having to include CRI staff salaries in their budgets, investigators can apply for funding from agencies that fund smaller grants. This means that investigators who are unfunded or have access only to small grants still have the opportunity to do investigator-initiated research, some of which will serve as the pilot studies needed for application for external funding. Further, they can gain valuable experience while potentially producing publishable results.

The results show that CRI has demonstrated its value and success from inception:

- In 2014, there were 82 new studies, for an increase of 61% from 2012.
- The number of PIs conducting research increased by 63% and the number of departments with faculty members engaged in research increased by 60%.
- The CRI is now facilitating more than 200 studies, working with more than 120 different investigators coming from all schools; the number of students and residents involved with these studies has increased dramatically.
- Additionally, 48% of the completed studies were published in peer-reviewed journals, and this scholarly activity has provided significant support for faculty seeking tenure and/or promotion.

Of greater significance than any individual statistic, however, is the fact that faculty are contributing to science and helping to improve healthcare and its outcomes.

Conclusion

The CRI has had many challenges to overcome. Some of these include strengthening the institutional culture in terms of its focus on investigator-initiated research, increasing knowledge and understanding of the clinical research process and the regulations that govern it, promoting awareness of the existence of the CRI and what it does, and convincing novice researchers of the importance of consulting a biostatistician in the beginning of the study design process. Further, a difficult challenge has been for CRI personnel to learn to work with the politics and differences associated with the various schools and campuses that make up TTUHSC.

So, what is in the future? The CRI's mission calls for it to accomplish a further expansion to all of the TTUHSC campuses and to increase the clinical research done in all the schools. Because of the institutional leadership, vision, and support, the CRI has already been able to facilitate the meaningful participation of TTUHSC faculty and trainees in investigator-initiated research, contributing to the scholarly activity ongoing in the institution.

The success of investigators breeds enthusiasm for research, as evidenced by the fact that faculty and trainees working with the CRI show continued interest in doing clinical research by returning to develop and conduct new projects. The programs of the CRI enable good clinicians and trainees to become good clinician scientists who turn promising research ideas into reality, which is an important part of growing an academic institution.

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Photos courtesy Texas Tech University Health Sciences Center

DATA-TECH CONNECT
Paula Smailes, RN, MSN, CCRC, CCRP

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Improving Technology Training to Facilitate Competency for the Clinical Research Professional

It is without question that the technological advances that have infiltrated the clinical research industry have created efficient workflows that allow for faster reporting of data with huge cost savings. As we read about technologies that impact research, it's easy to get caught up in discussions of hyper-efficient workflows massively streamlined by a techy gadget, or about the bells and whistles of some other product that improved the operations of a clinical trial. The end result can be the delivery of new drugs and devices to market faster, which, in turn, can save lives.

With advanced technologies becoming mainstream in clinical research workflows, the Joint Task Force for Clinical Trial Competency determined the necessity of incorporating technology into an essential job function.

However, systems powered by technology can often be complicated to use and may require extensive training. Furthermore, the quality of the training can have a direct impact on study success, implementation, and competency for the clinical research professional.

The Joint Task Force for Clinical Trial Competency

With advanced technologies becoming mainstream in clinical research workflows, the Joint Task Force for Clinical Trial Competency determined the necessity of incorporating technology into an essential job function. The task force identified eight competency domains for the clinical research professional, one of which is data management and informatics. This competency "encompasses how data are acquired and managed during a clinical trial, including source data, data entry, queries, quality control, and correction and the concept of a locked database."[1] Specific competencies under this domain are that the clinical research professional should be able to:

- describe the role that biostatistics and informatics serve in biomedical and public health research;
- describe the typical role of data through a clinical trial;
- summarize the process of electronic data capture (EDC) and the importance of information technology in data collection, capture, and management;
- describe the International Conference on Harmonization's Good Clinical Practice requirements for data correction and queries; and
- describe the significance of data correction and quality assurance systems and how standard operating procedures are used to guide these processes.[1]

Technology Training

There are many considerations when it comes to technology training for clinical researchers. Adult learners have different needs than their younger counterparts when it comes to education and training. Not everyone has the same comfort level with technology, and the learning curves can be big or small.

Assuring success for clinical research professionals as technology is adopted remains essential to their job performance and the industry. This may extend beyond initial training to ongoing optimization needs in order to build employee confidence and competence.

Specific to technology, clinical research training can come from a variety of sources. It could be representatives of the sponsor or contract research organization (CRO) who train site staff on the use of an EDC system or specialized medical equipment, such as an electrocardiogram machine. It could be a third party training staff to use a specific clinical trial management system (CTMS) or statistical software product to manage and analyze data.

For sites using electronic medical records (EMRs), these are sources rich in data that require targeted skills for data extraction. With the onset of research functionality in EMRs, a high level of technical proficiency is necessary for ensuring accurate data capture, patient safety, and study success.

EMR Training

To delve into the topic further, for clinical research sites, learning the EMR as an electronic source document and capitalizing on it is not always easy. Some EMRs have research-specific functionality for clinical research workflows, documentation, and research billing capture. For adequate training in these functions, an ideal setting would be a computer lab where everyone has his or her own computer to use. In the lab, a trainer leads the group and gives formal instruction on use; training will be stimulating, not boring, and will engage the end-user in a manner that is not overwhelming.

An unlikely barrier to technology training is technology itself. Smartphones should be turned off during training classes so that they do not distract from learning. "Technology breaks" can be taken over the course of the class so that users can stay on top of incoming e-mails or phone calls. Technology changes quickly, and keeping end-users current with updates can be done in with a variety of communication methods, such as staff meetings, targeted training efforts, and e-mail reminders of changes.

