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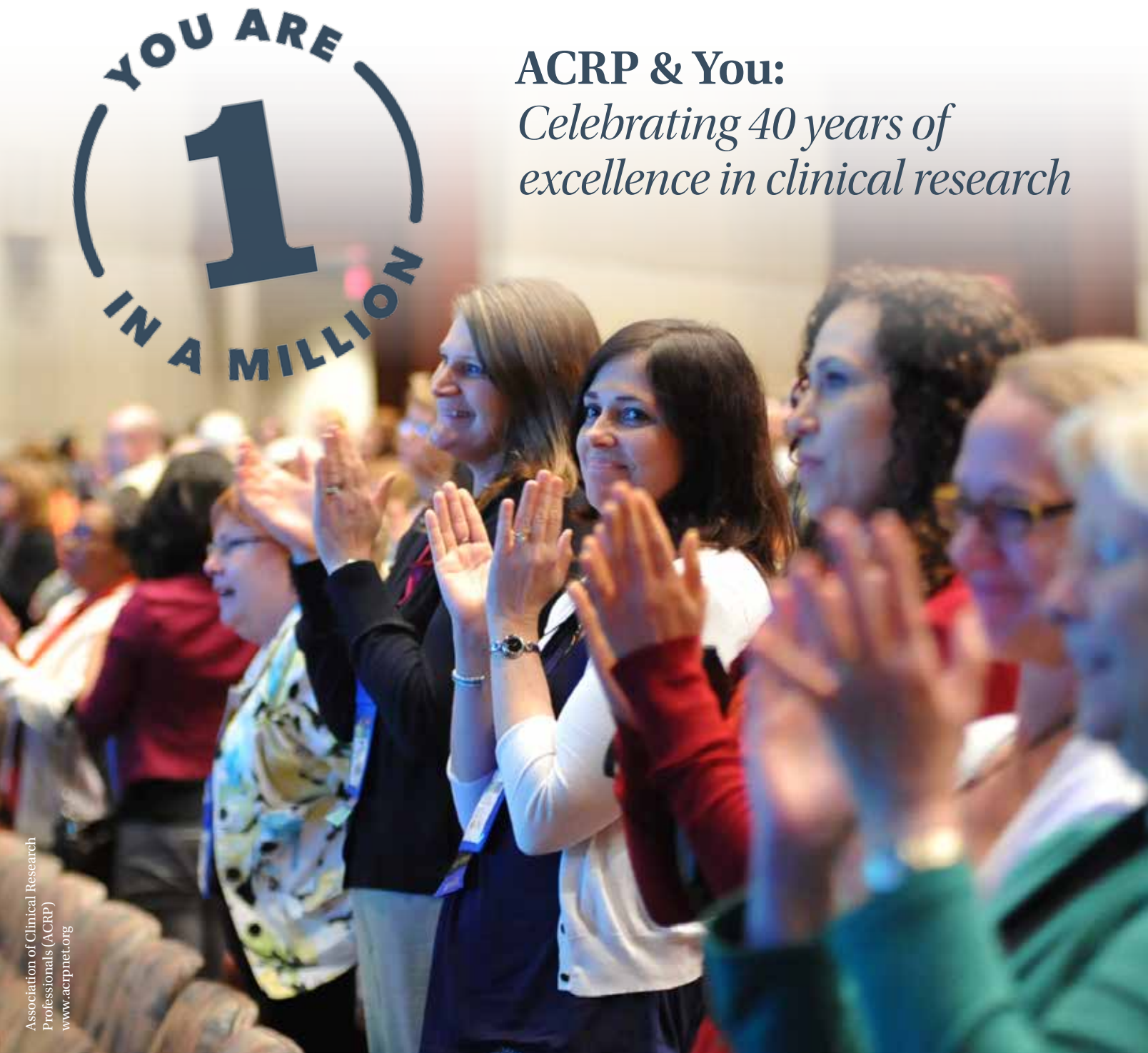

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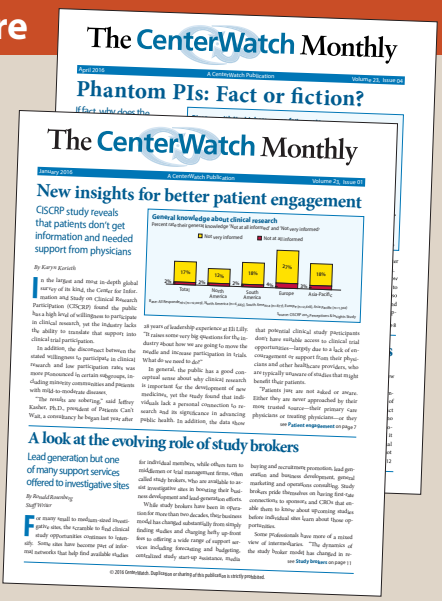

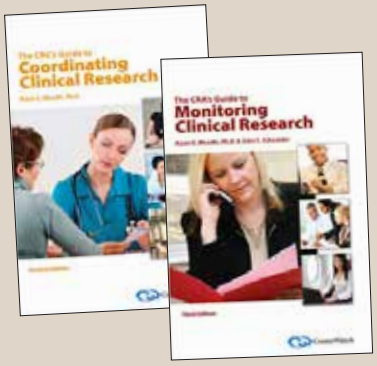

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The Authority in Ethical, Responsible Clinical Research

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CORRECTION: The current volume number was printed incorrectly in the February 2016 issue. Please make a note of the correct number (30) in any references you may have made to that issue.

At ACRP, we're honored to have been your voice and resource for the past 40 years. We think it's time you gave yourself a loud round of applause to recognize the incredible contributions you've made, and will continue to make, to promote excellence in clinical research and advance new therapeutic options for humankind.

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GUEST EDITOR'S MESSAGE

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

[DOI: 10.14524/CR-16-4013]

Revisiting the Future... AGAIN!

If you've seen my name listed as guest editor of previous issues of this journal, or remember the columns I contributed during my stint as chair of the Association Board of Trustees (ABoT), you might now be predicting that your very immediate future contains yet another nonscholarly column filled with pop culture references and self-demeaning disclosures of nerd-dom in a meager attempt to make a few points. Well, you'd be correct in your prediction. It was truly an honor to be asked to help assemble this edition of *Clinical Researcher* in celebration of the 40th anniversary of ACRP—especially not by undertaking a historical review, but by looking toward the future.

For the 30th anniversary of ACRP back in 2006, *The Monitor* (the predecessor of *Clinical Researcher*) published some "Visions of the Future," in which then-current and former ACRP leaders gazed into their crystal balls to report on where they thought ACRP would be at today's 40th anniversary. The results remind me of how we all had fun seeing if the *Back to the Future* movie's predictions for October 21, 2015 came true (biometric scanners and communication via flat screen TVs…yes, hover boards and self-tying shoes…close, flying cars…still waiting).

I must say that after reviewing the predictions for the Association, I am reminded of one of Yogi Berra's most quoted quips: "It's tough to make predictions, especially about the future." There were no colossal failures (equating to the *New York Times* 1939 prediction that "Television will fail…People don't have time to stop what they're doing and stare at a screen," or Dick Rowe of Decca Records' 1962 rejection to sign The Beatles because "Guitar groups are on the way out…[they] have no future in show business"), but let's just say that those who were so bold as to predict actual membership numbers were more optimistic than the Magic 8-Ball (whose responses are 50% positive, 25% neutral, and only 25% negative).

However, those who predicted that ACRP would maintain and/or enhance its reputation as a global leader in education, in certification, and in providing a voice for research professionals that will be heard among stakeholders…well, they obviously are in the good company of Paul the Octopus (the now-deceased U.K. cephalopod whose unbelievable 2010 World Cup predictions inspired teams predicted to lose to post octopus recipes on the Internet) and Nikola Tesla, who in 1909 predicted that "it will soon be possible to transmit wireless messages all over the world so simply that any individual can own and operate his own apparatus." (Dear *New York Times:* Anything to say about the longevity of stopping what we are doing to stare at those screens?)

Thus, in keeping with tradition and for kicks and giggles, we will repeat the exercise with leaders of the past 10 years predicting where ACRP will be on its 50th anniversary.

The Promises and Perils of Predictions

Ironically, my last column as ABoT chair in 2009 was also assigned to be about "the future" (in that case, what were to be the following five years). My big prediction was that, despite advances to the contrary, we would still need humans to run clinical trials. Score one for me!

Among many other things (such as quoting Ludwig Wittgenstein three times—I guess I was really into him then), I also called to readers' attention Arthur C. Clarke's First Law of Predictions, which

is "when a distinguished but elderly scientist states that something is possible, he is almost certainly right—when he states that something is impossible, he is very probably wrong." So I'm not just recycling my prediction of still needing humans to run clinical trials 10 years from now, I'm doubling down on my certainty on the matter.

I am neither a distinguished scientist nor elderly (so they say), but it seems to me it will still be impossible to run trials without us humans (although communications may be in hologram or avatar format). With that said, our skill sets will need to evolve in tandem with the rapid evolution of the machines and technology we use to maximize our efforts. Therefore, we will still need highly ethical, but differently trained, humans to drive the process.

Don't get me wrong, it would be great to sit around all day and play video games about the future (my wife already calls herself a "*Fallout 4* widow") or binge listen to futuristic David Bowie albums (R.I.P. Mr. Bowie, you will be missed). However, I'm afraid, for better or worse, that we humans have a lot more to do to keep the medical research engine going, and we will need technology's help (unless, of course, our future entails the prohibition of all computers and other thinking machines in favor of evolving our minds, like the Mentats did in Frank Hebert's Dune, to handle highly complex calculations).

Perhaps I'm wrong. Perhaps our future will be more dystopian, as in George Orwell's 1984, where instead of Big Brother, we'll have Big Government spying on our conversations, data scientists "correcting" our data, and clinical research coordinators (CRCs) being incentivized by the government to turn in their principal investigators (PIs) for billing fraud and research misconduct. (Oh, dear… when was 1984?)

Perhaps either during our clinical trials of the mind-controlling drug Soma (thanks Aldous Huxley's *Brave New World*) or our taste tests of Soylent Green (thanks, *Soylent Green* movie), our new electronic case report forms and clinical trial management systems will become self-aware, determine that human error is the real enemy of "clean data," and lock us all out of the system (thanks, Arthur C. Clarke's *2001: A Space Odyssey*), thus bringing about the extinction of PIs, CRCs, and monitors (thanks, *Terminator* movies).

Or perhaps, as H.G. Wells would have us believe in *The Time Machine,* it's all moot as eventually we will all be replaced by giant crab-like creatures of unknown origin (for which my excellent skills in killing Mirelurks in *Fallout 4* will thankfully have me prepared).

Today is Tomorrow Yesterday?

Regardless of the above, one certainty is captured by postmodern author/satirist Chuck Palahniuk, who states "The future you will have tomorrow won't be the same future you had yesterday." One of my favorite embodiments of that quote pertains to science fiction author and futurist Ray Bradbury (of the famous quote "We have too many cellphones. We've got too many Internets. We have got to get rid of those machines. We have too many machines now."). Making one of the most (if not possibly THE most) ironic days in literary history—after decades of telling publishers to "go to ___," Mr. Bradbury finally acquiesced in 2011 and allowed *Fahrenheit 451* to be published in eBook format (leading us to ask "at what temperature does an eReader start to burn?"). The future, indeed, is a moving target.

In closing, summarizing all of this can be done via the mantra of hope from *The Terminator,* "the future is not set…there is no fate but what we make ourselves." Thus, I can't tell you exactly what 10 years from now will look like because I (thankfully) am not determining that alone. I can, however, celebrate that it will be built with not only some of the greatest people I have (and will have) the privilege of knowing, but who also share the values of the ACRP mission and vision, which respectively mean they "promote excellence in clinical research" and that "clinical research is performed ethically, responsibly, and professionally everywhere in the world."

As you may know, my standard e-mail/letter signature doesn't use standard terms like "Sincerely," but is "Looking forward…," therefore I end this column in the same manner.

Looking forward…David.

I can't tell you exactly what 10 years from now will look like because I (thankfully) am not determining that alone. I can, however, celebrate that it will be built with not only some of the greatest people I have (and will have) the privilege of knowing, but who also share the values of the ACRP mission and vision.

David M. Vulcano, LCSW, MBA, CIP, RAC, (david.vulcano@hcahealthcare.com) is the Responsible Executive for Clinical Research in the Clinical Services Group of HCA (Hospital Corporation of America) in Nashville, Tenn., and served as chair of the ACRP Board of Trustees in 2009.

BY THE NUMBERS

Offering glimpses of trends that either look promising or problematic for the future of conducting clinical trials.

The overall rate of results reporting of probable, applicable clinical trials is **64%** since the ClinicalTrials.gov database went live in 2008, which reflects **66%** of industry-funded trials, **65%** percent of extramural NIH-funded trials and **46%** of "other" government and academic trials.

Source: Bloomberg BNA, www.bna.com/results-posted-clinicaltrialsgov-n57982067581/

Although patient-reported outcomes had not been highly popular in earlier practice, **68%** of clinical trials at recently surveyed Top 10 companies, **45%** at Top 50 companies, and **90%** at small pharmaceutical companies now involve implementation of these self-reported measures.

Source: Marketwired, www.marketwired.com/press-release/-2097503.htm

In interviews with **66** cancer patients at two Midwest Cancer Alliance partner clinics as well as an online survey of the public, nearly **30%** of respondents had a positive perception of clinical trials, but about **25%** perceived trials as a last resort treatment. Others expressed concern about safety or being a "guinea pig," or they feared the possibility of receiving a placebo.

Source: KU News Service, http://news.ku.edu/2016/02/16/ku-leading-collaborative-study-learn-about-minority-perceptions-cancer-clinical-trials

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CELEBRATING 40 YEARS

ACRP & YOU:

Building Community Together for 40 Years

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

Brent Ibata, PhD, JD, MPH, FACHE, RAC, CCRC, CPI, CHRC, (brent.ibata@gmail.com) is the 2016 chair of the Association Board of Trustees for ACRP.

You are one in a million.

At ACRP, we're honored to have been your voice and resource for the past 40 years. We think it's time you gave yourself a loud round of applause to recognize the incredible contributions you've made, and will continue to make, to promote excellence in clinical research and advance new therapeutic options for humankind. It might sound like a big claim, but it's mighty easy to back it up.

From Bench to Bedside

Let's just look at one example. ACRP member Cheryl L. Dalton, BSN, RN, CNN, CCRC, is the only certified nephrology research nurse in the state of West Virginia. "I have been involved in nephrology research since June 2000, and have had the opportunity to see many new therapies get approved for patients with chronic kidney disease, as well as end stage kidney disease," she tells us. Many of those therapies are being used today in her clinics and elsewhere. Her impact is tangible.

West Virginia has one of the nation's highest rates of chronic kidney disease, mostly due to diet, income, socioeconomic status, and the lack of nephrologists. Cheryl is justifiably proud that as part of the process of translating research from bench to bedside, her work "has allowed our patient population to have access to drugs they would not have had the opportunity to get outside of a clinical trial."

Reflecting back on her career, Cheryl says clinical research is important to her personally and professionally because it can improve the lives of patients. In addition, she enjoys other opportunities to give back. "Not only do I learn," she says, "I get to teach others about healthcare, and the patients love the individualized/specialized care they get."

There are tens of thousands of other stories amongst our membership that sound just like Cheryl's. That's one of the reasons we've recently launched our "You Are 1 in a Million" campaign. Via our website, blog posts, *Wire* e-newsletter, and in the pages of *Clinical Researcher* and elsewhere, we're going to feature your stories during this celebratory 40th anniversary year. There are many stories we hope will serve as both encouragement and inspiration to present and future clinical researchers.

Looking Back—Looking Forward

The U.S. bicentennial year of 1976 saw the birth of both ACRP and the Medical Device Amendments of the Federal Food, Drug, and Cosmetics Act. Forty years ago, personal wireless communication was achieved using citizens band (CB) radios, music was shared with vinyl 45s, and copies were made with carbon paper.

Clinical research has evolved significantly since 1976, and so has the clinical research professional. Clinical trial data can now travel instantly from an implantable investigational device into an electronic database thousands of miles away and to the principal investigator's smart phone. However, it's not all about reflecting on the past. In fact, it's even more exciting to contemplate advances in clinical research over the next 40 years. We are at the threshold of personalized investigational new drugs and new classes of minimally invasive investigational devices.

Risk-based monitoring. Online patient recruitment and data gathering. Informed consent. The clinical research associate shortage. We think it's fair to say that these are among today's hot button issues. While some may sound daunting, let's remember how far we've come in the past four decades. As an industry, we're more than a match for these challenges. If past is prologue, we're going to find new ways to vastly improve performance as we overcome these obstacles.