Geography and tight schedules can also hinder the training process. Alternative training methods such as eLearnings, WebEx meetings, and training reference manuals allow end-users flexibility regardless of location and time constraints. Whatever the method used, engaging the end-users in which method works best for them can be the first step toward training success.

Training Feedback

The best way to determine how training could be made better is to ask the trainees. Training satisfaction surveys can serve as a means of improving the quality of technology training. Satisfaction levels can be determined for both the trainer and the training content.

For example, ask your trainees to rate the trainer using a Likert scale by asking if:

- The trainer's expertise facilitated their learning
- The trainer's teaching methods (slides, handouts, manuals, etc.) were effective
- The trainer demonstrated respect for their needs
- The instructor addressed questions and concerns with explanations that were clear and concise
- The classroom pace set by the instructor was suitable for learning
- The instructor was prepared and organized
- The trainer encouraged participation
- The trainer provided time for breaks

Feedback can also be solicited on the training content itself, for example by asking trainees how closely they agree with statements such as these:

- I understand how to use the technology.
- I know how to get assistance after the class, if needed.
- Training goals and objectives were met.
- Course activities and exercises facilitated my learning.
- I feel that this course covered the material I need to be successful in my position.

Optimization

It's setting a high bar to say that, once a single, formal training has been completed, the end-user will be considered competent in research use of the EMR (or whatever the training goal was). One training session may not be enough to give most users all the confidence they need to be considered proficient. Training might be thought of as getting your learner's permit to drive, but you still need the license to be legal.

Given the amount of material presented, there may need to be refresher training or optimization. Optimization is the one-on-one end-user support that happens in the field in the end-user's workspace. This gives researchers an opportunity to ask questions in their own settings and apply what they have learned.

Usually, once researchers begin to use the functionality, questions arise that they wouldn't have thought of during training. In other words, at training, the users don't know what they don't know, and with more practical application, more questions are spawned. Optimization provides the necessary "at the elbow" support with the end-users in their environments to further polish their skills and achieve competency.

Conclusion

Clinical research has evolved to become highly dependent on technology. Because of this dependency, it is extremely important that clinical research professionals are competent in its use, and competency comes from education and experience.

Just like everything else, training must change as technology evolves. Using satisfaction surveys for training feedback can help raise the bar on end-users' needs, and point to ways for making training programs better. Quality training yields competent professionals.

Assuring success for clinical research professionals as technology is adopted remains essential to their job performance and the industry.

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Launch of Medicare's Oncology Care Model—An Opportunity for Administrative Reform

On July 1, 2016, Medicare began enrolling select oncology patients under its newest payment plan, the Oncology Care Model (OCM). The Innovation Center of the Centers for Medicare & Medicaid Services developed the OCM to address rising cancer care costs and increasing variation in treatment expenditures that were not sustainable for the U.S. economy. Many aspects of this new payment model have not yet been established, but will be based on public and provider commentary, as well as on preliminary data collected during the first months of the model's application.

While policy specifics tied to the OCM are still under debate, many stakeholders anticipate positive outcomes for both providers and patients.

There's Always a Catch

One caveat to the OCM is that it requires providers to strictly differentiate between therapies that are investigational and those that are consistent with nationally recognized clinical guidelines. Drugs or services deemed investigational may not be reimbursed under this payment model. As such, providers who regularly incorporate research treatments into their practice must provide an explanation and justification for billing in these circumstances as documentation of compliance.[1]

Medicare recognizes that implementing this new process may require additional efforts in revenue cycle management, coverage analysis, and patient management, and plans to reimburse these expenditures in one of the plan's three payment types.

The previous Medicare reimbursement policy only used the fee for service (FFS) payment system, which reimbursed for each drug, test, and service charged. This plan failed to recognize when higher priced drugs were used unnecessarily and when repeat tests and hospital visits occurred due to uncoordinated care efforts. These oversights have become great financial burdens and have hindered patient experiences.

The new OCM can be broken down into three payment types:

1. **Standard FFS payments for drugs, tests, and other care services**
2. **A $160 per beneficiary/per month payment for enhanced care coordination**
   This fee will be paid for each patient for each month during a six-month care "episode." An episode is initiated on the date of the first outpatient chemotherapy administration OR on the date of the initial Part D claim submission for patients receiving oral chemotherapy drugs. This amount is meant to cover the cost of transforming practices, and may be applied to implementing new electronic health record systems, hiring patient navigators, and outsourcing coverage analysis services or any other activities that improve cost and care efficiency.
3. **Performance-based payment (based on Medicare savings and achievement of quality measures)**
   Medicare will estimate the total cost of caring for a patient in the six-month episode. This benchmark price will be calculated separately for each participating practice, taking into account historic Medicare claims from that practice, cancer type, geographic location, and other factors. The difference between this benchmark price and the total FFS cost during the episode will be the maximum amount that a practice can pocket as performance-based payment. This maximum difference will then be multiplied by a ratio determined by care quality and patient outcome metrics to arrive at the provider's actual performance-based payment. In effect, the final payment to the practice is influenced by both its quality of care and its ability to operate in a cost-effective manner.[2]

Conclusion

The OCM initiative is aimed at healthcare providers looking to improve quality practices and organizational efficiency. By participating in this trial, providers have an opportunity to strengthen their administrative systems using Medicare dollars and to prepare themselves for impending policy changes. Above all, those who implement the new OCM guidelines could see both short- and long-term benefits from participating.

The OCM initiative is aimed at healthcare providers looking to improve quality practices and organizational efficiency.

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An Insider's Perspective on **FDA's "Year of Diversity in Clinical Trials"**

James Michael Causey

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The Food and Drug Administration (FDA) has declared 2016 to be the "Year of Diversity in Clinical Trials." However, that effort won't end when the calendar page flips to January 2017. Dr. Jonca Bull, MD, an ophthalmologist, is the first permanent director of FDA's Office of Minority Health, and heads many of the agency's initiatives. She spoke with *Clinical Researcher* Editor-in-Chief James Michael Causey in August. The interview was edited for clarity and space considerations.

Clinical Researcher: ***Beyond the idea of diversity in trials being a widespread problem that stretches across ethnicities and men and women, what more can you tell us?***

DR. BULL: The important thing is that we're really moving away from the trend of patients, or participants in a clinical trial, being homogeneous. As we learn more about subgroup characteristics and individual characteristics, it's not just about race and ethnicity, but also about information that is grounded in the patient's clinical context. You may need to prescribe a drug and make dose adjustments depending on other medicines being used that may have drug interactions, or depending on the size of the participant's body, just as examples.

Certainly what we've learned about sex differences in dosing has been that men's and women's bodies, no surprise, are different, particularly in terms of fat distribution and general weight. We also have to take into account the fact that weight overall can impact the distribution of a particular drug in a patient. We know from population data that there is a higher incidence of America's obesity epidemic in minority populations, particularly in minority women, so some dose adjustments may have to be taken into consideration.

The focus on demographic groups is really grounded in our evolving approach to personalized medicine, and in individualizing therapy and bringing literally more precision to that interface of the healthcare provider and the patient.

CR: ***Can you give us an example with a particular ethnicity and a particular disease?***

DR. BULL: A couple of examples come to mind, and I think these are ones that are well known. With diabetes, we know that there is a disproportionate impact in African Americans and Hispanics, specifically. There are also differences in Asian Americans.

In that last instance, it's important to screen at a lower body mass index in Asian Americans, because they tend to get diabetes without being obese. I think that's certainly a very important example, in terms of looking at the usual red flags to screen patients when diagnostics and things like hemoglobin and hemoglobin A1c measurements need to be done, and that they can differ across subgroups. It's really important that these kinds of differences are highlighted, because you can have a significant number of patients who are undiagnosed, but who may have the opportunity to have a much more favorable clinical course if they're diagnosed earlier.

More information and resources from the FDA Office of Minority Health are online at www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofMinorityHealth/default.htm

CR: ***ACRP's membership covers the entire gamut of the clinical trial industry and medical practice. We attract notice from people based at sites, sponsors, institutional review boards, and beyond. How can organizations like ACRP or even individual members help you get the word out about diversity?***

DR. BULL: What you're doing right now with sharing this interview is extremely helpful, because raising awareness is the key piece. Also, there are tools that we have available that can be downloaded and printed out for use at sites, where awareness of diversity is important since sites are helping to develop and execute clinical protocols. Having a very clear understanding of FDA's expectations—that these protocols should take into account the populations that are likely to need the product—is a consideration. Further, it's good when sites are appropriately situated such that the catchment area will recruit patients of diverse backgrounds when and where it's needed.

Broadening the educational opportunities about becoming clinical research associates and setting up sites is certainly an opportunity to increase the number of diverse scientists and clinicians who participate in clinical research, and could benefit from the resources provided by ACRP.

CR: ***How optimistic are you that we can change this dynamic? It's going to be a challenge.***

DR. BULL: Yes, you really have to pay attention to the context of the broader environment.

We're in a world now that presents unprecedented opportunities with electronic health records, and with large administrative claims databases to gather information. In some of the gaps that we currently see—through the use of registries, use of what we call "real-world evidence, real-word data"—we will be able to complement the data we get on the premarket side. It may actually be used on the premarket side.

The world that we're part of now is drastically different from where we were, for example, in the late 1940s, when we were in the early days of looking carefully at research ethics because of the abuses in World War II that led to the Nuremberg Code. We've added human subject protections because of the tragedy of Tuskegee. Where we are now, we have to look at and address issues of research being something where the participants take on a burden of risk to help science and with the hope of benefit to themselves, because beneficence is certainly a key part of research—that the benefits should outweigh the risk. There shouldn't be undue risk.

We've got work to do across the landscape here on many fronts. There was a recent survey done by Memorial Sloan Kettering that, again, addressed that people are willing to think about trials, but most Americans are not really interested in being in clinical trials. We've got to flip that switch and move the needle on that across the board.

As we learn more about subgroup characteristics and individual characteristics, it's not just about race and ethnicity, but also about information that is grounded in the patient's clinical context.

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QA Q&A CORNER

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Regulations, Records, and Razzle-Dazzle in Research

For this issue's column, we consider some of the complicating factors regarding responsibilities, documentation, branding, and screening in clinical studies.

Q. Who is responsible for ensuring that a clinical study complies with state and local regulations and requirements? Is this a clinical sponsor/monitor responsibility or a matter for the institutional review board (IRB) to address?

A: The U.S. Food and Drug Administration (FDA) has indicated that all parties involved in managing a study have a shared responsibility for complying with state and local laws. The IRB and the clinical investigator are responsible for ensuring that a consent form is signed by the subject or the subject's legally authorized representative (LAR). The issue of who is an LAR and able to sign a consent form in lieu of the subject, for example, is controlled by state law and institutional policy. This includes at what age a child becomes an adult (for consent purposes) and when one or both parents might need to sign for a minor child.

If you are not sure about the requirements in your state, consult the state's webpage on health/medicine issues and search on LAR or similar terms to find out the state's requirements in this regard. For more insights about LARs in consent situations, see the peer-reviewed article by Lindsay McNair and colleagues starting on page 22 in this issue.

Q. More and more studies include the use of a central laboratory or central reading facility to evaluate laboratory samples, electrocardiograms (ECGs), X-rays, etc. Is there any requirement regarding documentation of the qualification of these facilities?