We are both excited about the opportunities we have in our new roles with ACRP to help effect change and better recognize how great you are, especially as we mark the Association's 40th anniversary. Clinical research has changed dramatically in the past 40 years, and clinical research professionals like you will lead its next 40 years. ACRP will be with you every step of the way—sharing best practices with webinars and other educational opportunities, bringing the industry together to foster a stronger sense of community, and reminding each and every one of you the positive impact you have had, and will continue to have, on the lives of millions.

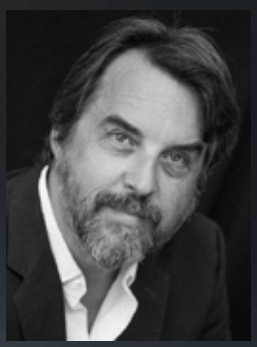
You are all part of a higher calling. You work hard. You work with passion. You work to get results. Thank you for letting us support your success.

You are one in a million.

Via our website, blog posts, *Wire* e-newsletter, and in the pages of *Clinical Researcher* and elsewhere, we're going to feature your stories during this celebratory 40th anniversary year. There are many stories we hope will serve as both encouragement and inspiration to present and future clinical researchers.

HERE'S TO THE NEXT 40...

This ACRP 40th Anniversary issue is a celebration. However, we aren't throwing a party for ACRP as an organization. This milestone is about members like you. Let's take a moment to look forward and backward together.



Guest Editor David Vulcano has done a masterful job gathering a number of interesting viewpoints from both recent and long-time ACRP members. You'll find some of voices in "Visions for the 50th Anniversary of ACRP… and Beyond" on page 38. Among contributions of memories and insights from many others in the ACRP family, Managing Editor Gary Cramer, a 10-year veteran on the ACRP staff, also shares some thoughts. As a relative newcomer, I learned a lot from everyone in this issue.

We hope our new "You Are 1 in a Million" campaign shines a congratulatory spotlight on you and your colleagues. Throughout the pages of this special issue of *Clinical Researcher,* you'll find eight inspiring stories from ACRP members who are justifiably proud of their contributions to advance drugs and devices being used today to extend and improve the quality of life for patients.

At the same time, I know each of you wants to do even better. You want to grow with the industry. You want to drive that growth…to continue to be a part of something bigger than yourselves. In this issue, we've purposely focused much of the content on looking forward.

I had the good fortune recently to speak with Kai Kight, a keynote speaker at our 2016 Meeting & Expo in Atlanta, Ga. A product of Stanford University's design and engineering program, he's passionate about inspiring new ideas and new leaders. His perspective continues to be fueled by his own growth as an innovative classical music composer.

"Why wait for others" to define your life path? Kight told me. Identify your own internal aspirations and desires. Consider new ideas. Take intelligent risks.

"If I fail, it's okay," Kight says, in some ways distilling his own message down to five words. Fear is the enemy of innovation. "We all have a natural instinct to run away from discomfort," he says. Don't fall into that trap. "The best musicians don't run away from that dissonance," he told me. "Bach was one of the first classical musicians to use that tension" to make incredible music. Harmony is about bringing different sounds together to create a new, stronger sound.

You might embarrass yourself trying something new, Kight admits. However, it's not a wasted effort if you learn from the experience. It's not "pain for pain's sake," as much as it is a strategic use of personal energy to take chances and reach new heights. "When I try a piece of new music, I can tell from the applause whether it is working or not," he says. "I learn from that. I keep improving."

I think Kight's got it about right. When a person (or an organization, for that matter) turns 40, it's not a bad time to reflect on one's life. It's fun, and well-deserved, to enjoy fond memories. Then it is time to put those moments back in the scrapbook. We've all got a lot to do in the next 40 years, too. Let's take that next step together.

All the best,
James Michael Causey
Editor-in-Chief

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Molly Downhour, MHA, BSN, NEA-BC, OCN

Consultant, Medix | Scottsdale, Arizona

"The therapy that I worked on that I am most proud of is Erivedge, an oral hedgehog inhibitor approved by the Food and Drug Administration (FDA) for metastatic basal cell carcinoma."

I was the research nurse for the Phase I clinical trial and dosed the first patient in the world on this drug (and for this novel targeted pathway). It was a grand slam, as the first patient was at the right dose and had a lasting response. Through the Basal Cell Network, we quickly became the leading enrolling site, treating patients from all over the country. It was breathtaking to see patients' external tumor sites respond to Erivedge and new healthy tissue grow. Through our efforts, the drug was approved five years and one week after the first patient took the initial dose (second fastest approval in FDA history). This was the first systemic therapy for patients with this rare cancer and finally a nonsurgical option. Erivedge was a huge win for people suffering from rare diseases, as it gives them hope that research will continue to find treatments to help them. With my vast experience with Erivedge, I was asked by Genentech to share my experiences and side effect management at the company's national sales conference. I was honored to share the story of Erivedge and help the sales team understand the impact it can have on patients' and their loved ones' lives.

Helping people has always been in my heart. It was the reason I went to nursing school. I cherished the small wins that I could achieve as a nurse to make someone's day a little better, despite facing a terminal diagnosis. I serendipitously fell into clinical research and it changed my life. I was touched by the courage and altruism the patients showed by participating in clinical trials. Personally, I enjoyed caring for clinical trial patients and having a positive impact on their lives and the millions of others who would benefit from the therapies we developed. As my clinical research career advanced, I discovered a passion for empowering sites to do research. As a clinical research consultant, I feel that I am contributing to advancing science and serving patients by optimizing operations and the infrastructure needed to do research at the highest level.

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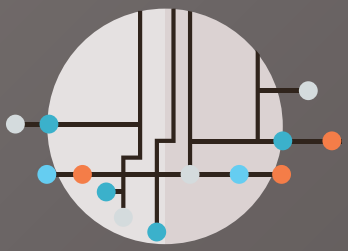

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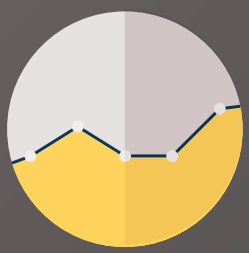

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Drug Products for Investigator-Initiated Research

PEER REVIEWED | Philip K. Burns

[DOI: 10.14524/CR-15-0040]

What happens when a clinical investigator is also the person with an idea for a new drug? He or she envisions how and why it works, and possibly has experimented with it to help understand it better, and to confirm the idea is on the right track. Then the researcher begins to think about his or her role as initiator and as the principal investigator (PI), and the roles of study coordinators, project managers, and patient recruiters who will be needed to manage the clinical study phases of the Investigational New Drug (IND)[1] process for approval through the U.S. Food and Drug Administration (FDA).

LEARNING OBJECTIVE
After reading this article, participants should be able to describe the responsibilities of sponsor-investigators regarding drug product quality in clinical trials they are conducting.

DISCLOSURES
Philip K. Burns:
Nothing to disclose

What about the physical drug itself? This article includes background information about the physical drug path that may be useful to investigator-initiated research teams. Unlike company-sponsored efforts, the source of the physical drug may not be clear. It could be a current drug or combinations of current drugs, with a new use, dosage type, or dosing structure. It may be a chemical that is not currently used as a drug, like a vitamin or food derivative. Or perhaps it's a new chemical entity, reflecting a revision to a precursor chemical, or an entirely new structure.

There are two major aspects for the drug's path forward. One is the clinical research path to provide evidence that the drug works and is not harmful to patients. The other path relates to the physical/chemical drug itself, as without it, nothing can be done. When the drug investigator is also the sponsor, he or she assumes 100% of the sponsor responsibilities that typically are managed by a sponsoring pharmaceutical company. The physical drug path, and the chemistry, manufacturing, and controls (CMCs) needed to produce a drug product for clinical trials and subsequent commercial distribution are discussed.

The Drug

The active pharmaceutical ingredient (API) must be obtained and converted into a finished drug for use in clinical testing. APIs may be obtained through manufacturers and suppliers if currently available, or through the chemical manufacturing process on a small scale. There are many forms the finished drug can take, such as tablets or capsules, liquids, creams or ointments, sterile injectable, skin or buccal patch, or an inhaled product.

The physical drug may seem to be the easiest issue to deal with in the overall investigational process, especially when compared to the clinical research involved. In reality, producing a drug with the right physical properties to meet metabolic conditions requires specialized chemistry knowledge, equipment, and supplies. Without a proper development plan, product quality and variation can pose risk to patients and the project.

Small-scale manufacturing in a lab or pharmacy produces limited quantities of drug. The limited scale or imprecise equipment can result in product and batch-to-batch variation. This can affect drug quality, leading to negative impacts on patients, clinical responses, and consistency of outcomes. In addition to drug quality concerns, the veracity of the drug quality can be questioned if the testing is not properly qualified and documented.[2] This can result in patients being put at risk, and delays of the project and FDA reviews and approvals. Corrective action often requires repeating production and clinical efforts.

When it comes to the drug product development and the clinical efforts, the legal responsibilities for all aspects of the requirements belong to the sponsor. These requirements are established first and foremost to protect the public and patients' rights. Some necessary and useful drugs have never made it to the market, or did not stay on the market, because these requirements were not properly met.

Getting the Drug Made

There are four major aspects of getting a drug made:

1. Manufacturing of the API
2. Manufacturing of the drug product(s)
3. Packaging of the final drug product
4. Testing of the API and drug product ingredients, processes, final form, and the stability of the API and finished drug product

(Packaging of the API is an aspect of manufacturing the API, but does not have the criticality of packaging the drug product for clinical trials. The manufacturing of the drug product will include the manufacturing of placebo products needed for the clinical trials.)

Pursuance of the physical drug isn't just linked to the clinical plans. Many activities must precede having the dosage ready for first usage in patients. Depending on the history of the drug (new chemical entity, current drug, etc.) some pre-IND stage activities require the API and drug be put through pharmacology and toxicity studies in animal models. Other activities are required to develop a final form for use, and to provide the assurance that all of the drugs used for the clinical trials are equivalent and meet defined specifications. These assurances must be met before the drug product is administered to humans.

Facilities, Equipment, Personnel

The facilities used to manufacture the API and drug product should be registered for those purposes with the FDA. (The FDA has specific registration requirements for APIs, drug products, testing labs, and other supporting facilities in the drug development and commercial stages.) Some early-stage activities may be allowed in nonregistered facilities, but that action can lead to delays, significant efforts to justify activities, or rejection of the activities.

Depending on the phase of clinical trials, the facility should be qualified and validated. Qualification provides documented and testing evidence regarding the environment (heating, ventilation, air conditioning, cleaning, microbial levels) and the utility supports (electricity, steam, hot water, process water and water quality). Additional current Good Manufacturing Practice (cGMP) quality systems[3] are required, such as procedures, calibration, documentation, etc. cGMP requirements are extensive, and not typically practiced in a pharmacy or lab setting.

In addition to the FDA, other regulatory agencies may have oversight within the facility, dependent on the activities performed. These can include the Drug Enforcement Administration[4] for scheduled drugs, class materials, and specific equipment reports; the Environmental Protection Agency[5] for environmental exposures of the chemicals; and the Occupational Safety and Health Administration[6] as relates to occupational exposure of workers to activities, chemicals, and solvents. Most companies have their own internal structures to ensure compliance with regulations and laws, but liability can still extend to use of their services without assuring their controls.

Like the facility, any equipment used in the manufacturing, packaging, and testing of the drug product needs to be qualified and validated. Qualification assures that it has been installed properly and is operating as intended. Validation is testing of the equipment for specific purposes, and is different from operational qualification checks. In addition, there are specific validation requirements based on processes and test methods (discussed below). The quality system controls must extend to the equipment.

The personnel performing manufacturing, packaging, and testing; support personnel (like maintenance, quality); and supervision/management must all be qualified and trained for their assigned tasks. This includes training on the quality systems used to control the facility and equipment, and in the cGMP regulations.

Manufacturing

The chemical synthesis of APIs can be simple to complex and influences the manufacturing process and costs. It can also influence its use in the drug product and the stability of the API and drug product. The primary factors are the ingredients, the process and controls, and the specifications.

INGREDIENTS

Availability and quality influence the selection of ingredients. Some may be readily available but their quality questionable. The long-term

There are two major aspects for the drug's path forward. One is the clinical research path to provide evidence that the drug works and is not harmful to patients. The other path relates to the physical/chemical drug itself, as without it, nothing can be done.

The legal responsibility and liability for assurance that drug requirements are met is equivalent to that taken for the clinical trial efforts. Attempts to save time or money on the physical product or its requirements are shortsighted and can put at risk all the good work completed or planned.

implications of availability and quality need to be thought through. Lower quality ingredients can result in unacceptable levels of impurities or influence the ability to purify the final drug substance. Some ingredients impact the intended final product's reaction rates or conditions, and can result in expensive processes. Early-stage use may be low and seem to be inconsequential, but scaling up to clinical or commercial levels could be problematic and expensive.

PROCESS AND CONTROLS

If the chemical process can be varied, then the effects of any variations on the long-term research need to be assessed. Variations could cause issues with costs of ingredients or impact the physical structure of the final form. This structure can have a major impact on drug product formulation and processes. Once the primary process is established, then the specific process controls and purification need to be finalized. These efforts support the development reports, which then impact the process validation. (Process validation refers to validating the specific ingredients, equipment, processes, and controls to produce a known compound of specific and defined attributes.)

The final API will need to be physically and chemically characterized. This information is used to develop the API specification. That specification includes the product attributes that are critical to its use (as a drug product), and includes limits of manufacturing and degradation impurities. Part of this characterization includes stability testing of the API. That testing assesses the impacts of temperature, moisture, and time on the API, and includes assessing for protective aspects of packaging. Accelerated stability testing and forced degradation are also performed using acids, bases, and light exposures.

DRUG PRODUCT

Each of the drug products (dosage forms, strengths) undergo efforts similar to the API—ingredients (formula), processes, and controls. Unlike chemical synthesis, most drug product processes change the physical characteristics of the API and the ingredients added. These physical characteristics can have a direct impact on the properties, stability, and pharmacokinetics of the finished product.

Validation ensures the equivalence of drug products from batch to batch, or before and after any process changes. Control of product variation is critical to ensure the equivalence of clinical trial materials and their potential effect on clinical outcomes. Making multiple small batches in a pharmacy or lab can result in significant unit variability that directly impacts clinical outcome statistics. To set the proper batch size, consider the long-term demand for the drug, through multiple clinical efforts, laboratory testing, and stability assessments (plus sufficient retained samples as required for all studies).

The drug product specification is developed to ensure the proper level of API is present and the physical state (dosage form, color, condition, etc.) of the drug product is appropriate for use. It also ensures that active ingredient is stable, based on levels of degradation impurities. The API can degrade due to the environmental conditions it is exposed to and its interaction with other ingredients. The physical state of the drug can change due to these exposures. Stability is influenced by environmental exposure and the protective nature of packaging.

Packaging

Packaging is critical to providing protective conditions for the contents of a package. In addition to the packaging container and its closure, there are other critical aspects of packaging at the clinical (and then commercial) stages.

- **Labeling** identifies the contents of the package and includes specific directions for the dispenser or user of the product contained. The controls for creating and printing this labeling, and attaching it to the packaged product, assure the medications given match the clinical protocol design criteria.
- **Blinding** is a specific type of labeling of product or placebo to ensure there are no biases in the clinical trial effort (by the staff or the patient).
- **Traceability** of packaging and supporting records and documentation (including distribution) provides assurance of the identity of any given drug product and package as being of a specific API, manufacturing, packaging and labeling batch, and handling of that batch post production (including use by the laboratory).

Testing

Testing provides the evidence of outcomes from the physical drug and clinical trials. The veracity of the drug, the clinical protocol, and the tests all must be assured. Evidence is achieved through testing.

Lack of evidence, no matter how minor, can result in patient risk and questioning of the drug quality, clinical efforts, and the statistical outcome. Typically the only way to overcome such a condition is to repeat the efforts. Repeating any of the manufacturing, testing, and/or associated clinical trials will have a significant impact on the project's cost and result in a delay of product approvals.

The facility and equipment qualification and validation, and the personnel requirements that apply to manufacturing and packaging, also apply to laboratories. A minor exercise like calibration checks of a laboratory balance can have major implications on test results. (Example: If calibration failure results in the incorrect amount of standard being weighed, and that standard is used for critical stability or clinical trial testing, the resulting data may not appropriately reflect (+ or -) what actually occurred.)

Drug standards must be established and characterized. These standards (typically from a batch of the API that has been further purified) are used to qualify subsequent standards or directly for testing. Some standard lots can be used for years, so their initial and ongoing quality and storage, and re-verification, can impact laboratory outcomes for those years.

Just as manufacturing processes are validated for outcomes, analytical test methods must be validated. Analytical methods taken from the *United States Pharmacopeia-National Formulary* are to be qualified for their use in the lab. The requirements for method validation are extensive and specific. They include linearity, accuracy, precision, system suitability, detection and quantitation limits, and robustness. They serve not only to assess the methodology, but also the equipment, the laboratory, and the personnel involved.

Analytical methods are needed for testing the specification properties and attributes of the API and drug product. Examples of these chemical and physical tests include:

- Assays looking for trouble spots, including impurities (via manufacturing processes, residual solvents, and degradation)
- Methods for identification of the API and drug product against a recognized or qualified standard
- Explorations of the API's and drug product's physical properties such as structural elucidation and dissolution
- Examinations of biological properties (at the microscopic level, etc.)

These methods may apply to the final forms of the API and drug product, or may be used to test intermediate forms for validation or process controls, or after packaging as applied to stability and shipping integrity. (Similar method validation efforts apply to the specific analysis of patient biological fluid samples from clinical trials.)

Conclusions

The thought and background research efforts that lead to major projects resulting in new drugs or drug forms represent exciting and impactful steps on the road to improvements in healthcare. The clinical trial efforts of the various research team members are seen as a continuation of the earliest stages of the research. The development of the physical drug is critical to the clinical research efforts in pursuit of drug approvals. The physical drug efforts are part of the stepwise reporting of CMC activity to the FDA, through the IND and various clinical phases of drug research and development.

How the physical drug is produced can impact the patients, costs, timing of supply, and acceptance of the drug product. The quality of the activity can influence the potency, precision, and accuracy of the drug and its use in the clinical environment. The compliance of the activities to registration, reporting, statutory, and guidance requirements will influence their acceptance by the regulatory authorities and serve for long-term evidence of performance of the drug product to meet those requirements.

The legal responsibility and liability for assurance that drug requirements are met is equivalent to that taken for the clinical trial efforts. Attempts to save time or money on the physical product or its requirements are shortsighted and can put at risk all the good work completed or planned. Proper support and direction can help ensure all outcomes move toward supporting the product's approval by the regulatory agencies. These efforts support the overall value and intellectual property of the drug. Knowledge of the physical drug product activities helps the sponsor-investigator, and all of the various supporting managers and coordinators, to ensure that drug variability is not the source of clinical variation. This ensures clinical research reflects clinical outcomes and not product issues.

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Key Considerations for Social Media Recruitment Platforms

PEER REVIEWED | Deborah D. Rupert, MS, CCRC, MA

[DOI: 10.14524/CR-15-0019]

Through a variety of social media platforms, the Internet offers access to a relatively large and untapped pool of potential clinical trial participants. The Pew Research Center's January 2013 survey on Internet & American Life concluded that 72% of adults have searched for health-related information at least once during the past year.[1]

In the context of low overall participation rates, the question becomes: How can clinical trial professionals better employ social media for study recruitment? Despite rising demand and ample interest from such professionals, and even institutions on a more global level, there is a notable lack of progress on this front.

Popular social media sites have grown exponentially over time, changing the way users interact socially (Facebook), network professionally (LinkedIn), and find medical care (ZocDoc). The challenge is to harness what have become familiar platforms to achieve improved recruitment into clinical trials.

A detailed discussion of tactics is beyond the scope of this article; however, several potential approaches seem promising for expanding upon tried-and-true recruitment methods (e.g., promoting recruitment-focused social media website use through physician-patient interactions) as well as more alternative approaches (e.g., advertisements or links on support group or pharmaceutical websites).

No matter what approach is used for channeling patients toward social media–based platforms, success depends on adequately addressing the needs of these potential participants.

What Patients Want: Accessibility

A recent survey in *Medical News Today* reported that almost 85% of patients were not aware that clinical trials were a possible treatment option.[2] To this point, no singular site has acted as an all-encompassing educational and recruitment tool for the public for clinical trials. None of the most widely known clinical trial recruitment–related sites to which patients have the most direct access (in terms of ease of discovery), such as ResearchMatch[3] or PatientsLikeMe,[4] nor ClinicalTrials.gov,[5] which provides a great deal of data on active trials, but does not serve as a recruitment tool, quite provide a "start-from-the-beginning" approach. Instead, patients must fend for themselves as they sift through various sites with disparate focus: disease/ailment education, support groups and networking, physician searches, news updates, scientific research, company marketing, etc.

Patients, whether they become self-informed or are informed by family, friends, or physicians that clinical trials may be the right fit, find an overwhelming amount of data when they turn to the Internet. For example, in the last 15 years, the ClinicalTrials.gov database of U.S.-based trials has registered more than 180,000 studies—an increase of approximately 4,000%.[5] While this site is an excellent and increasingly comprehensive tool for researchers, and for a very select group of patients "in the know" (e.g., who themselves work in healthcare or healthcare-related fields), this growth undeniably makes the site difficult to navigate.

What patients need is an easy-to-understand, hierarchical-based platform to help guide them through the labyrinth of information with the

LEARNING OBJECTIVE
After reading this article, participants should be able to describe the pros and cons of integrating a social medial platform into the patient recruitment processes, and identify the foundation elements a successful platform would require.

DISCLOSURES
Deborah D. Rupert, MS, CCRC, MA:
Nothing to disclose

72% of adults have searched for health-related information at least once during the past year.

85% of patients were not aware that clinical trials were a possible treatment option.

primary end goal of presenting a "match" to clinical trial options, and with the secondary goal of enhancing patient understanding of the field of clinical trials.

Patient Networking

Participant-to-participant interactions—the core of social media—have largely been excluded from the arena of clinical trials due to the concern for potential bias on a trial's outcome or future recruitment. Patient-to-patient communication has generally been reserved for support group sites.

At the same time, researchers are beginning to reach out to support group websites, bridging clinical trials to these more socially oriented platforms. In one such recruitment effort, a team of Mayo Clinic cardiologists coordinated with a patient-run support group known as WomenHeart: The National Coalition for Women with Heart Disease. In doing so, the website became a bridge between a large pool of potential patients seeking to join a clinical trial and Mayo's researchers, resulting in a virtual registry and DNA biomarker bank. Most remarkable was that the impetus for approaching WomenHeart, as a social media recruitment platform, was proposed by a survivor of heart disease.[6]

Given today's ever-connected world, the era of subject-subject isolation is coming to an end. Patients show an increased interest in sharing their experiences; turning to platforms like Facebook to create illness-focused online communities. Clinical trial participants also seek a greater perspective, a trend reflected both in the growth of online communities (e.g., PatientsLikeMe[7]) and in the longstanding history of typical questions directed toward clinical research coordinators (CRCs) (e.g., the number of participants enrolled at institutions and common adverse events) during the consent process or follow-up.

Despite the potential risks, such as those to privacy, the field of clinical trials must meet this change prepared to use it to good advantage. By offering a platform for patients to discuss clinical trial options within specific disease categories, a social media–based recruitment site could draw more attention and more interest from the general public.

It is not the place of research personnel to encourage or facilitate conversation between study participants. Rather, a social media–based recruitment site itself is a means by which patients with shared interests (not shared study participation) could seek each other out. The decision whether, and how much, to share with others remains in the hands of the patient.

No matter what approach is used for channeling patients toward social media–based platforms, success depends on adequately addressing the needs of these potential participants.

Understanding the Patient Experience

Patient-centric research is becoming the focus and driving force of the future. Steps must be taken to: 1) better understand the patient's clinical trial experience, 2) strengthen the connection between patients and researchers, and 3) cultivate an environment in which participants recognize their role in the progress of clinical research.

Patient testimonials regarding clinical trials may become an important part of a patient's decision to participate in one trial over another. Learning about other patients' experiences with similar treatments (as part of clinical trials or otherwise) is a powerful motivation for study participation, retention, and treatment compliance.

Patient feedback through social media is also an avenue to improve the design of and implementation of trial work, while addressing quality assurance issues. Researchers can fine-tune further studies based on patient data and align their studies with patients' concerns and health issues (e.g., helping select clinically meaningful endpoints).

Another key aspect of successful patient-focused recruitment websites is the ability for patients to control the privacy level of their data. The Institute of Medicine survey reported that the number one fear of patients was that their health information would not be kept confidential.[2]

Regardless of the platform or type of information, individuals are constantly called upon to make personal decisions for sharing information on social media–based websites. Patient-controlled access means providing various data-sharing options or levels, which are selected by the patient (e.g., choosing whether to link their medical records directly to the site, providing their own medical history or only certain components, or opting out entirely).

Platforms built on collecting data from patients and allowing data access to researchers represent a

Given today's ever-connected world, the era of subject-subject isolation is coming to an end. Patients show an increased interest in sharing their experiences; turning to platforms like Facebook to create illness-focused online communities.

modernized version of Health Insurance Portability and Accountability Act (HIPAA) contracts. One such platform is PrivateAccess, which provides patient control of medical records and personal information based on the patient's selected privacy settings. On the opposite side of the equation, PrivateAccess provides access of patients' data to researchers and partners with ClinicalTrials.gov. A potential additional layer of security could be provided by assigning users a code making anonymous any information they present.

Addressing the Researcher Perspective: Efficiency in Screening and Recruitment

In a recent survey conducted by Pfizer, Inc., it was reported by physicians that 31% "did not refer patients to trials due to, among other things, lack of information."[2] A physician's time is a limited resource, and while many physicians show great dedication to clinical trial work, their focus is providing the best patient care possible. They are further faced with the impossible task of knowing the details of every clinical trial for which a patient may be eligible, and the screening and enrollment requirements of those protocols.

Tools to support physicians and their research staff in the increasingly involved recruitment process are needed. In one example, to better equip physicians, Case Western Reserve University developed a software program known as Trial Prospector. This system provided oncologists at Seidman Cancer Center in Cleveland, Ohio a report that matched patients to their cancer trials against the eligibility criteria for any of the University Hospitals Case Medical Center's 300 trials.[8]

Social media is increasingly being used to support the physician-patient relationship, although more commonly in the context of standard medical care (e.g., ZocDoc or use of text messages for communication), rather than to support clinical trials. The same approach can be taken for clinical trial recruitment; however, the success of the social media–based clinical trial platform, as for other platforms, will depend upon physician involvement. The key would be not just to refer patients to the platform, but to also allow physicians to access the site.

A simple algorithm based on a patient's lab reports and demographic data, which are automatically uploaded from electronic medical records, is one means of providing the physician a list of appropriate clinical trials. However, physician-patient communication will be further enhanced by expanding on existing algorithm-based sites by allowing physicians and CRCs to announce messages to groups of patients (e.g., those participating in a particular trial).

Further, the involvement of hospitals and individual physicians (principal investigators and sub-investigators) is key for successfully recruiting for site-specific trials while also allowing patients to gather information on trials outside that research site. In the long term, a social media–based recruitment effort will only be as successful as the intrinsic relationships involved (between physician and patient, between patient and CRC, and between hospital and physician).

Support of Big Pharma

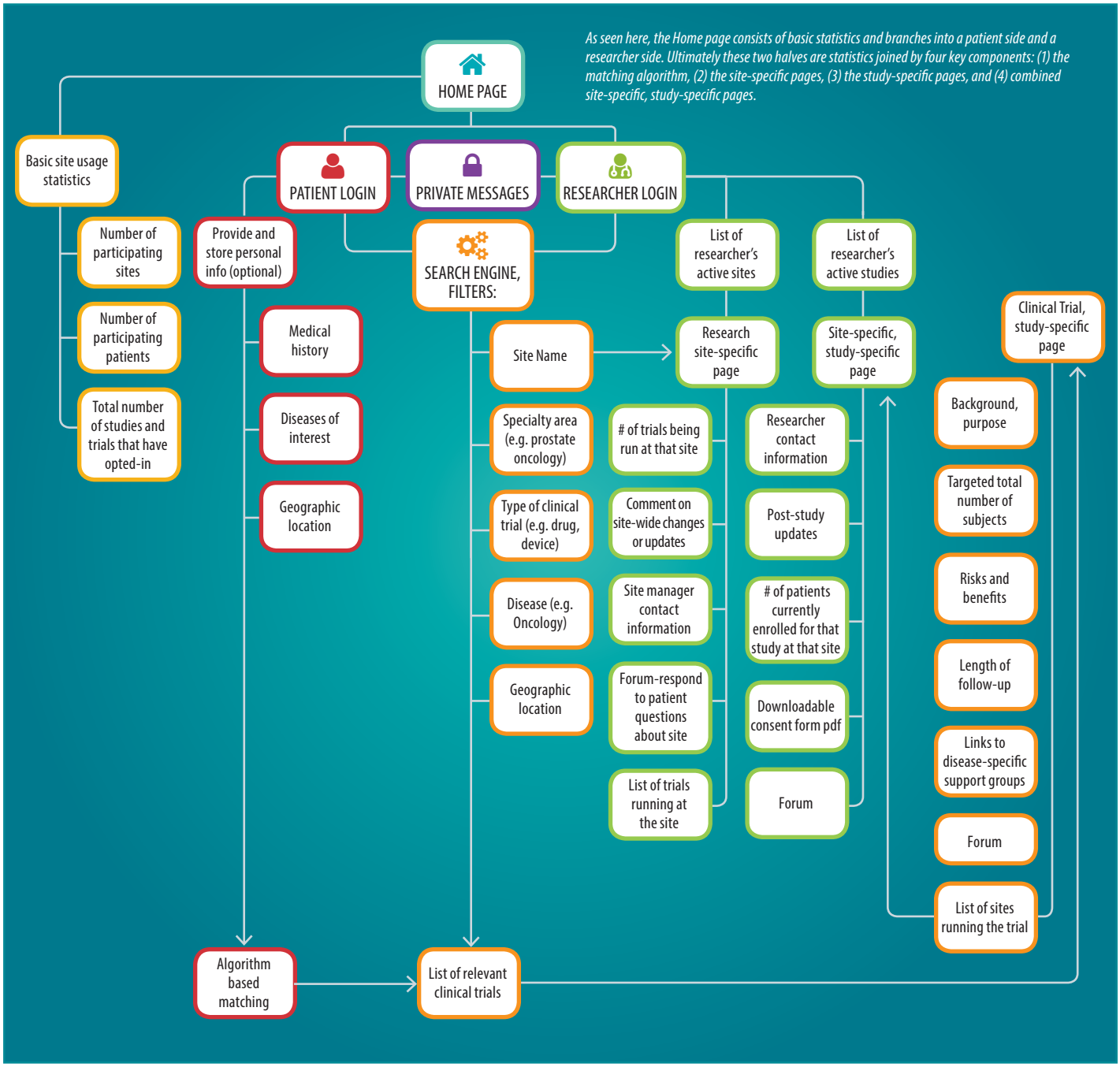
To better understand the perspective of sponsoring companies ("big pharma") and their incorporation of social media into clinical trial work, the Tufts Center for the Study of Drug Development convened a focus group of 20 such companies, including contract research organizations. The goal of this focus group was to examine the current and future use of social media in clinical trials from a corporate perspective. The resulting report was not limited to recruitment initiatives, but given the topic of this article, recruitment conclusions are discussed here.[9]

Companies surveyed agreed that social media use is widely distributed and poorly tracked, calling for a more centralized system and improving its management. It was further determined that the current use of social media is limited to gathering results on using marketed products. Of the small amount of social media used for recruitment, less than one-third of companies interacted directly with patients.

Companies that reported using pre-established social media communities used Facebook. It was also reported that growth in using social media for recruitment is expected with 75% and 42% of U.S. and Western European companies, respectively, planning to increase initiatives.

Participation in clinical trials, especially drug studies, is complex; therefore, patient involvement

FIGURE 1: Hierarchical map of proposed ideal social media–based clinical trial recruitment and retention tool.



must be encouraged starting at the recruitment stage. Some big pharma companies are currently allocating resources toward social media. In partnership with PrivateAccess, Pfizer is attempting to accelerate its drug clinical studies and shorten the timeline for bringing drugs to market.[2] Working together, Pfizer and PrivateAccess also want to recruit other companies into the online community, such as research sites and patient advocacy groups.

Proposed Design for a More Ideal Social Media–Based Recruitment and Retention Tool

The ideal social media tool sifts through the dispersed, and sometimes obscure, sources of information to educate, match, and create a multi-connected communication for patients searching to participate in clinical trials (see Figure 1 for a visualization of a proposed design for this tool).

To begin with, the website is expected to integrate an algorithm-based matching system. However, patients must also be able to search for areas of interest, including those not necessarily pertinent to their own medical concerns, but those of a loved one, or to gain a greater understanding of clinical trials prior to taking action. This calls for a website designed to match patients to trials in manners beyond providing multiple filters by which to narrow searches based on location, disease (e.g., oncology, cardiology, gastroenterology), subcategory of disease (e.g., ophthalmology oncology, hypercholesterolemia, irritable bowel syndrome), and trial type.

Social media–based clinical trial recruitment efforts should also collect and distribute information on what most who work in the field consider "commonly understood" aspects of clinical trial participation. Such aspects include a historical background relevant to aspects of clinical trials (e.g., the foundations of HIPAA), key term definitions, the purposes of principles such as intent to treat, types of clinical trials, what to expect when participating in those various types, and other frequently asked questions.