A: The FDA regulations do not specify what documentation is required to demonstrate that a facility is qualified to perform such work. The 2009 guidance on "Investigator Responsibilities: Protecting the Rights, Safety, and Welfare of Study Subjects" does mention these third-party organizations. It specifically mentions that there are often critical aspects of a study performed by parties not involved in patient care and not under the direct control of the clinical investigator. This would include clinical chemistry testing, radiologic assessments, and ECGs, all of which are often performed by a central, independent facility retained by the sponsor.

In these cases, the central facility provides the test results directly to the sponsor and to the investigator. Since the sponsor contracts for these services, the sponsor is responsible for ensuring that these parties are competent and able to fulfill their responsibilities in the study.

Q. Some studies have suggested that "branded" clinical trials enroll study subjects much more quickly than non-branded trials. Is this relevant to subject enrollment?

A: Clinical trial branding involves the use of acronyms to name either a clinical trial (such as the MRFIT, or Mister Fit Trial, standing for the "Multiple Risk Factor Intervention Trial"). In some cases, logos are added to the acronym to give the trial a visual identity, as well. Such acronyms may also serve several other purposes, including shortening/simplifying what are often lengthy and complex trial names/titles for easy referencing in communications and publications. The acronyms can also create and foster a sense of identity for the individuals who are participating in a specific trial.

FDA regulations and guidance do not specifically mention clinical trial names or acronyms. However, sponsors are prohibited from representing "in a promotional context" that an investigational product is safe or effective for the purposes for which it is under study, or otherwise promoting the product (see 21 CFR 312.7 and 812.7 in the *Code of Federal Regulations*). To the extent that a clinical trial name or acronym may appear to be promotional, the FDA or an IRB could ask the sponsor to change it.

Q. Are there any FDA requirements/standards establishing the length of time a study participant must wait after leaving one drug study before beginning the screening process for another drug study?

A: FDA regulations do not specify a timeframe that should elapse between a subject's enrollment in two successive trials. However, it is important that there be an adequate washout and recovery period to ensure that subjects are appropriately protected (including against adverse product interactions) and risks are minimized.

While a 30-day washout is common, many study protocols specify a longer time period (60 or 90 days). Information about pharmacokinetics (e.g., absorption, dissolution, metabolism, excretion) would certainly be relevant. It can be very important for a clinical investigator to be informed of his/her subjects' medication and recent clinical trial history in order to best protect the safety of the research participants.

There are now certain limited circumstances where a subject may in fact be enrolled in a study with more than one investigational product or two different, but complementary, investigational trials at the same time. This is sometimes the case for serious and life-threatening diseases that often necessitate unique approaches to treatment, including multidrug treatment study designs.

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PEER REVIEWED
Shirley Trainor-Thomas, MHSA
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Increase Awareness of Research in Your Organization by Using THE MARKETING MEGAPHONE

Marketing is crucial to the success of any clinical research program, and while many organizations excel at marketing study opportunities to the community, there is often a disconnect when it comes to an organization's internal awareness of research. Many organizations conducting clinical research already have tools in place to facilitate successful study operations, but if physicians are unaware of these resources, they may shy away from research.

According to one poll, only **7%** of American patients have been informed by their doctors of research studies for which they might be eligible.

Marketing your research department's capabilities is the most effective way to create awareness among your administration, physicians, and other staff. By connecting with staff directly and conveying the benefits of clinical research, your program will be well on its way to building successful partnerships with physicians and staff, and to distinguishing your organization as a contender in the research community.

Diving into Internal Awareness

When it comes to successfully enrolling patients into a clinical trial, fledgling and experienced research sites alike should know that quality marketing is essential. Radio ads, television commercials, and mail-outs are all great ways to communicate with potential study participants to ensure successful accrual.

While these tactics are all necessary, they neglect to ameliorate one of the largest frustrations experienced by research directors around the country: lack of organizational awareness of clinical research. Administrators, staff, current patients, and even physicians are often unaware of the benefits of clinical research, and the positive impact it has on patients and the organization as a whole—be it a for-profit regional hospital, an academic medical center, a community clinic, an institute focused on a particular condition, or some other health-related enterprise.

Marketing your research program internally is the best way to successfully build a reputation of innovation for your organization. In fact, in a 2012 survey conducted by a national healthcare marketing firm, 89% of respondents indicated that they perceive the presence of a clinical research program as a sign that a hospital is more innovative than its research-naïve competitors.[1]

With the enthusiasm of your administration and the buy-in of your staff and physicians, you are on track to setting your site apart from the rest of the crowd in the clinical research world. As the old adage goes, success breeds success; the same is true for your clinical research program. Once your organization begins to conduct studies successfully, interest in research will spread and garner new attention. However, what steps must be taken to promote the benefits of research to your entire organization?

89%

of respondents perceive the presence of a clinical research program as a sign that a hospital is more innovative than its competitors.

Put One Foot in Front of the Other

The first stride toward success is to explain the "halo effect" of research to your site's administration. Research brings far-reaching returns for healthcare organizations; it can make a difference in everything from increasing revenues and attracting patients who might have gone elsewhere, to contributing to cancer center accreditations or foundation fundraising.

Research-related activity often increases ancillary service volume due to protocol requirements, such as diagnostic tests beyond standard of care. Many healthcare organizations use their clinical research programs as physician recruitment tools, as well. There truly is financial value, quality value, and strategic value to having a successful research program in a healthcare organization.

Persuading your site's leadership of the benefits of research serves as a gateway to fiscal opportunity and program recognition throughout the institution, both of which lend themselves to increasing physician and staff onboarding. However, one of the biggest hindrances to physician buy-in and participation is a lack of knowledge of the resources made available to them. Clinical research can often seem overwhelming to busy physicians and their staffs, primarily due to inexperience, or the copious amounts of paperwork.

If your organization has already made an investment in research by hiring coordinators, data managers, and other study personnel, market these provisions to your physicians through personal phone calls, visits, and meetings. With the correct resources and dedicated support staff in place, physicians' perceptions of research shift from burden to opportunity.

By allowing physicians to focus on providing the most cutting-edge treatments to their patients, your site will distinguish itself as an innovative and patient-centered organization, while the behind-the-scenes aspects of research are performed seamlessly by your research support team.

The View from the Outside

According to one poll, only 7% of American patients have been informed by their doctors of research studies for which they might be eligible.[2] The impact of these numbers is felt most by smaller private or community hospitals that are not as known for their research endeavors. This information leads us to the final aspect of internal marketing, marketing clinical research to existing patients.

Conveying the opportunities of research to your patients will provide them with additional options, as well as an increased level of care and attention. There are many instances in which hospitals received letters from patients expressing their gratitude to nurses for the exceptional care, when it was actually the research coordinators who offered that extra attention. This type of feedback plays well into patient experience scores.

Posters, bulletins, and your website are all helpful outreach tools for promoting patient participation and garnering interest in research. Marketing studies to your patient base not only ensures that they continue to rely on your organization in the future, it also boosts your reputation for patent satisfaction and for being the local destination for cutting-edge care.

Conclusion

As you strive to grow your research program, there are other higher level strategic tactics that may be beneficial as well, including the development of a research vision statement and the establishment of a research advisory board. The basic foundation of any program is key though, and in research, that comes from the support of the hospital's leadership, physicians, and staff. Once you have focused a portion of your efforts toward building enthusiasm around clinical research internally, you are well on your way to becoming recognized as a solid contributor to the clinical research enterprise.

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Off the *WIRE,* On the *CRbeat*

Did you know that ACRP's e-newsletter, the *Wire,* was introduced as a monthly communication to the Association's members in 2002? Or that in 2008, it transitioned to an every-other-week schedule and was opened up to the general public to read? Or that, as of its October 13, 2016 issue, its current editor will have assembled 250 consecutive issues of the publication?

It's all true; the *Wire* has been around a long time, serving up news, opinions, and resources across the spectrum of the clinical research enterprise. It has undergone multiple changes in format, focus, and frequency to keep up with the times and readers' needs. And now, it is time to change again.

Following the arrival in late September of a new and improved ACRP website experience for all keyboard- and mobile-based visitors to the Association, our plan is to retire the *Wire* and launch its successor, *CRbeat,* as a weekly e-newsletter in late October.

Why *"CRbeat"*? Beyond "CR" being a handy way to refer to clinical research, the new name more directly points to how we hope every week to hit, via coverage in *CRbeat,* the high points of the very latest national and international developments in the research enterprise, and to more broadly and rapidly share with all interested readers more content from other ACRP news sources—among them, the *Clinical Researcher* journal, the ACRP Blog, and press releases about the Association's initiatives.

So, change is in the air this season at ACRP. Meanwhile, part of the title to this article harkens back to the many years the *Wire's* editor pulled together excerpts from the e-newsletter's most recent and popular stories for use in an ongoing column in *The Monitor,* the predecessor journal to *Clinical Researcher.* That column, "Off the *Wire,*" retired along with *The Monitor* itself in February 2014, but makes a return in spirit in the following news briefs, which reflect some of the most popular topics covered in the last months of the *Wire's* long run.

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NEW RESEARCH METHOD QUESTIONS TRADITIONAL EFFICACY TRIAL MODEL

Traditional efficacy trials have limited relevance to everyday clinical practice and should be changed, according the authors of a new study into chronic obstructive pulmonary disease (COPD) treatments.

The report published on September 4 in the *New England Journal of Medicine* details a new method of testing effectiveness of drugs that puts the patients' clinical experience at the heart of the process.

Led by Profs. Jorgen Vestbo and Ashley Woodcock from the University of Manchester's School of Biological Sciences, the research team conducted an effectiveness and safety trial of fluticasone furoate-vilanterol to manage COPD. Instead of a traditional randomized cohort selected using strict criteria, the new study used specific, representative patients drawn directly from general practitioner (GP) practices in which they were receiving care for COPD.

Entitled the Salford Lung Study, the clinical trial recruited 2,799 patients with COPD from 75 GP practices in and around Salford in Greater Manchester. The GP practices were involved in ensuring the study not only had access to specific COPD patients, but also that the usual clinical care provided by the practices was built into the trials—the study was therefore rooted in a real clinical environment unlike the traditional efficacy trial model.

"Our findings challenge the automatic transfer of findings from efficacy studies to clinical guidelines or everyday clinical practice," said Vestbo. "Involving the GP practices in the Salford Lung Study allowed the team to create an unsupervised environment for the patients, enabling important factors in usual clinical care—such as adherence, frequency of dosing, and persistence of good inhaler technique—to rightly influence the trial outcomes. This is a major deviation from the traditional model, but one we believe will deliver a more accurate set of results regarding effectiveness and safety of new medicines and treatments."

USE OF INTERNET IN MEDICAL RESEARCH MAY HINDER RECRUITMENT OF MINORITIES, POOR

Recruiting minorities and poor people to participate in medical research has always been challenging, and that may not change as researchers turn to the Internet to find participants and engage with them online, a new study suggests.

Researchers at Washington University School of Medicine in St. Louis say that unless explicit efforts are made to increase engagement among under-represented groups, current healthcare disparities may persist.

In a study of 967 people taking part in genetic research, the investigators found that getting those individuals to go online to get follow-up information was difficult—particularly if study subjects lacked high school educations, had incomes below the poverty line, or were African-American.

The new findings are available online July 28 in the journal *Genetics in Medicine*.