Providing these tools will increase patient education and reduce CRC and physician burden. Well-informed patients admitted into a clinical trial are more likely to become interested, active, and well-retained participants for the duration of a study.

The extent to which trial or study information is presented on a site will depend upon the opting-in and privacy settings of different parties into the system allowing patients, physicians, and researchers (and research sites, institutions, and companies) to determine their levels of data sharing and involvement. The most basic option, under the circumstances where none of the interested parties chose to opt-in, would result in publically accessible information.

Public information includes materials drawn from the company's website, certain past publications, press releases, ClinicalTrials.gov, and other clinical trial listings. Thus, the functionality of the proposed site remains its ability to educate and ease the search burden that currently exists for interested participants.

On the other end of the spectrum, under conditions of institutional review board approval and where all parties choose to opt-in, details such as specific study personnel contact information, number of subjects enrolled in a given trial and at a given site, the follow-up timeline, and other pertinent information would be included and expanded upon. One could even imagine including patient testimonials and reports on their experiences for each clinical trial included on the site.

> What patients need is an easy-to-understand, hierarchical-based platform to help guide them through the labyrinth of information with the primary end goal of presenting a "match" to clinical trial options, and with the secondary goal of enhancing patient understanding of the field of clinical trials.

Each individual study site would also have its own page to present site-specific information, including research personal contact details, pertinent news and updates, and the trials into which the site is currently enrolling. Site-specific pages would link to site-specific, study-specific pages.

Whereas study-specific pages would present information about the study's performance at sites across the nation and about the sponsoring company, site-specific, study-specific pages would include details such as a downloadable PDF of the study consent form, a study synopsis from the principal investigator, and comparative statistics. Facilities conducting similar trials could have access to each other's results (depending on the privacy settings of the study sites) to allow for an exchange of information and to produce tangible data for "what works."

Patients' involvement would be encouraged through personalized (and potentially anonymous) individual accounts. Through these accounts patients, could provide varying levels of background, change their privacy settings, and customize the features of the website to their needs. Patients can also provide medical records release from institutions at which they receive care, allowing lab data to be more efficiently transferred. Thus, patients and research sites would have ownership over the website content, similar to Facebook or LinkedIn.

The website would act as a semi-open forum for patient-research-physician communications. These communications may be public "posts" or private "messages" depending on the format in which they are submitted. For example, both site-specific and study-specific pages would allow for communication between research staff and interested potential participants in open forum discussions.

Thus, patients could ask more general questions about a study site, or more specific questions about a study at a particular site within the respective forums. Indirectly, this helps patients educate

each other and reduces the time research sites spend answering similar questions. However, individual patients can also send particular sites, CRCs, or physicians private messages, or use the contact information provided on the site-specific pages to send e-mails or text messages outside the application.

The need for a one-stop centralized clearinghouse that helps patients and physicians sift quickly through overwhelming data is unarguable. For social media–based recruitment to become a reality, several entities must unite within the same platform:

- a database containing patient demographics and history to compare against clinical trial inclusion/exclusion criteria;
- a matching algorithm to accomplish that comparison;
- geographic mapping of studies based on the sites currently enrolling; and
- modules for communication between different parties.

Conclusions and Further Considerations

Social media tool development for clinical trials is a field in its infancy. However, it is clear from the current trends that social media will develop into a reliable recruitment and retention platform in the next five to 10 years. Importantly, social media should not be considered a panacea, but rather as an additional tool (with its own set of limitations) for implementation with traditional recruitment approaches.

It is hoped that this article acts as a "jumping-off point" for further discussion into the roles social media will play in the field of clinical trials. Intellectual discussion on the practical and logistical aspects of regulatory concerns tied to social media in this context warrants further contributions.

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Challenges and Training Needs for Clinical Research Associates—A Survey

PEER REVIEWED | Niranjan Kulkarni | Arun Bhatt, MD, FICP, FICR | Jeroze Dalal, PhD

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Clinical research associates (CRAs) perform a vital role in monitoring clinical trials. Monitoring undertaken without adequate CRA training, including competency assessment and following a monitoring methodology, can spell disaster.[1] Frequent changes in regulations across global regions, variances in participation across multinational and multicenter trials, development issues faced by newer sites, and challenges associated with complex protocols have increasingly emphasized the demanding role played by CRAs.[2]

LEARNING OBJECTIVE
After reading this article, participants should be able to evaluate training strategy for CRAs, adopt the best training approaches for different monitoring activities, avoid factors leading to issues being undetected, and prioritize development of soft skills.

DISCLOSURES
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Arun Bhatt, MD, FICP, FICR;
Jeroze Dalal, PhD:
Nothing to disclose

As there is hardly any published information aimed at understanding CRAs' perceptions of the challenges they face in performing their roles and their expectations of training requirements, the survey described in this article seeks to address these topics.

Materials and Methods

The survey was conducted amongst clinical research professionals who were working or who had worked as CRAs, and only those who consented were requested to respond to the questionnaire, which was designed using Google forms.

The survey questionnaire addressed:

1. Time spent on each activity during monitoring visit and time and effort required for achieving expertise on a scale of 1 to 5 (1= Minimum, 5=Maximum) for the following monitoring activities:
   - Informed consent form (ICF) review
   - Investigational product (IP) accountability
   - Source document verification (SDV)
   - Training provided to the site staff
   - Interaction with principal investigator (PI)
   - Resolution of data queries
   - Site file review
   - Reporting adverse events (AEs) and serious adverse events (SAEs)
2. Importance of the above monitoring activities in protecting the rights, safety, and well-being of subjects and ensuring data integrity graded as not important, somewhat important, or very important
3. Reasons why issues go undetected during monitoring, including:
   - Study-related factors
     - »too many documents to refer to for comfirming compliance
     - »complexity of protocol
     - »no clear guidance on minimum requirement for source documentation
   - Training-related factors
     - »lack of therapeutic area training
     - »inadequate training of monitors
     - »inadequate training to site staff
     - »lack of adequate monitoring experience
     - »lack of monitoring tools
   - Time management–related factors
     - »time constraints
     - »interruptions during monitoring visits

These were graded on a five-point scale indicating strongly disagree, disagree, neither disagree nor agree, agree, or strongly agree. The grades for agree and strongly agree were combined for analysis.

4. Preferred approaches to learning monitoring activities; the five preset options were co-monitoring visit, interactive workshop, self learning, classroom training, and web-based training (only one option could be selected)
5. Adequacy of training provided to a CRA: less than adequate, adequate, more than adequate
6. Need for standardization of site training for the informed consent process, source documents, data entry, site file, and reporting AEs and SAEs (the three preset options were standardization is required, standardization is not required, and no idea)
7. Importance of the soft skills (communication, computing, leadership, presentation, team work, negotiation, conflict management, and interpersonal) graded as not important, somewhat important, or very important

Descriptive statistics were applied for analysis of the responses to the above items.

Results

The survey was open from August 12, 2014 to March 2, 2015. We received 192 responses, of which the majority (165, 86%) were from Asia. Two responses (or 1% each) came from the United States, the Pacifica region, and from Europe, while 21 (11%) came from other regions. The response rate is unknown because respondents were asked to forward the survey to their networks of CRAs. The distribution of monitoring experience was 40% of respondents with more than five years, 45% with two to five years, and 15% with less than two years.

TIME SPENT ON DIFFERENT ACTIVITIES DURING MONITORING VISITS

SDV was rated as the most time-consuming activity by 70.3% of respondents (see Table 1), followed by ICF review (26.6%). The least amount of time was spent on interacting with PIs.

TABLE 1: Time Spent on Different Activities During Monitoring Visit

	Individuals (n=192) responding on a scale of 5 (maximum) to 1 (minimum) (% of total response)				
Monitoring Activity	**5**	**4**	**3**	**2**	**1**
SDV	135 (70.3%)	46 (24%)	8 (4.2%)	3 (1.5%)	0 (0%)
ICF Review	51 (26.6%)	41 (21.4%)	45 (23.4%)	38 (19.7%)	17 (8.9%)
IP Accountability	33 (17.2%)	57 (29.7%)	56 (29.2%)	36 (18.7%)	10 (5.2%)
Reporting AEs and SAEs	29 (15.1%)	42 (21.9%)	64 (33.3%)	46 (24%)	11 (5.7%)
Resolving Data Queries	26 (13.5%)	44 (22.9%)	71 (37.1%)	44 (22.9%)	7 (3.6%)
Site File Review	21 (10.9%)	45 (23.4%)	64 (33.3%)	49 (25.6%)	13 (6.8%)
Training Site Staff	13 (6.8%)	34 (17.7%)	73 (38%)	63 (32.8%)	9 (4.7%)
Interaction with PI	12 (6.3%)	21 (10.9%)	59 (30.7%)	64 (33.3%)	36 (18.8%)

TIME AND EFFORT REQUIRED FOR ACHIEVING EXPERTISE IN DIFFERENT MONITORING ACTIVITIES

More than 50% of the respondents considered SDV as an activity requiring maximum time and effort to achieve expertise (see Table 2).

TABLE 2: Time and Effort Required for Achieving Expertise in Different Monitoring Activities

	Individuals (n=192) responding on a scale of 5 (maximum) to 1 (minimum) (% of total response)				
Monitoring Activity	**5**	**4**	**3**	**2**	**1**
SDV	103 (53.6%)	55 (28.6%)	26 (13.6%)	7 (3.7%)	1 (0.5%)
ICF Review	55 (28.6%)	54 (28.1%)	44 (23%)	26 (13.5%)	13 (6.8%)
IP Accountability	35 (18.2%)	49 (25.5%)	58 (30.3%)	43 (22.4%)	7 (3.6%)
Reporting AEs and SAEs	43 (22.4%)	60 (31.2%)	61 (31.8%)	24 (12.5%)	4 (2.1%)
Resolving Data Queries	27 (14.1%)	49 (25.5%)	68 (35.4%)	38 (19.8%)	10 (5.2%)
Site File Review	28 (14.6%)	48 (25%)	74 (38.5%)	33 (17.2%)	9 (4.7%)
Training Site Staff	30 (15.6%)	63 (32.8%)	68 (35.4%)	28 (14.6%)	3 (1.6%)
Interaction with PI	26 (13.5%)	53 (27.6%)	65 (33.9%)	39 (20.3%)	9 (4.7%)

ACTIVITIES PERCEIVED TO PROTECT RIGHTS, SAFETY, AND WELL-BEING OF SUBJECTS AND ENSURING DATA INTEGRITY

More than 50% of the respondents considered reporting AEs/SAEs, ICF review, training of the site staff, SDV, IP accountability, and meeting PIs to be very important activities to ensure protection of the rights, safety, and well-being of subjects (see Table 3).

TABLE 3: Perceived Importance of Activities in Protecting Rights, Safety, and Well-Being of Patients

Monitoring Activity	Individuals (n=192) rating each activity (% of total response) as…		
	Very Important	Somewhat Important	Not Important
SDV	146 (76%)	44 (23%)	2 (1%)
ICF Review	178 (92.7%)	12 (6.3%)	2 (1%)
IP Accountability	133 (69.3%)	55 (28.6%)	4 (2.1%)
Reporting AEs and SAEs	182 (94.8%)	10 (5.2%)	0 (0%)
Resolving Data Queries	61 (31.8%)	105 (54.7%)	26 (13.5%)
Site File Review	52 (27.1%)	116 (60.4%)	24 (12.5%)
Training Site Staff	149 (77.6%)	42 (21.9%)	1 (0.5%)
Interaction with PI	114 (59.4%)	77 (40.1%)	1 (0.5%)

ACTIVITIES PERCEIVED TO ENSURE DATA INTEGRITY

More than 60% of the respondents considered that reporting AEs/SAEs, SDV, site training, resolving data queries, IP accountability, and ICF review were very important to ensure data integrity in a clinical trial (see Table 4).

TABLE 4: Perceived Importance of Activities in Ensuring Integrity of Data

Monitoring Activity	Individuals (n=192) rating each activity (% of total response) as…		
	Very Important	Somewhat Important	Not Important
SDV	166 (86.5%)	25 (13%)	1 (0.5%)
ICF Review	132 (68.8%)	53 (27.6%)	7 (3.6%)
IP Accountability	134 (69.8%)	55 (28.6%)	3 (1.6%)
Reporting AEs and SAEs	167 (87%)	24 (12.5%)	1 (0.5%)
Resolving Data Queries	139 (72.4%)	48 (25%)	5 (2.6%)
Site File Review	71 (37%)	105 (54.7%)	16 (8.3%)
Training Site Staff	143 (74.5%)	49 (25.5%)	0 (0%)
Interaction with PI	83 (43.2%)	100 (52.1%)	9 (4.7%)

PREFERRED APPROACHES TO LEARN MONITORING SKILLS

Taking part in a co-monitoring visit was considered the preferred approach for learning ICF review, IP accountability, SDV, site file review, and meeting with PIs (see Table 5). For site training and reporting AEs and SAEs, interactive workshops were preferred by more than 30% of the respondents; web-based training was identified as the preferred approach by 29.7% to learn data query resolution.

TABLE 5: Preferred Approaches to Learn Different Monitoring Activities

	Individuals (n=192) rating a particular approach as the best for learning the listed monitoring activities (% of total response)				
Monitoring Activity	Co-Monitoring Visit	Interactive Workshops	Self-Learning	Classroom Training	Web-Based Training
ICF Review	97 (50.5%)	65 (33.9%)	10 (5.2%)	14 (7.3%)	6 (3.1%)
IP Accountability	114 (59.4%)	35 (18.2%)	24 (12.5%)	12 (6.3%)	7 (3.6%)
SDV	121 (63%)	43 (22.5%)	16 (8.3%)	6 (3.1%)	6 (3.1%)
Site File Review	74 (38.5%)	38 (19.8%)	37 (19.3%)	35 (18.2%)	8 (4.2%)
Training Site Staff	53 (27.6%)	63 (32.8%)	14 (7.3%)	35 (18.2%)	27 (14.1%)
Meeting PI	98 (51%)	47 (24.5%)	27 (14.1%)	12 (6.3%)	8 (4.2%)
Resolving Data Queries	41 (21.4%)	35 (18.2%)	34 (17.7%)	25 (13%)	57 (29.7%)
Reporting AEs and SAEs	50 (26%)	66 (34.4%)	9 (4.7%)	38 (19.8%)	29 (15.1%)

ADEQUACY OF TRAINING PROVIDED BY THE SPONSORS

For all monitoring activities except PI interaction, the training provided by sponsors to the CRAs was considered adequate or more than adequate by more than 50% respondents (see Table 6). However, 50.5% of respondents considered training provided for conducting meetings with PIs less than adequate.

TABLE 6: Adequacy of Training Provided on Monitoring Activity

Monitoring Activity	Individuals (n=192) rating the training provided (% of total response) as…		
	More than Adequate	Adequate	Less than Adequate
ICF Review	37 (19.3%)	140 (72.9%)	15 (7.8%)
IP Accountability	9 (4.7%)	119 (62%)	64 (33.3%)
SDV	23 (12%)	110 (57.3%)	59 (30.7%)
Site File Review	12 (6.2%)	110 (57.3%)	70 (36.5%)
Training Site Staff	11 (5.7%)	110 (57.3%)	71 (37%)
Meeting PI	8 (4.2%)	87 (45.3%)	97 (50.5%)
Resolving Data Queries	16 (8.3%)	132 (68.8%)	44 (22.9%)
Reporting AEs and SAEs	22 (11.5%)	139 (72.4%)	31 (16.1%)

REQUIREMENT TO STANDARDIZE TRAINING FOR SITE STAFF

More than 50% of the respondents stated that standardization was required for training site staff on the informed consent process (87.5%), reporting AEs/SAEs (84.4%), the required level of details in source documentation (75%), site file maintenance (68.8%), and data entry (59.9%).

REASONS FOR ISSUES GOING UNDETECTED DURING MONITORING

According to 74% or more of the respondents, common reasons for issues going undetected during monitoring were too many documents to refer to in order to confirm compliance, complex protocols, no clear guidance on minimum requirements for source documentation, and time constraints during monitoring (see Figure 1).