"We don't know what the barriers are," said first author Sarah M. Hartz, MD, PhD. "We don't know whether some people don't have easy access to the Internet or whether there are other factors, but this is not good news as more and more research studies move online, because many of the same groups that have been under-represented in past medical research would still be missed going forward."

SURVEY REVEALS HOW SPONSORS VIEW THE ROLE OF CROs IN CLINICAL DEVELOPMENT

A recent survey by Worldwide Clinical Trials reveals that 62 percent of respondents are more likely to engage a clinical research organization (CRO) partner for clinical research than they were five years ago, demonstrating the increasingly vital role that CROs are playing in modern drug development, and the importance of partnering with a CRO that offers medical and scientific expertise.

Conducted at DIA 2016 last June in Philadelphia, Pa., the survey gauged the opinions of nearly 300 drug development leaders and executives from pharmaceutical and biotechnology companies who visited the Worldwide Clinical Trials booth during the DIA meeting. According to Peter Benton, the company's president and COO, in response to a question about the impact of innovative approaches from a CRO, 29 percent of respondents said that innovation in overall trial management would have the greatest impact on clinical development, while 26 percent said that innovation in patient recruitment and retention would have the second biggest impact.

When considering barriers to a new drug development, those surveyed selected the cost of discovery research and clinical development, regulatory guidance, and the risk associated with the clinical development process as the most critical issues.

CONGRESS URGED TO DELAY COMMON RULE UPDATES, EXAMINE PROTECTION OF RESEARCH PARTICIPANTS

A new report from the National Academies of Sciences, Engineering, and Medicine that examines the regulations governing federally funded research recommends that Congress authorize and the president appoint an independent national commission to examine and update the ethical, legal, and institutional frameworks governing research involving human subjects. The commission should make recommendations for how the ethical principles governing human subjects research should be applied to unresolved questions and new research contexts.

The executive branch should withdraw the Notice of Proposed Rulemaking (NPRM) for the "Common Rule" (formally known as the Federal Policy for Protection of Human Subjects), the report says. The regulatory structure protecting human research subjects should not be revised until the national commission has issued its recommendations and the research community, patient groups, and the public have had a chance to consider and react to them.

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ON THE JOB

Zegabriel Tedla, MD, MBA, Dip HI

Bridging the Clinical Research Divide: Perspectives on Working as an Investigator and as a Monitor

You never know someone until you walk in their shoes. You might think that what they are doing is not right; however, it does not necessarily mean that your perspective is right.

In this column, I want to look closely at the different perspectives that investigators and monitors have in conducting clinical research. Having worked as both an investigator and a monitor, I realize that seeing things from another person's perspective can raise your own awareness and enable you to find better solutions, especially if there is occasional discord in your working relationship.

A Call for Collaboration

Without collaboration, there is little opportunity for progress. These words could not be more truthful, based on my experience as a clinical research professional. Having worked in clinical research for more than 10 years now, I do realize that there is no single path to success in conducting clinical trials. Clinical research associates (CRAs) and investigators, in particular, need to work closely together to protect study patients and produce credible data, two of the most critical elements of clinical research.

In this regard, CRAs often play a delicate role when serving as an important link between the investigator and sponsor. On the one hand, they do this by providing reliable monitoring responses of the activities performed during the monitoring visits, including the approaches adopted and those suggested to the researcher to correct or prevent potential problems to the sponsor, who wants concrete results. On the other hand, they try to build up respectful relations through meetings with investigators to discuss monitoring findings, the conduct of a trial, and the management of subjects.

Although most CRAs and investigators share the same expectation and goals in conducting clinical research, the relationship between these two parties has not always been smooth. Some even describe it as being delicate and difficult to navigate. Some observers cite the difference in levels of understanding and knowledge of research ethics and regulations between them as a possible cause for discord.[1,2] Given these claims, I hope that sharing my experience of working first as an investigator and then as a CRA may contribute toward a better understanding of the other person's perspective, and help build a bridge across the clinical research divide.

Two Roles, Many Rules

When I first started working in clinical research as an investigator many years ago, my main function was geared toward two distinct roles: clinician and scientist. As a clinician, I fulfilled my duties to provide patients with optimal care and proper follow-up. As a scientist-investigator, my duties were to follow the rules, procedures, and methods described in the protocol.

I must admit, I found these seemingly distinct tasks to be somewhat in conflict from the start. Because in some contexts, as a clinician I had an obligation to provide the patient with the best care; in others, as an investigator I had only an obligation to provide the subject with the care available under the protocol. For example, an ethical dilemma can arise when the control arm of a study does not correlate with the standard treatment typically prescribed during the conduct of a clinical trial.

Such a setting has distinctly different challenges from those encountered during routine clinical practice, and is one in which even the most astute investigators may encounter unexpected difficulties and experience a contradiction between their roles as a clinician vs. scientist. This can lead to them being misperceived as having a lack of commitment on their part to protect participants' safety and welfare in research.

Given my subsequent experience as a CRA, I have also realized that the task of a monitor focuses on two major functions: an ethical function related to protecting the research subjects, and a technical function related to monitoring specific activities during the research procedures. The need to ensure that these two tasks are appropriately handled compels monitors to be proactive in their communication efforts, and to work to create a positive atmosphere with every study investigator they come across.[3]

Striking a Balance

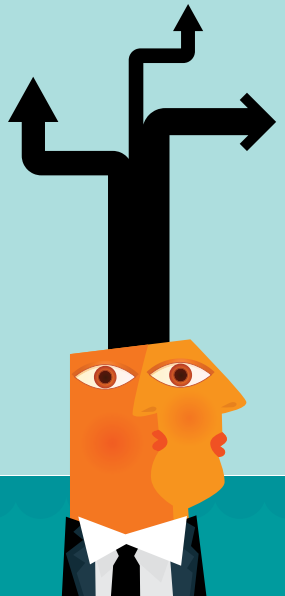
Investigators and monitors must work in ways that allows them to benefit from their collaboration, and there are many professionals from both sides who confirm that working in agreement with each other makes cooperation easier, helps to avoid misunderstandings, and motivates them for better performance. Still, there are occasions in which differences in interpretation of rules and requirements cause friction between these two parties.