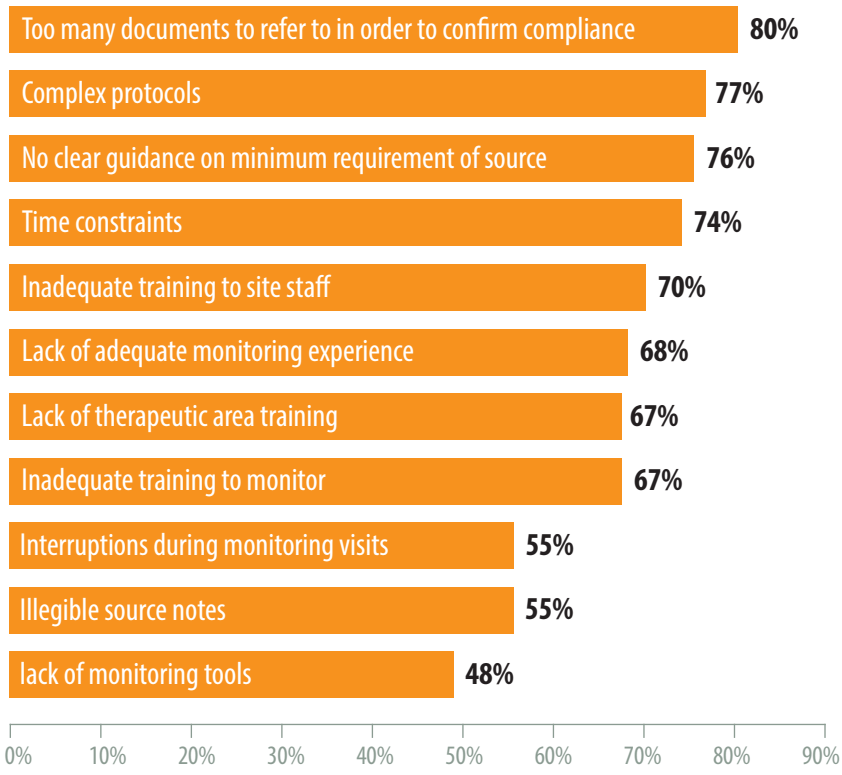
IMPORTANCE OF SKILLS REQUIRED BY CRAS

More than 50% of the responding CRAs considered communication, interpersonal, conflict management, negotiation, teamwork, and presentation skills very important (see Table 7).

TABLE 7: Clinical Research Skill Areas for CRAs

Skills	Individuals (n=192) rating each skill (% of total response) as…		
	Very Important	Somewhat Important	Not Important
Computing	71 (37%)	114 (59.4%)	7 (3.6%)
Leadership	84 (43.8%)	100 (52.1%)	8 (4.2%)
Presentation	111 (57.8%)	77 (40.1%)	4 (2.1%)
Team Work	137 (71.4%)	51 (26.6%)	4 (2.1%)
Negotiation	157 (81.8%)	32 (16.7%)	3 (1.6%)
Conflict Management	157 (81.8%)	34 (17.7%)	1 (0.5%)
Interpersonal	161 (83.9%)	31 (16.1%)	0 (0%)
Communication	184 (95.8%)	8 (4.2%)	0 (0%)

FIGURE 1: Reasons for issues going undetected



Discussion

MONITORING ACTIVITIES: PERCEPTIONS VERSUS PERFORMANCE

Our survey showed that more than 50% of respondents considered reporting AEs and SAEs, ICF review, training of site staff, SDV, IP accountability, and meetings with PIs as important activities for human subjects protection. For ensuring data integrity, all of these activities except interacting with PIs were considered important by more than 60% of respondents. However, the most time was spent on SDV onsite by 70.3% of respondents, on ICF review by 26.6%, and on interaction with PI or training the site staff by nearly 6%. This is also reflected in the responses for time and effort required to achieve expertise, where more than 50% consider SDV as the most difficult activity in which to achieve expertise.

Our survey showed that more than 50% of respondents considered reporting AEs and SAEs, ICF review, training of site staff, SDV, IP accountability, and meetings with PIs as important activities for human subjects protection.

The respondents' major focus on SDV during monitoring at the cost of other activities, especially ICF, AE and SAE review, interaction with PIs, and training site staff is cause for concern. Their predominant focus on SDV could be due to the industry's practice of monitoring 100% of data, increasingly complex protocols, and a lack of medical background among some CRAs.

The U.S. Food and Drug Administration regulations do not mandate that monitors should check every source datapoint at each and every investigator site.[3] According to one study, SDV—a manual review process—is only 85% accurate.[3] However, 100% SDV has become a standard industry practice, as the industry believes this practice to be the best way to ensure the validity and integrity of clinical trial data.[3] Hopefully, risk-based monitoring may lead to changes in industry practices for SDV.

Although CRAs consider reporting AEs/SAEs important, the actual time spent doing so may be

In the future, computing skills are expected to become vital as sponsors adopt risk-based monitoring approaches, which involve working with sophisticated systems and software.

less than it seems at first, since it may be thought of as part of SDV. Meanwhile, ICF reviews may be limited to checking signatures and dates on the ICF and the adequacy of the consent narrative.

Interaction with the monitor is crucial for the PI to receive independent feedback on the performance of his/her site, noncompliance to protocol or regulations, overall data quality, areas of risk/improvement, and any actions he/she needs to take to ensure that the highest quality standards are met at the site. Hence, the importance of interaction with the PI cannot be undermined. Further, training of site staff has a direct impact on the way the clinical trial is conducted, and the availability of well-trained site staff helps CRAs to perform their work efficiently.

The results showed less focus on site file review and resolution of data queries than on other tasks. Site file review is indispensible to ensure that the essential documents are accurately filed in a timely manner, and are available to demonstrate compliance with good clinical practice and regulatory requirements.[4] Resolution of data queries is also necessary to obtain high-quality data.

Less time spent on activities other than SDV could be due to perceived time constraints and inadequate training of monitors. Other reasons that were reported for issues going undetected included the complexity of protocols and multiple documents for review, which may be interlinked.

Clinical trial protocols have become more complex, demanding, and burdensome for monitors and sites. According to Getz et al., between 1999 and 2005, the average number of inclusion criteria increased threefold, and the average number of procedures grew annually by 6.5%, reaching a median number of 35 procedures in 2005. In 2012, a typical Phase III protocol included 50 eligibility criteria, 167 procedures, and 13 endpoints.[5,6] This is compounded by the fact that more than 66% of CRAs come from a nonmedical background.[1] Hence, they could face difficulties while reviewing physicians' notes (illegible handwriting, use of unfamiliar terms or shorthand, difficult-to-understand endpoints). This also implies a possible gap in training on familiarity with clinical documentation practices.[1]

It is difficult to ascertain the amount of experience that would make a CRA capable of monitoring a study independently. Hence, competency assessments held prior to and periodically after CRA undertake independent monitoring are strongly recommended.

TRAINING: ADEQUACY AND PREFERRED APPROACHES

More than half of the respondents reported inadequate training for conducting meetings with PIs. Also, 30% to 37% felt that training for conduct of SDV, IP accountability, site file review, and site staff training was inadequate. This could have a significant influence on a CRA's functioning and performance, in terms of managing all activities required to ensure subject protection and data integrity during a monitoring visit.

A majority of the respondents preferred face-to-face training approaches. Co-monitoring was rated as the most preferred approach by 50% to 63% for critical activities like SDV, IP accountability, meeting PIs, and ICF review. In addition, interactive workshops were favored by the respondents.

The hands-on experience of monitoring activities and interactions with experienced colleagues or study managers help trainee CRAs learn the intricacies of the job and retain more than in a classroom environment or a web-based module. An effective co-monitoring program advances the knowledge and skills of CRAs.[7]

There is an increasing trend in the amount of web-based training. This may be because of time and cost constraints, technology advancement, training standardization requirements, and work being performed remotely by CRAs. Our survey suggests that web-based training is perceived to be the least preferred way to learn most monitoring activities. Sponsors may want to make an effort to replace or to combine web-based training with hands-on training and/or with interactive workshops.

IMPORTANCE OF SKILLS

More than 95% of the respondents rated communication skills as very important. However, these skills are often overlooked in CRA training.[8] Communication skills should be imparted early in the monitor's career, along with technical training before starting independent monitoring.

Other skills rated very important by more than 50% of the respondents were interpersonal, conflict management, negotiations/teamwork, and presentation. In addition, the overall responses emphasize that CRAs have to learn time management skills, assertiveness in terms of minimizing interruptions during monitoring, and the art of providing objective feedback on site performance.

Usually, CRAs are exposed to these skills in workshop settings; however, their use can only be sharpened in on-the-job situations during actual monitoring. Inadequate knowledge and lack of some skills (e.g., assertive communication, negotiation, time management) could explain why CRAs devote less time to some important activities (e.g., interaction with PIs).

In the future, computing skills are expected to become vital as sponsors adopt risk-based monitoring approaches, which involve working with sophisticated systems and software. Thus, CRAs have to be savvy about information technology.[9] In addition, they should be able to use their analytical skills to derive appropriate action plans based on available data metrics.

Some of the limitations of this survey include that there was no information on respondents' electronic data capture system usage, therapeutic areas of specialty, and routine level of study complexity. A detailed analysis of this information may open new facets to the discussion.

Conclusion

In conclusion, our CRA respondents are aware of the vital role they play in ensuring protection of clinical trial participants' rights, safety, and well-being, as well as protecting data integrity, but they often are unable to balance the requirements of SDV and other critical activities. In this regard, the industry's focus on risk-based monitoring looks promising; however, this practice will almost certainly still require all essential training requirements for CRAs and sites being fulfilled to provide its intended benefits.

The generalizability of the survey findings are limited by the relatively small sample size, and by the fact that a majority of respondents were from Asia. However, the results garnered from this survey can be good indicators to the leadership of sponsor organizations that they need to prioritize the development of CRA skills. This includes allocating adequate amounts of training time for each monitoring activity, adopting the best approaches to train CRAs on different monitoring activities, and working toward avoidance of factors leading to issues going undetected in studies.

Disclaimer: All opinions expressed herewith are those of the authors, and do not reflect the views of their organizations.

Interaction with the monitor is crucial for the PI to receive independent feedback on the performance of his/her site, noncompliance to protocol or regulations, overall data quality, areas of risk/improvement, and any actions he/she needs to take to ensure that the highest quality standards are met at the site.

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HOME STUDY HS

Daily Challenges to the Future of Clinical Trial Conduct

OPEN BOOK TEST

This test expires on April 30, 2017

(original release date: 4/1/2016)

Drug Products for Investigator-Initiated Research

1. Drug sources for a clinical trial are typically managed by:
- **A.** A local pharmacy
- **B.** A pharmaceutical company
- **C.** An analytical laboratory
- **D.** The U.S. Food and Drug Administration

2. Drugs require the right physical properties to meet:
- **A.** Suitable appearance
- **B.** Ease of location
- **C.** Consumer preferences
- **D.** Metabolic conditions

3. Limited scale or imprecise equipment can result in:
- **A.** Operator safety issues
- **B.** Incomplete sampling
- **C.** Product variation
- **D.** Utility disruptions

4. What is the primary reason to establish legal responsibilities for drug requirements?
- **A.** Protection of the public and patients' rights
- **B.** Support for collection of product taxes
- **C.** Enforcement of patent and trademark rights
- **D.** To follow individual state laws

5. The drug product must be assessed for which of the following prior to its administration in humans?
- **A.** Size in relation/proportion to the patient
- **B.** Total count of the dispensing container
- **C.** Likelihood of confusion with existing products
- **D.** Whether it meets defined specifications

6. Low and questionable quality ingredients can result in:
- **A.** Unacceptable levels of impurities
- **B.** Excessive dust in the process
- **C.** Greater demands for addition of water
- **D.** Inadequate storage locations for inventory

7. Which of the following is a consequence of making multiple small batches of the drug product?
- **A.** Depletion of holding containers
- **B.** Increased sample disposals
- **C.** Product unit variability
- **D.** Complex lot numbering

8. The critical aspects of packaging include:
- **1.** Labeling
- **2.** Traceability
- **3.** Sealing
- **4.** Blinding
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

9. Lack of testing evidence can result in:
- **A.** Additional investigator requirements
- **B.** Production delays
- **C.** Patient risk
- **D.** Detailed document reviews

10. A drug standard is typically taken from a batch that is:
- **A.** Produced first
- **B.** Stored in glass
- **C.** Low in moisture
- **D.** Further purified

Key Considerations for Social Media Recruitment Platforms

11. Successfully using social media platforms to recruit patients primarily depends on:
- **A.** Addressing the needs of the study's principal investigator
- **B.** Using an online system to run all aspects of the clinical trial
- **C.** Addressing the needs of the targeted patient population
- **D.** Honing the aesthetics of the social media recruitment platform

12. According to a recent study, what percentage of patients were unaware that clinical trials were a treatment option?
- **A.** 65%
- **B.** 75%
- **C.** 85%
- **D.** 95%

13. Approximately how many studies are currently registered with ClinicalTrials.gov?
- **A.** 180,000
- **B.** 200,000
- **C.** 150,000
- **D.** 100,000

14. Which of the following is a drawback of using ClinicalTrials.gov for patient recruitment?
- **A.** An insufficient number of studies are registered with this site
- **B.** Poorly informed patients may find it difficult to navigate
- **C.** It provides insufficient detail about many of the listed trials
- **D.** It is not promoted enough to patients by clinical researchers

15. Although prevalent in patient support groups, patient-to-patient communication has historically been uncommon in clinical trials because:
- **A.** Legal restrictions on such activities are placed upon research sites
- **B.** Patients involved in support groups may not also be involved in studies
- **C.** Good clinical practice discourages site staff from allowing patient interaction
- **D.** It may lead to bias on a trial's outcome or future recruitment

16. One area of concern when using social media platforms for recruitment is:
- **A.** An overwhelming number of patients will approach study personnel
- **B.** Patients will decline participation in clinical trials due to overload of information
- **C.** Patient privacy protection is an ongoing and challenging issue
- **D.** Once a platform is up and running it cannot be inactivated

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

17. **Which of the following software platforms was created at a major university to support researchers' study recruitment efforts?**
- **A.** Trial Prospector
- **B.** ZocDoc
- **C.** PrivateAccess
- **D.** PatientsLikeMe

18. **Which of the following social media platforms is currently used to support physician-patient relationships in the context of standard medical care?**
- **A.** Trial Prospector
- **B.** ZocDoc
- **C.** PrivateAccess
- **D.** PatientsLikeMe

19. **According to a study done by the Tufts Center for the Study of Drug Development, what percentage of pharmaceutical and biotechnology companies in the U.S expect to increase their use of social media for patient recruitment?**
- **A.** 50%
- **B.** 65%
- **C.** 75%
- **D.** 95%

20. **Which of the following is the most fundamental aspect for the proposed ideal social media–based recruitment tool?**
- **A.** A coded database containing patient demographics and history
- **B.** Geographic mapping of studies based on the sites currently enrolling
- **C.** Its ability to integrate an algorithm-based matching system
- **D.** Modules for communication between different parties involved in the process

Challenges and Training Needs for Clinical Research Associates—A Survey

21. **Per the survey, on which monitoring activity did most CRAs (respondents) spend the maximum amount of time during monitoring visits?**
- **A.** Interaction with principal investigator
- **B.** Resolving data queries
- **C.** Source document verification
- **D.** Site file review

22. **Per the survey, on which monitoring activity did CRAs (respondents) spend the least time?**
- **A.** Interaction with principal investigator
- **B.** Resolving data queries
- **C.** Source document verification
- **D.** Site file review

23. **Maximum time and effort are required to achieve expertise in which of the following monitoring activities?**
- **A.** Interaction with principal investigator
- **B.** Resolving data queries
- **C.** Source document verification
- **D.** Site file review

24. **Which of the following activities was perceived as most critical for protecting the rights, safety, and wellbeing of subjects?**
- **A.** Investigational product accountability
- **B.** Reporting AEs and SAEs
- **C.** Resolving data queries
- **D.** Site file review

25. **Which of the following activities was perceived as least critical for ensuring the integrity of the data?**
- **A.** Investigational product accountability
- **B.** Reporting AEs and SAEs
- **C.** Resolving data queries
- **D.** Site file review

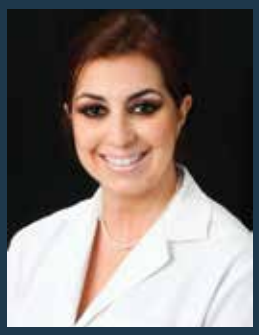
26. **Which training approach was rated as the most preferred for the majority of monitoring activities?**
- **A.** Classroom trainings
- **B.** Co-monitoring visits
- **C.** Self-learning
- **D.** Web-based training

27. **Which of the following is a preferred approach for learning to resolve data queries?**
- **A.** Classroom trainings
- **B.** Co-monitoring visits
- **C.** Self-learning
- **D.** Web-based training

28. **According to most of the CRAs (respondents), less than adequate training is provided for which of the following monitoring activities?**
- **A.** Informed consent form review
- **B.** Investigational product accountability
- **C.** Meeting principal investigator
- **D.** Resolving data queries

29. **What is the most common reason for issues going undetected during monitoring?**
- **A.** Interruptions by patients during monitoring visits
- **B.** Inadequate training by monitors to site staff
- **C.** Lack of proper monitoring tools due to budget cuts
- **D.** Too many documents to confirm compliance

30. **Which skill was rated as "very important" to CRAs by the highest number of survey respondents?**
- **A.** Computing
- **B.** Communication
- **C.** Teamwork
- **D.** Presentation



Sonia Carolina Robazetti, MD, CCRC

Houston, Texas

"Clinical research is the foundation for a better tomorrow."