Some investigators rue the rigid interpretation of rules and meticulousness on the part of monitors who espouse zero tolerance for unintended mistakes and seem to visit sites only in situations where staff have done something wrong. Meanwhile, CRAs counter these claims by stating that investigators falsely blame monitors for pedantry, when a proper understanding of the rules and regulations for conducting ethical research should be demanded of investigators.

Whichever perspective one considers, I have come to realize that the shared goals of patient safety and accurate data are what ultimately drive the success of this partnership. Further, the critical development and management of this partnership requires patience, productivity, and transparency by all partners.

To work effectively in clinical research requires not only training, but also a unique set of traits, skills, and abilities. There are specific attributes that particularly characterize effective clinical research professionals and separate them from the rest of the pack. For example a monitor needs a good level of rapport to make a connection to the emotional state of a very busy and overworked investigator, so that issues can be dealt with in a calm manner. Meanwhile, investigators who realize that a combined effort is required to ensure

Investigators and monitors must work in ways that allows them to benefit from their collaboration, and there are many professionals from both sides who confirm that working in agreement motivates them for better performance.



participants' welfare and greater data integrity, and who present with a friendly, open, and professional demeanor from the start can quickly establish a positive image and bolster their own reputation in clinical research.

Getting the Relationship Right

In clinical research, there is a need to develop a diverse range of relationships to achieve common goals. A key challenge one often faces in this regard is to develop the "right type of relationship." For example, the relationship is often quite different between a monitor and the study coordinator at one site vs. at another site, or between the monitor and a study nurse or investigator at the same site.

Relationships in clinical research often require the parties to first develop a mutual understanding based on shared expectations and goals, and to appreciate the challenges each other is facing. This enables all sides to become readily familiar with each other's character, working standards, processes, and systems, thereby contributing to greater consistency in delivering results.

Chemistry between personalities also plays a major part in building these types of relationships. For example, if a monitor has been friendly and respectful to study staff from the start, shares monitoring information in a collegial and cordial manner, and doesn't always just lecture about errors, he or she increases the investigator's motivation to positively contribute to the whole monitoring process and will receive a better appreciation from study staff in return. Still, too often frustration and discord may come from both sides and strain the relationship. Ways to improve this strained relationship include discussing intentions up front, communicating unique working situations, being flexible, and sharing the common goal of wanting the study to be completed with few hurdles and hitches.

Importantly, building relationships is a reciprocal process. Investigators should also realize that teamwork is what makes the difference in reaching important site selection, activation, and data analysis milestones, all driven by monitoring visits. Investigators and site staff need to appreciate the fact that monitors spend a substantial portion of their time onsite, gathering and sharing study information, in order to identify ethical risks associated with study procedures and to prevent the occurrence of significant problems.

Once again, given the fact that monitors have the unique perspective of being able to help identify potential issues based on their first-hand observations, investigators should also try to develop trusting relationships with their monitors from the beginning. This increases the likelihood that clinical trials will be run successfully, on time, and on budget.

Considering Compliance

Poor compliance with the tenets of Good Clinical Practice (GCP) compromises the rights and safety of a study, negatively affects the monitor-sponsor-investigator relationship, and often results in extra work in the form of dealing with issues such as correction of trial data. Thus, understanding GCPs well is an essential element of investigator competency. However, medical training in its current form doesn't always address the real-world ethical challenges that investigators face on a daily basis in clinical trials.[4,5]

Whenever I look back now on my previous role as an investigator, I often wish I had the same ethical understanding and regulatory knowledge then as I have at this moment. So many things that I was required to do as an investigator—from fulfilling various ethical principles and regulatory guidelines, to adhering to study procedures and the protocol, to filling out the vast amount of paperwork to be submitted—would indeed have made so much more sense.

I now believe that clinical investigators should make an ongoing effort to obtain training that more broadly addresses ethical and regulatory issues related to the conduct of clinical research, in addition to understanding study-specific requirements. If an investigator is uncertain whether a particular situation or course of action would violate ethical standards when conducting clinical research, it's advisable to consult with other experienced investigators who are knowledgeable about ethical issues, or with responsible study monitors, in order to choose a proper response. Such consultations help investigators to avoid departures from accepted ethical research practice and to prevent those most serious deviations that constitute research misconduct.

In this regard, I really consider myself fortunate to have worked closely with a number of talented and driven investigators and monitors over the years. To them, I give full credit for providing me guidance and helping me to develop my career both as an investigator and a monitor. They have made me realize that, even if workplace relationships are constructed around work-related tasks, successful collaboration goals are achieved through the shared satisfaction levels and attitudes of collaborators.

Conclusion

For me, to have bridged the clinical research divide and experienced working on both sides of the field has been educational and rewarding. To share this experience and perspective with other researchers is what clinical research is all about—working together to achieve common goals.

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QUICK TAKES:
Shallow Pools, Payment Plans, CAPAs, and QA

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 of these and others, go to https://acrpblog.org/.

CLINICAL TRIALS OFTEN UNDERMINED BY SHALLOW SUBJECT POOL

Clinical trials underserve the public health and, in some cases, limit the value of the data amassed from a pool of subjects, say a number of experts in the field and officials at the U.S. Food and Drug Administration (FDA). Too often "minorities are underserved and it may impede their health," suggests Lea H. Becker, senior clinical research coordinator with the Department of Emergency Medicine at the University of Virginia Health System. [For more on this topic, see the interview with FDA's Jonca Bull beginning on page 48.]