I participated in the very early stages of the HPV vaccine studies. I am so proud to be part of the trajectory of the vaccine, and to see it available today so we can prevent more deaths from cervical cancer. Through my involvement in the research with HPV, I became a cervical cancer prevention advocate. I started to volunteer in free cervical cancer screenings, and then merged that with work in the See, Test & Treat Program, which is a philanthropic program of the College of American Pathologists (CAP) Foundation. Through our events, we tested more than 500 underserved women and treated the ones with abnormal pathology. Our experience demonstrates that a well-organized screening program can deliver high-quality care with rapid turnaround time in a single visit to screen at-risk women locally. This program serves as an example of screening and prevention that can have a substantial impact in at-risk communities throughout the country. I am currently on the Board of Directors of the CAP Foundation and co-chair of the National Cervical Cancer Coalition in the Houston Chapter, and on the Steering Committee at the national level. Through all these activities, I hope to continue to contribute to the decrease of cervical cancer deaths in my state.

We are not only participating in the future, we have the chance to share a life-changing experience with patients and families. We are part of the healing process, even when the only thing we did was give hope to the ones who crossed our path. We may not have the answers, we may not be the cure, but we are the guardian angels of the patients who participate in research, and I cannot think of a better job.

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Visions for the 50th Anniversary of ACRP... *and Beyond*

Guest Editor David Vulcano asked past leaders of the volunteer boards for ACRP and its affiliate organizations to gaze into their crystal balls and make some predictions about where the Association will find itself a decade or more from now.

Norbert Clemens, MD, PhD, CPI

2015 Chair, Association Board of Trustees

Taking into account the improved research quality achieved through the certifications offered by ACRP, I envision a further increase in the visibility of our Association over the coming decade. The revision of ICH-GCP, rapid introduction of new technologies both in pharmaceutical/biotechnology and medical devices, and increasing demand of research on a global scale will be driving this. ACRP will be recognized as the leading body for providing the highest quality level of continued education and certification for clinical researchers in all areas of research conducted on a worldwide scale.

Deborah Lasher, RN, MPH, CCRC, CCRA

2008 Chair, Association Board of Trustees

The 50th anniversary of ACRP in 2026 will herald widespread recognition of clinical research as a primary career path. This will be fueled by the exodus of great numbers of 'Baby Boomers' retiring from the profession during the next decade, leaving an unprecedented gap of professional talent. I foresee that patient advocacy groups will demand greater inclusion in clinical trials. ACRP will continue to evolve as a trusted industry leader in shaping professional education and facilitating partnerships with nonprofit organizations as the "Voice" of the clinical research profession.

Gary A. Shangold, MD, FACOG, CPI

2013 Chair, Association Board of Trustees

2004–5 President and Chair, American Academy of Pharmaceutical Physicians

Over the past decade, we have experienced continued, and sometimes dramatic, evolution in the field of clinical research. The widespread adoption of electronic data capture, the emergence of quality by design and risk-based monitoring, and the continued trend toward globalization of standards of excellence in the performance of clinical investigations have accelerated and become the new normal. The decade ahead will almost certainly be characterized by further progress toward complete realization of these and other developments in our field. I foresee ACRP evolving as well as it confronts its fifth decade. I believe that the concept of "membership" as we have known it up to now will gradually give way to a new model of lifelong "affiliation," wherein clinical research professionals will be accustomed to turning to ACRP for the fulfillment of their needs for professional education and growth, as well as for career opportunities, throughout their professional lifetimes. ACRP will continue to emerge as a central repository of knowledge and expertise, and will have expanding influence in matters relevant to setting standards for professionalism and providing input and feedback to health/regulatory authorities around the globe on matters pertaining to clinical research. Its influence will be brought to bear not by virtue of ACRP acting as a single entity, but rather through numerous collaborations with an expanding, powerful network of like-minded professional organizations; acting in concert, we will continue to change the world for the betterment of research subjects and clinical investigation.

Deborah L. Rosenbaum, CCRC, CCRA, CCRP

2014 Chair, Academy Board of Trustees

The last 10 years or so have seen growth in many areas for ACRP, particularly the certification programs. As our programs achieved national accreditation by the National Commission for Certifying Agencies, we saw the formation of the Academy of Clinical Research Professionals, a separate entity from the Association with the focus of overseeing the ACRP certification programs. As the Academy matures, we are embracing opportunities for diversity of certification in the future that will represent the ever-evolving clinical research professional roles in the industry.

Valerie D. Willetts, RN, BSN, CCRA

2011 Chair, Association Board of Trustees

ACRP has adjusted its sails to go with the wind, in keeping with the quote from H. Jackson Brown, Jr.: "When you can't change the direction of the wind—adjust your sails." Meeting the needs of the membership and potential membership by offering information through media like ACRP GCPartner and networking through the Online Community pages and focus group discussions, as well as trending articles in the *Clinical Researcher,* is the "new now" for ACRP. Adjusting the sails includes changing from the former "Global Conference" to the new ACRP Meeting & Expo framework, with a clinical research community look and feel providing an inviting environment for connecting with our colleagues. Looking forward means anticipating change and moving with the times. It will be interesting to see the opportunities that ACRP identifies and the new strategies that are developed for the evolution of the Association with forward-thinking ABoT and Academy Board leadership: "Be the change that you wish to see in the world," as Mahatma Gandhi said.

Greg Koski, MD, PhD

2008 President and Chair, Academy of Pharmaceutical Physicians and Investigators

Four decades ago, a small group of dedicated research coordinators recognized that what they did was not something that just anyone could do—that it required mastery of a defined body of knowledge and its effective application. A vision for professionalization of the endeavor was born. Since that moment, ACRP has led the way and set the standard for professional development in the clinical research endeavor. The organization and its dedicated volunteers have helped us to better understand and appreciate the skills and knowledge required to develop competency, but they have brought the tools of professionalism to bear, including rigorous education and training requirements and objective, examination-based assessment of essential knowledge and its application. None of this could or would have happened without ACRP, but the work is far from finished. The "pros" must continue their work and the value of professionalism needs to be recognized and rewarded appropriately by the stakeholders. We are in the midst of a major transformation in clinical research, and we will continue to look to ACRP for its leadership. Congratulations to the entire team!

Kathryn L. Kimmel, CCRC, CCRA

2013–present, Association Board of Trustees member
2011 Chair, Academy Board of Trustees

I predict that in 2026, certification of all research professionals will be required to conduct certain aspects of clinical research. Due to the accreditation and high standards of the certification offered by ACRP, it will be the preferred certification for research professionals, supported by sponsors, contract research organizations, and regulatory authorities around the world. ACRP will lead the industry in providing training/internships for those just entering the research field to quickly prepare them for certification. ACRP will also provide high-quality, up-to-date courses that are easily accessible for those seeking to maintain their certification.

Charles H. Pierce, MD, PhD, FCP, CPI

2013 Chair, Academy Board of Trustees

ACRP has been and will hopefully be, down the path, the backbone of the education and certification of the coordinators (CRCs) and the monitors (CRAs) who are the voice of subject safety. As the number of those who know the regulations and ethics of clinical research expands, so too will the safety of not only the subjects, but also of the investigational products being studied. My hat is off to all those who knew the rules when I started out as a Doc who thought he knew how to do research.

Clara H. Heering, MSc, MSc

2012 Chair, Association Board of Trustees

In the past 40 years, ACRP has been a beacon of knowledge leading clinical research professionals to competency in ethical conduct of clinical trials, to friends for life, and to job security. In 2056, ACRP will have continued to be this beacon, growing its unique inclusive leadership role in a transforming world.

Dr. Jose Balaguera
Barranquilla, Colombia

"Clinical research is the future of civilization in the war against health issues, and I am proud to be a small part of the war against many diseases that not long ago were a death sentence to many."

During the past 11 years, I have worked in areas including diabetes, atrial fibrillation, coronary heart disease, asthma, COPD, dyslipidemia, and sickle cell, among others. The impact on public health has been tremendous; with trials like IMPROVE-IT, ORIGIN, and ROCKET AF, we have contributed to change many paradigms in these areas, and we have given to humanity medications like rivaroxaban or apixaban—both are alternatives to warfarin. In diabetes, we have contributed to new therapies that will improve life quality and reduce the possibility of a catastrophic end of life to many patients.

Reflections on Living the Research Life

Julie M. Haney, RN, MSL, CCRC

Roswell Park Cancer Institute

When I started working in the clinical research field more than 25 years ago, I did not even know what clinical research was, let alone the value of certification. My first role in the field was as a research assistant working in an academic medical center loosely affiliated with a local university. My first day on the job was the most confusing and frustrating day of my life! What was this strange language people were speaking; acronyms and reference sources that I have never heard of, and documents that were more complicated than most of my college text books!

My supervisor at the time stated that we all had to learn about GCP and how it related to CFR regulations and the work we were doing so that we could then develop applicable SOPs for our research floor. GCP, CFR, and SOPs? It was time to dive in and learn all about it.

Twenty-five years later, it's time for me to help spread the word on how passing my Certified Clinical Research Coordinator (CCRC) exam helped raise the bar in clinical research. Certification was truly a celebration of achievement in my career, as well as in my commitment to clinical research excellence. Because of my commitment and belief in certification, I was able to advocate to a few employers along the way about providing higher compensation to others who had made that very same commitment to showing that they had reached a high level of understanding and excellence in their field.

While certification was a goal of mine in 1999, I never dreamed that it would lead to a lifelong career! I was certified in June of 1999 and have maintained that certification without interruption ever since. After realizing the benefits of certified research professionals, my current organization developed clinical research career ladders based on entry level and experience for staff with certification.

I have never experienced boredom in any of the positions I have held in the research field. I have worked in academic medical centers, private research centers, and physician offices; all exposing me to another piece of the vast field available in research. I have held a variety of positions within ACRP, including chapter offices, and now serve as a peer reviewer of articles submitted to the *Clinical Researcher* journal.

Certification means a personal sense of accomplishment and pride! If you're looking for the same, log onto the ACRP website to learn more about it, then grab a study buddy and dive into what I am sure will be a rewarding career in clinical research!

MILESTONES IN ACRP HISTORY

1976
Research nurses Sarah Boyer and Anne LeSher begin the formation of what was then called the Associates of Clinical Pharmacology during another organization's meeting in Seattle, Wash.

1977
First slate of officers elected, with LeSher named President

1984
First independent meeting held in Tucson, Ariz.; first employee hired; first journal adopted

1987
First office space rented in Madison, Wis.; new journal launched

1988
Denise Olson named first Executive Director; *The Monitor* debuts as a quarterly magazine

1992
First CRC certification exam offered

1993
Home office temporarily relocated to near Seattle

Cheryl Myers, RN, CCRC

Greenville Health System

I have been involved in several trials where new treatments have been approved. The one I am proudest of is the Essure coils trial. Our site was the only U.S. site involving the Essure coils. Many women today are getting the Essure coils for permanent birth control. We had a lot of success with these subjects and very few side effects. I am proud that we helped get this important new device on the market and approved by the Food and Drug Administration.

I was also involved in trials regarding Lysteda, which has impacted many women with heavy menstrual bleeding. In fact, one of the nurses who came to work later at our site was taking Lysteda, and I told her how we had done the study for that investigational drug. She told me how that medication had changed her life.

Other proud moments have been all the infertility trials I have been involved in, where women were able to conceive and have children after being on the investigational medications.

I have been a study coordinator for 18 years, and have seen a lot of changes during that time. One of the biggest changes has been risk-based monitoring. I've also seen the lack of research in women's health since the Women's Health Initiative Report came out.

I think in the next 40 years, things will be all electronic—including informed consent, source documents, and all regulatory documents. I hope more health studies involving women will occur that improve their lives.

Jerry Stein, PhD

Summer Creek Consulting LLC

A milestone that impacted government and industry was the Clinical Trials Transformation Initiative (CTTI). Beginning in 2008, CTTI examined clinical trial practices and focused on the efficiency of current data and site monitoring practices. This initiative was led by a combined public-private partnership composed of academic (e.g., Duke University), industry (e.g., sponsor companies), and government (e.g., Food and Drug Administration [FDA]) leaders. Their dialogue led to the issuance of new FDA and European Union monitoring guidelines allowing for risk-based monitoring approaches. This outcome has had a significant effect on monitoring activities. It continues to have a growing impact on industry practices and the daily lives of thousands of clinical monitors and data managers. I attended the 2009 workshop in Washington, D.C., but was a very minor player. I also helped the FDA to publish an article on this topic in *The Monitor,* which was the predecessor of ACRP's *Clinical Researcher* journal.

Home office moved to Washington, D.C.; Frederic Harwood, PhD, named Executive Vice President

1994

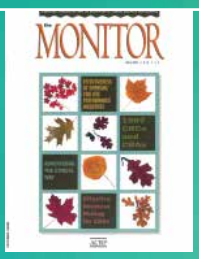
ACP

1995

First CRA certification exam offered; first U.S. local chapters open

Organization renamed Association of Clinical Research Professionals; *The Monitor* goes full-color, begins offering Home Study tests

1996



1997

Canada Chapter forms; first Association website launched

ACRP
Association of Clinical Research Professionals

Membership surpasses 10,000; Gary Lightfoot named first CEO

1999

2001

First certification exam for investigators offered

David Morin, MD, RPh, FACP, CPI

Holston Medical Group Sites

In 1979, while I was a fourth-year pharmacy student studying medicinal organic chemistry, our professor drew a chemical structure on the board and labelled it "SQ14225." He said, "Remember this compound. It will change how we practice medicine." To this day, I still remember the compound number and deceptively simple formula for what was the accumulation of many years of research on the renin-angiotensin system. The compound was captopril, the first orally active angiotensin-converting enzyme inhibitor for the treatment of hypertension and congestive heart failure. It was developed by Miguel Ondetti, Bernard Rubin, and David Cushman. Squibb filed for the patent in 1976, and it was approved for use in 1981.

The importance of the breakthrough cannot be overstated. Prior to the discovery of this class of medications, treatment of congestive heart failure was rest, digoxin, and diuretics. Undoubtedly, countless lives have been saved by this and other similar medications, which warrants its inclusion as one of the biggest advances in medicine in the past 40 years.

Teri Crumb, MSN, RN, CCRC

Spectrum Health System

I have been a clinical research nurse for 14 years and certified with ACRP for 10 years. I have been a part of some great clinical trials in my career. However, nothing comes close to the cystic fibrosis trials that I coordinated with Vertex Pharmaceuticals. I attended a Cystic Fibrosis Foundation (CFF) annual conference in 2007 and heard speakers explain the support the CFF was giving small businesses to conduct research on new compounds for the condition. Within just a few short years, we were chosen as a site for the VX-770 trial for what is now the Food and Drug Administration–approved drug known as Kalydeco. Families were very cautious about a placebo-controlled trial of a new compound for their young children. We were witness to life-changing events in the lives of kids taking this new drug. They were reporting changes in their symptoms that seemed almost unimaginable—things were getting better.

2002

Thomas Adams named President and CEO; home office moved to first Alexandria, Va. location; *Wire* e-newsletter launched

2003

Scholarly articles in *The Monitor* begin to be peer reviewed

2005

ACRP and Academy of Pharmaceutical Physicians and Investigators (later Academy of Physicians in Clinical Research) form affiliation

2006

The Monitor switches from quarterly to bimonthly publication

2007

Chapters launched in India, United Arab Emirates, and East Africa, joining others set up earlier across the globe; ACRP rebranding includes change to current logo

2009

James Thomasell named Acting President and CEO, later named Executive Director; ACRP's members-only Online Community launched

The following are excerpts from some of the entries submitted to the first-ever ACRP Certification Essay Contest…

- Many years ago…I was one of the newly accredited CCRCs and was quite pleased with the publicity we received [as being among the earliest people to earn the designation from ACRP]. A couple of months later, someone with whom I had interviewed the previous year called me quite unexpectedly and asked if I was interested in interviewing for a newly created position at his company. When I arrived for the interview, he told me that he had seen my name and what I had done in arranging for [my employer] to be a test site, and that he was impressed with my initiative. He offered me a job that I accepted, and which put me on a path in my career that has been both rewarding and professionally satisfying.
- When I was asked to start the certification process 10 years ago by my boss, I had been working in research for about five or six years. I didn't know anything at all about ACRP. I contacted another clinical research nurse I knew because I knew she had been working on getting "certified." I asked her the best organization to get certification through, and she immediately said, "ACRP." I went to a class held by ACRP to help me in learning about the certification process. My boss was telling all of the research staff that we all needed to be certified because it showed competency in our field. She said certification would also not only let sponsors know we were competent in the field, but would help us in our career and our salaries. She said the sponsors would be "more likely" to use our site for future studies if we showed that everyone at our site was ACRP certified. I became the first clinical research nurse certified by ACRP at my site.
- To me, becoming a certified coordinator establishes credibility and a dedication to continual learning. It raises the bar by establishing our profession as an important contributor to the healthcare industry. It also shows leadership and a responsibility to the advancement of clinical research, improves professional development, and above all, brings important autonomy to our research efforts. Personally, I feel that having the CCRC designation has shown my colleagues and industry partners how committed I am to my career.
- [The day in my research assistant and coordinator career came when I had] gathered enough experience and was able to sit for the ACRP CCRC certification exam. The hospital I worked for was very supportive of me and helped me through the certification process, as they knew that the one coordinator they currently had would be leaving soon. As soon as I had my CCRC certification, I was given a coordinator position and a substantial pay raise at the hospital. My ACRP certification served as a huge stepping stone for my career in research. I then worked for eight years at the oncology clinic at our hospital and became a very respected trial coordinator with the staff and MDs. I was never made to feel that I was inferior or unable to work as a coordinator, and I attribute this to my certification.

2010 Certification exams transitioned to digital format; CCRC and CCRA exams independently accredited by National Commission for Certifying Agencies (NCCA)

2011 *The Monitor* wins big in ASAE: The Center for Association Leadership competition; ACRP Professional Development Pathways developed

2012 CPI certification exam accredited by NCCA; ACRP home office moves to current Alexandria location

2013 First three of what will soon be many courses offered in new eLearning format

2014 ACRP partners with European Clinical Research Infrastructures Network in annual celebration of International Clinical Trials' Day; *The Monitor* rebranded and renamed *Clinical Researcher*

2015 James Kremidas named new Executive Director; global job analysis survey launched and development of Joint Task Force for Clinical Trial Competency begins

2016 ACRP begins a year-long celebration of its 40th anniversary with launch of "You Are 1 in a Million" campaign

Beth Jackson, MT(ASCP), CCRA

San Diego, California

"I continue to perform clinical trial monitoring because I feel like I am making a contribution to enhancing healthcare."

I started my career as a medical technologist in West Virginia. However when I moved to California, my hematology credits were not accepted. I worked in the field of plant biology until I landed a job at small device company. I began by procuring specimens for product development. I ended up conducting the clinical trials for the influenza dipstick test that was the first ever to receive CLIA waiver! I am extremely proud to have been a part of that achievement. In the years since, I have worked for other companies and continue to perform clinical trial monitoring because I feel like I am making a contribution to enhancing healthcare. The other benefit from monitoring is that I love the interaction with site staff and learn something new from every single site with which I work.

THREE "GIVENS" That Will Always Drive Successful Drug Development

Kenneth A. Getz, MBA

[DOI: 10.14524/CR-16-4012]

There is much to celebrate as we reach ACRP's 40th anniversary. The clinical research enterprise has been remarkably productive, and has delivered important medical therapies across a wide range of disease conditions. Research and development pipelines have grown steadily during the past four decades, fed by such innovation drivers as high-throughput screening, proteomics, and genomics. Rising numbers of promising new medical therapies demand greater capacity from, and coordination among, a global community of clinical research stakeholders.

The next 40 years look as exciting as the last. Trends and changes are unfolding that will profoundly impact how our enterprise manages its innovations and how it will operate and perform, including the growth of precision medicine; the consolidation of research sponsors and service providers; the convergence of clinical research and clinical practice; the use of wearable and mobile devices and new technology solutions; and more sophisticated uses of large and growing structured and unstructured data and information for scientific and management purposes.

Perennial "Givens" for the Next 40 Years

Other well-wishers in this issue of *Clinical Researcher* touch on and predict where these exciting developments will take us, and the changes and challenges that must be anticipated along the way. I wanted to share some consistent themes, or "givens," that will be as important—if not more so—in the next 40 years as they have been in the past four decades. Throughout my career as an observer of the clinical research enterprise, I generally invoke these three "givens" when I riff on the implications of any new research that I have conducted:

1 Relationships drive a successful clinical research enterprise

No matter how hard we try to drive speed and efficiency with new technology solutions and process improvements, or how tightly we manage study timelines, success always rests with the quality and caliber of our relationships. The time and care that we take to build expectations and solidify as a team; to establish alignment; to clearly delineate roles and responsibilities; to convey respect and establish

trust; to invite and accommodate timely input; to give partners the support and room that they need to excel—time and time again, these are the characteristics that define drug development success.

Research from a variety of sources (e.g., ACRP, Avoca, the Clinical Trials Transformation Initiative, CenterWatch, TransCelerate, Tufts Center for the Study of Drug Development, etc.) has shown that there are a number of essential and integral relationships that are neglected and often dysfunctional. Sponsor relationships with contract research organizations (CROs) and sponsor/CRO–investigative site relationships are two such areas. Recent attention on improving the relationship between clinical research professionals and patients/advocacy groups/the public/healthcare providers/payers—and impassioned efforts to establish and drive higher levels of engagement and partnership with these communities—will go far in helping the clinical research enterprise to achieve success in the future.

2 Transparency and disclosure are essential

Stakeholders throughout the clinical research enterprise readily agree that transparency and disclosure are the critical building blocks of trusting and lasting relationships. Moving forward, we must commit ourselves to improving transparency and disclosure, and to raising our standards to as high a degree as possible. This includes not only increasing the amount of and access to data and information, but also to providing it in languages and terminology that can be best understood by communities of varied and diverse levels of comprehension.

Industry-wide behaviors often belie our general agreement with this "given." To name but a few areas, operating and financial data often are not shared between sponsors, CROs, and investigative sites; public and private sector conflicts-of-interests are not consistently and adequately disclosed; poor compliance and incomplete and highly technical information in ClinicalTrials.gov renders this public information source insufficient; and although we are obligated to do so, most sponsors are not providing clinical trial results to their study volunteers.

3 Balance must be achieved between scientific excellence and feasible execution

Scholarly research has consistently shown that scientific and logistical complexity is inversely related to high performance and efficiency. As drug development programs have become more complex, so too have they become costlier, riskier, and longer in duration.

Partners in any relationship succeed when their expected contributions are feasible and achievable. For our study volunteers, feasibility includes not only access to clinical trials, but also convenience and comfort. Time will be well spent challenging great drug development science at the outset, so that it can be viably executed and all partners in a given program can succeed in supporting it.

Today's study designs have the highest relative number of procedures and eligibility criteria on record. Our operating models frequently involve complex and fragmented, poorly coordinated global teams of internal and contract service personnel. In response, some of the impacts include how contract and budget negotiations are protracted; study start-up and overall cycle times are extended well beyond initial plan; recruitment and retention rates continue to decline; change orders and protocol amendments increase; and investigative site performance varies greatly, with a high percentage failing to enroll or under-enrolling study volunteers.

No doubt the results of our scholarly research will continue to fuel my riffs and rants on these "givens." They are key principles that will go far in delivering successful drug development programs regardless of individual strategies and tactics employed. Further, through training, certification, education, communication, and networking, ACRP will play a major role in helping to ensure that these "givens" are addressed!

Best wishes and congratulations to ACRP on its 40th anniversary.

No matter how hard we try to drive speed and efficiency with new technology solutions and process improvements, or how tightly we manage study timelines, success always rests with the quality and caliber of our relationships.

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PI CORNER
Jeff Kingsley, DO, MBA, MS, CPI, FAAFP

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The Evolving Role of the PI

Predicting the future is a fool's errand. Yet that is what I've been tasked to do for this column. So let's look 10 years into the future at the undiscovered country of 2026.

Well…first, let's look at the forces involved in how principal investigators (PIs) conduct (or don't) clinical trials today. The future doesn't simply happen—it's the inevitable result of the forces applied as time marches onward.

Increasingly, research coordinators and a site's capabilities are becoming more important than the experience or capabilities of the physician in determining site selection.

Current Condition	Physicians are the largest barrier to the success of research trials. Not you, of course. You're different. The largest reasons for this barrier to success include lack of time to participate, lack of residual mental bandwidth to focus on research, fear of losing a patient from the practice, and fear of the patient's reaction to a discussion about research.
Resulting Pressure	These physician-centric factors stymie subject enrollment and site startup, and drive our industry to develop other strategies to compensate. New vendors and new industries are cropping up to bring research directly to the patient, thereby bypassing the physician and physician practices.
Current Condition	We do not have enough experienced, competent, certified PIs. Experienced investigators are quitting because research is becoming harder and regulations are becoming increasingly onerous.
Resulting Pressure	This lack of experience at the investigator level is driving decision making in other areas of the research team. Increasingly, research coordinators and a site's capabilities are becoming more important than the experience or capabilities of the physician in determining site selection.
Current Condition	The cost of research is reaching unsustainable levels because of the ceiling on product pricing once Food and Drug Administration approval is reached. The cost of clinical development cannot grow beyond the ability to recoup that investment once the product reaches the marketplace.
Resulting Pressure	Contract and budget negotiations at the site and contract research organization (CRO) are increasingly restricted by price considerations over quality considerations. If price trumps quality, sites are forced to hire and structure accordingly.

Current Condition	Technology is facilitating remarkable advances in our ability to collect data in the patient's home and other "real-world" settings.
Resulting Pressure	Entrepreneurial spirit is driving growth where opportunity exists. The pressures listed above are providing larger opportunities to push research beyond the normal medical practice and into the patient's home. Additionally, "real-world" data are increasingly respected over data obtained in a clinical setting.
Current Condition	Telemedicine is becoming universally accepted as a means of evaluating patients and delivering care. As acceptance is increasing, cost is decreasing.
Resulting Pressure	Telemedicine is emerging as a viable solution to harnessing the experience of the hard-to-find highly experienced, competent clinicians.
Current Condition	Regulators are placing increasing pressure on electronic health record (EHR) companies to utilize a common methodology so that healthcare records are transferable across software platforms.
Resulting Pressure	Early in any industry, differentiation reigns. Early entrepreneurs in an industry resist allowing interconnectivity so that their product or service remains unique, and they erect a larger barrier to entry for competitors and a larger switching cost for customers. However, the societal benefits of standardization and consolidation eventually drive fewer unique platforms. This occurred with shipping containers, video recording devices, software languages, and cell phones; it is occurring with EHRs today.
Current Condition	Patients are increasingly empowered to take ownership of their EHRs and of their medical decision making.
Resulting Pressure	Patients are not only empowered, but are also capable of managing their own healthcare decision making. Direct-to-patient marketing is pushing into the research arena just as it did in clinical medicine more than 20 years ago.

Our reactions today change what tomorrow looks like. If you don't like what the future looks like, do something about it today.

Gazing Into the Crystal Ball

So back to 2026. Where do the aforementioned current conditions and resulting pressures lead me in my predictions?

In 2026, highly experienced, competent, certified PIs are increasingly sought after. The global economy has accelerated research, but the medical community was unable to fulfill the need for a quality PI at every site across the globe. As a result, the PI in 2026 is a central role—much as was the role of the lead investigator or medical monitor in 2016. To make this possible, PIs will become licensed in multiple states and will be responsible for the patients in those states.

Research enrollment in 2026 is strongly a direct-to-patient endeavor, and patients easily self-refer into research trials. EHRs communicate across platforms and patients have the ability to access their records and provide them immediately to the research team, without any need to slow the process by involving a medical records department at another facility.

The vast majority of research data are collected outside of the research facility with wearables, implantables, and other monitoring devices. Data are collected in the patients' homes, in their workplaces, while they're driving, and while they're exercising. What little data there are to collect at a research site are largely collected by highly trained and certified research staff without the need for a physician to be present, and without the need for local physician oversight, because PI oversight is centrally mediated.

Telemedicine facilitates physician interaction with research patients so that the most highly experienced investigators are now available to interact with patients wherever they may be. Research sites are accredited and are routinely re-evaluated for levels of quality.

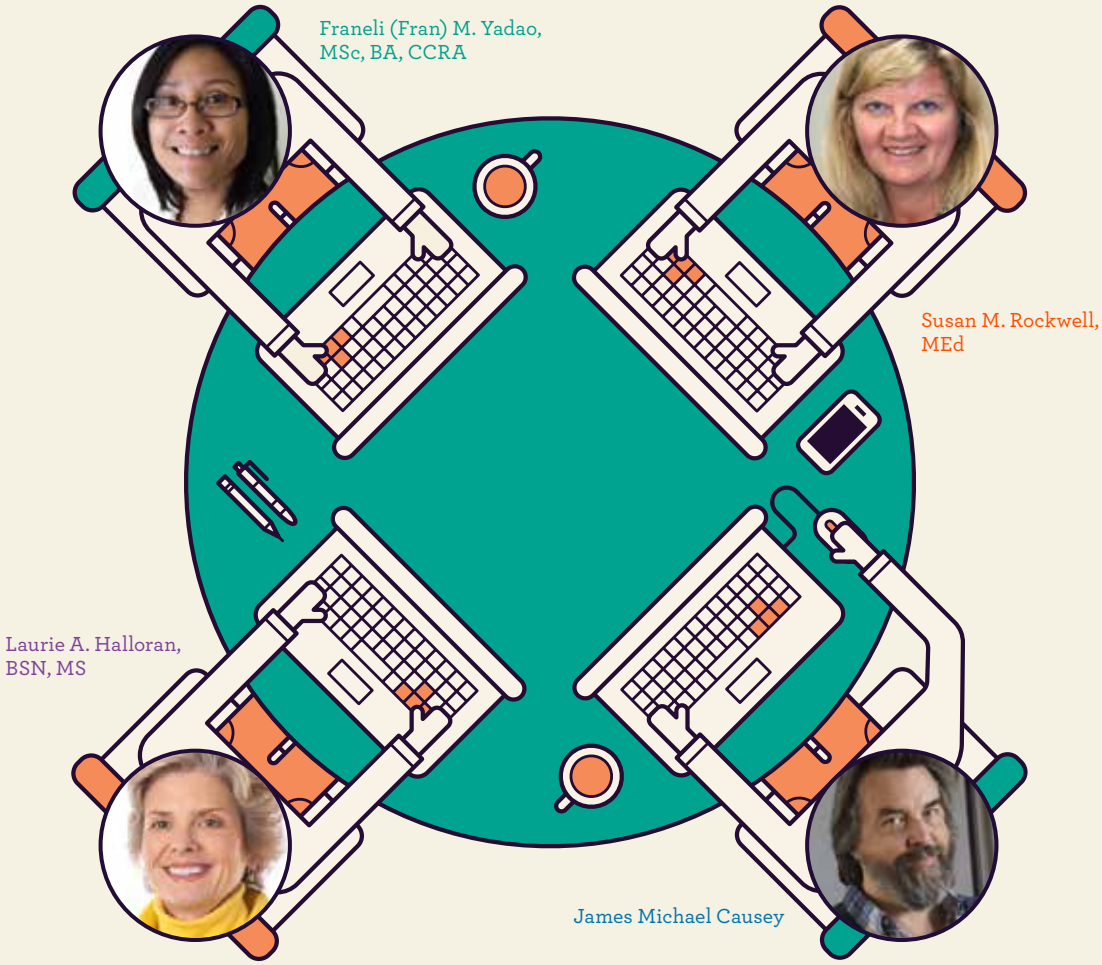
In Closing

Am I certain that this is the future? No. But this is where I believe today's forces can lead us. This can change. Our reactions today change what tomorrow looks like. If you don't like what the future looks like, do something about it today.

Jeff Kingsley, DO, MBA, MS, CPI, FAAFP, is founder and CEO of IACT Health in Georgia, and serves on the Finance Committee and Business to Business Working Group for ACRP's Board of Trustees.

Clinical Researcher ROUNDTABLE:

Triumphs and Travails from the Front Lines



In a recent wide-ranging discussion, **Franeli (Fran) M. Yadao, MSc, BA, CCRA,** a team manager at Emergent BioSolutions, **Susan M. Rockwell, MEd,** executive director for medical device strategy with ICON plc, and **Laurie A. Halloran, BSN, MS,** president and CEO of Halloran Consulting Group, shared their greatest professional triumphs, what's surprised them most in the last several years, and advice they'd give to someone considering joining the clinical research field. The virtual roundtable, conducted by *Clinical Researcher* Editor-in-Chief **James Michael Causey** in early February, began by asking each participant what inspired them to become a clinical researcher.

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FRAN: I got into clinical trial research about 20 years ago. I'm a clinical operations manager right now, and have always loved the field. I fell into it after earning a master's degree in science, where I saw the world starting to shrink before me into a very small sort of research lab area, and realized that I really wanted to be with people and that clinical research gave me the opportunity to do that.

SUSAN: I've been in the medical device industry for over 25 years. I'm working with my third contract research organization (CRO). The previous two were acquired. I'm hoping this will be the last. I worked in clinical operations originally, and now have moved more into business development and strategy.