On the positive side, Becker is encouraged by a survey she recently conducted that looked at 500 consent conversations in an emergency room environment. It suggested that the recruitment gap has closed tight between minority and white patient populations. "I was really happy about it," Becker says, "I believe it reflects a concerted effort" at the facility bolstered by outside community outreach. She does note that conditions in an emergency room are "very different" than in other settings. Regardless, she advocates the adoption of what she calls "thinking tools" to help other facilities close that recruitment gap.

"Be clear on who you are approaching, and how much they need to know about a study in advance," advises Becker. Conversely, ask yourself why you are not approaching a particular group. Do you believe, based on anecdotal evidence or your own perceptions, that some groups simply don't follow up and are too much of a hassle to recruit? "That's not fair," Becker says.

By applying thinking tools, it is easier to draw disparate populations into a clinical trial, Becker adds. She allows that egregious lapses in clinical trial ethics that have been brought to light over the years have sometimes highlighted racism as an issue in research that might have made industry professionals overly cautious in their outreach to underrepresented groups. Sensitivities related to clinical trials remain an important factor in some minority populations.

PRESS SPONSORS WITH NEW PAYMENT PLANS

Clinical trial site managers do themselves a disservice if they don't press sponsors to consider monthly payments as opposed to the industry standard quarterly schedule, says Nikki Couturier, BSRT, CCRC, a budget and contract specialist with IACT Health.

"Sponsors are showing more willingness to work with sites on payment frequency," Couturier says. In the past, payment schedule terms tended to be very strict, she adds.

That said, Couturier has observed something of a shift of late; sponsors have become more open to negotiating other payment terms if a site pushes back. "Don't accept their payment rate at face value," she suggests. A site's price tag should reflect its own financial statement in terms of real costs in a specific situation.

Sites should also be skeptical when a sponsor says it is offering what other sites get, Couturier says. "That's not [always] true." While it makes sense to ask a sponsor how much time a given task or project might take, use that figure only as a starting point for your own calculations.

In the past, "we had no idea how to evaluate our costs," Couturier says, but she worked with her team and other personnel to change that. She uses her own experiences as a Certified Clinical Research Coordinator (CCRC) to help gauge how much time a project will take. When some aspect of the work is out of her realm of experience, she goes straight to clinical staff who have a track record in that arena. Ultimately, they base their charges on a real-world hourly assessment, instead of charging by task.

Couturier has also had some success with a new wrinkle—a tiered budget. Describing it as a "huge breakthrough," IACT has been able to negotiate deals where the site agrees to two sets of contract budget terms. Couturier explains that the second set only kicks in and allows them to charge more if they exceed enrollment goals (for example in one recent trial, $5,000 per patient), "once we've proved we can do it ourselves our own way."

Couturier cautions, though, that the enrollment goals should not be forced in-house as a pressure-filled incentive, but rather more as a goal.

FDA INSPECTORS RENEW CAPA FOCUS

While matters related to how informed consent is obtained at study sites remain at or near the top of most U.S. Food and Drug Administration (FDA) inspectors' checklists, they've also shown an increasing interest in corrective and preventive action (CAPA) programs, says Dr. DeAnn Cary, director of research with Sharp Healthcare in San Diego, Calif.

Cary's employer has more than 200 trials in process at any given time, she says. Part of her job involves overseeing Sharp's local institutional review board staff.

Though it isn't common, FDA inspectors can show up in your waiting room unannounced, Cary says. Typically, however, you'll have some notice that they plan to come calling. Regardless, it can be a nerve-wracking experience.

"The prospect of a regulatory inspection can be anxiety provoking for sponsors and contract research organizations, and for clinical investigators and their site teams," notes Terri Hinkley, RN, BScN, MBA, CCRC, deputy executive director of the Association of Clinical Research Professionals.

At Sharp, a community-based health system with seven hospitals and trials running the gamut from neonatal to Alzheimer's, successful, relatively stress-free FDA inspections are about preparation and keeping the prospect of an inspection in mind every day. It doesn't have to be an all-consuming fear, of course, Cary stresses.

There are any number of ways to work smart and prepare for an FDA inspection. "There's no reason you can't be prepared," Hinkley says.

For example, Sharp works closely with her team of investigators. Every quarter, six investigators are tapped to write nine-page self-assessments to ensure they are inspection ready at all times.

"It's not to catch them out as deficient," Cary says. "It's a tool to make sure they have what they need." The exercise gives everyone peace of mind, she adds. "If the FDA comes knocking at the door, we can feel comfortable handing over our regulatory document binder."

IACT HEALTH OFFERS QUALITY ASSURANCE TIPS

Dogged dedication to reviewing documents and keeping training on the cutting edge at study sites are keys to an effective quality assurance (QA) program, says Katrina Quidley, regulatory manager with IACT Health in Columbus, Ga.

"We review every interim monitoring visit letter as it comes in," Quidley says of her efficient shop. Letters are sorted by reviewer so that trends, such as dosing errors, can be caught early in the cycle, she adds. IACT takes a hard look at letters as a group each week, in order to catch patterns and trends that might spell trouble down the line.

Training and communication are equally important components of a strong site QA program, Quidley says. While IACT formally updates its training manual annually, managers review its components every six months, and have regular informal meetings and communications to consider new tools and tactics gathered at events such as the Association of Clinical Research Professionals' annual Meeting & Expo.

IACT also conducts full-scale quarterly meetings, plus informal gatherings and e-mail communication on an ongoing basis, to best share new ideas and incorporate those into training sessions.

Among other benefits, such diligence helps give clinical research coordinators at sites better understanding of (and more input on) the reasons behind (and development of) standard operating procedures, Quidley says.

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