LAURIE: I was a nurse and I just wanted to work during the day, and to wear real clothes. I worked in a pediatric intensive care unit, and my first job was as a clinical research associate (CRA) at a CRO (PAREXEL) in clinical research's early days of the 1980s. After 10 years of working and moving into a role which I'd describe in retrospect as internal operations consulting, the company had become pretty large. I was expecting my first child, and wanted some work/life balance, so I started my business and then had the baby (bad idea)!

So over the next five years, I worked in a couple of different biotech companies and in both of the jobs I was in senior-level clinical positions. I realized through those experiences that there was a real need for senior-level strategic expertise to come in as an on-demand team, and the vision of Halloran Consulting Group was formed. We affectionately call the kinds of companies we first worked with "two guys and a molecule," though we now service companies like this in the biopharma as well as the device and diagnostic space. We have almost 125 companies that we work with right now, and more than 70 employees. We're growing very rapidly and are having a really wonderful time helping our clients.

CLINICAL RESEARCHER: In this 40th anniversary issue, we're highlighting how amazing the people in this industry are and the important work that you all do. Sometimes it's overlooked. When you close your eyes and think about it, what are you most proud of professionally?

FRAN: I was thinking about this when you asked me to participate. To answer that question, I think that it goes back to our motivation for being in the field of clinical research in the first place. Why are we here anyway? If we were nurses before, what made it necessary for us to leave that satisfying feeling of being present and helpful to the one person that's in front of us at that particular point in time? For the people I work with every day, I think that what it comes down to is following our mission statement in all we do. Our department's mission statement is "Every patient counts – every life matters."

Having that sort of patient focus in the research that we do, and trying to really focus that into excellence in the field, whether we are CRAs, scientists, data managers, or biostatisticians, within our group—that is what we strive for. Looking at the trials that I feel most proud of professionally, they're the ones in which there was no alternative treatment for a particular clinical indication, for instance some expanded access programs and rare disease studies I've been involved in.

SUSAN: Probably two things. One was managing a very large drug-eluting stent trial from start to finish for U.S. approval. It was a real challenge, and it was with a large medical device company. There was a lot involved with bringing that product to market, and it's used every day now. That was certainly a high point. The other is the ongoing progression in how I've worked with a small, a medium, and now a large CRO; and the small CRO was completely medical device focused, the medium one was about a third focused on medical devices, and the large one has a smaller device component to it.

What I'm proud of professionally is helping grow that medical device market at each CRO, and being able to provide additional services to the medical device industry. That's an ongoing challenge, and there's a lot of excitement at ICON. I feel good about how we've been able to offer those types of services to the industry and help with clinical research.

LAURIE: There are early and later stage examples here. On one of my first studies as a CRA, we were doing a big data rescue mission on an early HIV treatment. I was out in San Francisco for the better part of a year, working 16-hour days to try to get the data in. It was a drug for pneumocystis pneumonia. I didn't realize it when we first started, but I felt like it was a really important thing to do to help the patients back then, who had no treatments in the late 1980s.

The second thing I feel really proud of is the work that we do now at Halloran. We really help companies by providing the expertise to further their product development as efficiently and cost effectively as possible. They are so resource constrained that one bad decision can doom the company, and I'd like to think we apply our decades of knowledge in the scenarios that have the highest probability of success, with the most limited resources possible. Sometimes we work with them to decide to stop developing something that isn't feasible from a regulatory perspective, so they conserve money to use on something with more promise. Conservation is lacking in a lot of companies right now, and critical for the long-term health of the industry.

Every patient counts, and every life matters.

My advice is to strongly consider the medical device industry.

CLINICAL RESEARCHER: Good point. Fran, what kind of advice would you give to someone considering entering the field?

FRAN: I think what I would tell people is that, regardless of the walk of life that you're starting out from, to not think of clinical research as a field where you can say, "I'm going to stop here." This field is not a good one for people who aren't curious or willing to learn. It is a good field for generalists. There's just so many of us that have come from different backgrounds that, no matter what the experience you have in your past, it's good and can be used for your future career in clinical research.

Also, I would tell people that soft skills are just as important as technical skills. In this multi-disciplinary field of clinical research, it is the ability to connect with people that will lead to success. Regardless of what your role happens to be, it's the interpersonal relationships that will get the job done regardless of what you're doing in the field, it's the interpersonal relationships that will get the job done.

SUSAN: My advice is to strongly consider the medical device industry, for the following reasons: Both in the U.S. and Europe, they've really tightened up regulations that encourage more clinical trials.

In the U.S., the Food and Drug Administration (FDA) has tightened up the guidelines and regulations for 510(k)s, which is the way to get a medical device on the market if it is similar to other products. You're not saying that your device is something that no one else has; you're saying that it's similar to other products, kind of a "me too" device. In the past, the FDA was pretty loose about how you compared your product to something else on the market. They've really tightened that up. Now it has to be very, very similar—almost exactly the same. Going through the 510(k) process lessens your regulatory burden. Typically, you don't have to conduct very involved clinical trials. By making it tougher to go down the 510(k) route the conventional way, it's opened the door for more clinical trials.

In Europe, there are fairly new medical device directives. Actually the ones for in vitro diagnostics are expected to be released this year. As a result of these new directives, Europe has tightened up the need for more clinical trials for medical devices. Now that regulations have been tightened up, there's going to be more clinical trials, more jobs, and it's going to grow the medical device industry.

LAURIE: My advice would be along two lines. One, realize that if you want to succeed, you have to both work hard and think of new ways to do things better. I think as an industry, we're mired in a lot of "this can't be done" risk aversion. People who can think about the possibilities and of how we need to make changes and improvements are going to be the superstars here.

The second area is a combination of embracing technology and developing soft skills that will ultimately be more important than a rigid "box checking" mentality. Success will go to those who embrace technology, who are able to really harness its power to adopt the efficiencies we use every day in our connected world to the risk-averse world of clinical research, and who look for solutions instead of problems by thinking more strategically.

CLINICAL RESEARCHER: We've touched on this a bit already, and you three are very aware of this, but in the industry now we've got signing bonuses being thrown around like you see for professional athletes. People are getting $10,000 to be lured from one place to another. Do you foresee a time when this will burst? Fran?

FRAN: I wish that you hadn't started with me, because I have not looked for a job in quite some time! I gauge what's going on with the job market by the number of recruiting calls that I get. I think that you're going to get up swings and down swings in the industry. I think right now, things are moving along extremely well, but we will hit pockets of distress. Overall, I think that whatever happens with the global economies, clinical research and the industry will ultimately follow.

I do think that what is going to change in the next few years are the skills needed; we've already seen it. We've seen it in the last 10 to 15 years that there will be a constant change in what is required in order to access those jobs, and what those job skills are actually going to look like. While I think that you might see fluctuations in demand, I also think that what we need to be more cognizant of is not so much how many people are needed and how many jobs are out there. Instead, people need to really try to position themselves to fit the skill sets that are needed for those jobs, and to stay ahead of the curve.

SUSAN: If you are interested in being a CRA, or if you are a CRA, you have a career for life. I don't know about other people, but on some stressful days I think, "I am just going to go back to being a CRA." You can pretty much ask for whatever you want. There is not a CRO out there that is not terribly short staffed.

I don't think it's a good thing overall, but I think it shows that there's an increase in clinical research, so that's good for our industry and good for jobs. However, I think that we need to figure out ways to better develop CRAs. There's that catch 22. Sponsors want CRAs on their projects who already have experience, but how do you get that experience? There are programs now, like remote monitoring, that certainly help cut down on the amount of onsite

monitoring, but I think there's always going to be a very big need for CRAs, whether they're onsite reviewing data or in house. If you're interested in clinical research and like to travel, being a CRA is a hard job, but you can make a good salary. That's number one.

The other point I want to mention is that for medical devices, there are four main geographic areas that are hubs of companies—the Northern California, Southern California, Minneapolis, and Boston areas—but we're also seeing a lot of growth in other states. There are some good reports that the California Healthcare Institute puts out each year that give a review of that state, as well as the nation. There's job growth in Utah, Michigan, Ohio, Wisconsin, North Carolina. This is actually for both pharma and medical device. I believe that we're going to continue to see this growth. Whether you want to work for a sponsor, a CRO, or be a contract CRA, there's going to be jobs.

CLINICAL RESEARCHER: Susan, so do you see the trajectory just going up and up or holding steady? You don't see any bust or any precipitous drop?

SUSAN: Right. The reports that I looked at, and as head of strategy I look at this kind of thing, it's going up. It's a steady increase and has been for a number of years in the medical device industry. Pharma has plateaued a little bit, but if you're a CRA or in jobs like that, they're always going to be there. The other area too, is if anyone has leanings toward the Asia Pacific Area, that's a huge research area that, if you can align yourself with a company that's doing research there, or have interest in even living in that area, there are huge, huge opportunities for research.

LAURIE: The only thing I would add is that people who are thinking about a long-range goal in their career might want to look into regulatory affairs, because there's so much opportunity there. It's a close sibling to clinical research, but brings more broad exposure and isn't just a higher level clinical operations position.

FRAN: I was actually thinking in another direction too, with all of the quality risk management buzz these days. Really, clinical quality assurance (QA) seems to be a field where those of us who have been through inspections and audits might want to go. I've seen quite a few of my colleagues say, "You know, I'm going to take a QA hat and go in this direction, because this seems to be where people are going to be needed in the next while."

CLINICAL RESEARCHER: Let's switch things up and get slightly existential here. If the you of five or 10 years ago was sitting here right now, what do you think would be the most surprising development to that you of the past?

FRAN: It's the speed at which we've taken on social media and the technologies that bring that to clinical research and how we do it. Things like your electronic informed consents, things like clinical trial information available on Facebook/Twitter, things like web-based patient diaries. That is incredibly surprising to me. I would not have even imagined it 10 years ago, five years ago. It was inevitable that it would come. I just was not prepared for the speed.

Also, it's hard to get your mind around risk based monitoring especially for those of us who do a lot of outsourcing; some of our CRO partners are so siloed that it actually makes risk based monitoring hard to implement. If you're trying to pursue a well-rounded approach to reviewing your data, to bring the biotstats silo in with your medical folks silo in with your clinical scientist silo in with your clinical operations - it's challenging. Then moving the risk based approach into the field and having more of a compliance/overall systems quality assessment at the sites is also hard because sites are used to the old way of monitoring. Overall you are not only trying to get site people up to speed on the skill sets they now need, you're also trying to break down the barriers within your CRO's infrastructure and your own infrastructure to get it to work.

SUSAN: Two things. One is that we see a lot of big companies in both pharma and devices that acquire smaller companies, but I tell you what, I never expected Medtronic to buy Covidien. I never saw that coming, which happened last year. Seeing two really big device companies merging like that—they're usually the ones, both of them, that are buying all the smaller companies. The second thing is, I would not have guessed five years ago that in vitro diagnostics would be the largest part of the medical device industry. It's a huge segment, and it's been that way for at least two or three years, and it's projected to be the largest part of the medical device industry at least out to 2020.

LAURIE: I could not have predicted how many pharma companies have chopped off large groups of their people to swing in the direction of outsourcing until it hurts. I would've predicted that we would be better at harnessing technology for the efficiency that it brings. Five years ago, I thought monitoring was going to change drastically, because of the risk-based monitoring FDA guidance almost urging it. I'm actually shocked that it hasn't changed much at all.

CLINICAL RESEARCHER: Thank you all so much. This was fun. I've certainly learned a lot, and I hope our readers have, too.

I would've predicted that we would be better at harnessing technology.

Deborah Miller, CCRC

Logan, Utah

"I wrote a book on patient recruitment titled Winning at Patient Recruitment: Achieving Enrollment Goals Through Outbound Telephone Screening."

Early in my career in research, I was tasked with patient recruitment involving dialing outbound to patients who were members of a large healthcare organization. I excelled at it, and was on my way to a rewarding career in clinical research. Since starting my clinical research journey in 2009, I have worked in endocrinology, pulmonary, oncology, and most recently pediatric studies involving a full range of conditions. I speak at industry conferences on patient recruitment and, more recently, site management.

I love my career in clinical research. It is personally rewarding and allows me to help patients learn about new treatment options that they may not have considered. I am always surprised by the number of people who are naïve about research. I hope I am able to help them navigate through the informed consent process and at the conclusion of the process, have a better understanding of what participation would involve.

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Can we Halve the Incidence of Failed Clinical Trials in the Next 10 years?

Clara H. Heering, MSc, MSc

Developing an investigational product is like parenting a child; as parents, we are fully responsible for the first 18 to 21 years, and then we hope that our child can handle its own future.

Children first spend their days at home, and then go to school, and sometimes have nannies; investigational products go through preclinical stages, are then developed with investigator teams, and sometimes with contract research organizations.

Human factors enable a consistent and systematic understanding of why unintended mistakes (errors) are made between people, between people and processes, and between people and technology.

With schools, we have spent many years focusing on the outcomes of education only—the school grades children have—rather than looking at the full picture of education. Similarly, in the realm of clinical trials, we were conducting source data verification on procedure outcomes, rather than understanding and verifying the process that led to the outcome.

In many of the same manners as for the schooling of our children, our industry is shifting to an enhanced approach for process as well as outcome support and verification. We are taking steps to adopt the wonderful change of including behavioral sciences in clinical research conduct. We are seeing the first results of the shift to a more balanced focus on both outcome and procedure.

What are We Learning from this New, Balanced Approach?

Where I work, we conducted an analysis of seven clinical trials with a total of 4,193 subjects enrolled, in which we deployed a risk-based prevention, detection, mitigation, and learning approach focused on what matters to patients. In this approach, clinical research associates (CRAs) classify the root cause of detected significant errors in "human factors," prior to working through the best correction and prevention approach with, for example, the investigator site staff.

Among other issues, we analyzed the detected errors in the protocol-required blood sampling at investigator sites and found that:

- 29% (65 out of 228) of errors detected in the lab sampling procedures at site were due to the human factor labeled "Process"; and
- 12% (28 out of 228) of errors detected in the lab sampling procedures at site were due to the human factor labeled "Communication."

The types of errors included a lab sample not taken as required, a freezer temperature log not kept up to date, and many others. In our traditional "teaching" model, CRAs would have focused on the outcomes, and retrained the site. With our new approach, CRAs not only detect and record the procedural errors, they also describe the root causes and associate them with the most appropriate human factor, which in turn supports an error-specific, tailored corrective and preventive action.

This framework for Human Factors Analysis and Classification of errors enables a consistent analysis of any systematic errors. Aggregation is multifaceted; the outcomes of the analysis are specific and actionable, and support continuous improvement by CRAs, site staff (at individual, regional, and countrywide levels), entire study teams, and even entire research programs. For example, based on the human factor "Process," one preventive action was "…a blood sampling tool (sticker) has been created to highlight the different samples required for different treatment arms."

The aviation industry used this type of framework, and was able to halve the incidence of plane crashes[1] in 25 years. Imagine if our industry could halve the incidence of failed clinical trials, and achieve this much faster as we learn from the aviation industry and the new behavioral sciences.

What Will it Take?

How would a Human Factors Analysis and Classification System support halving the number of failed clinical trials? Human factors enable a consistent and systematic understanding of why unintended mistakes (errors) are made between people, between people and processes, and between people and technology. Focusing systematically on fixing and preventing re-occurrence, as well as on learning from these errors, will reduce the "noise" in the data, and data will be derived from patient diagnostics with more precision and more accuracy.

Let's consider an example. Imagine weight is your primary outcome; if the scales are all calibrated and the subjects are all undressed to the same extent, variability will be reduced from measurement to measurement. Add to this a few requirements, such as timing of day and voiding status, and the data will, in theory, be even more precise and accurate, and analysis of the data will show trends with less noise and less variability.

In practice, we know sites may add variability by making mistakes in the weighing of subjects to these enhanced protocol requirements. So, adding to this level of precision and accuracy in protocol requirements the verification by monitors that the requirements are implemented, as well as addressing any error with Human Factors Analysis and Classification, will prevent re-occurrence of those errors, enabling much enhanced and reliable outcomes of clinical trials.

The end result should be a reduced number of failed clinical trials, and over time, maybe even a halving of failed clinical trials.

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Clara H. Heering, MSc, MSc, (clara.heering@gmail.com) is vice president for clinical risk management with ICON Clinical Research and served as chair of the ACRP Board of Trust.

Deborah L. Ansel, CMA, CCRC

Summerville, South Carolina

"Whatever your position is in this industry, take this message to heart: You do matter. You can be proud. You are increasing the odds of longer, healthier lives for millions of people around the world."

It was the end of a very long, stressful week in my career as a senior clinical research associate (CRA) when I received an e-mail from ACRP and this was the first sentence: "Clinical research professionals like you are increasing the odds of longer, healthier lives for millions of people around the world." WOW…there it was…written in a perfect sentence…the reason that I continue to remain in this industry even on crazy weeks like this…I have a job that makes a difference!

I spent six years as a study coordinator in Phase II through Phase IV clinical trials in various therapeutic areas with both pediatric and adult subjects. I got to know my subjects because they sometimes would qualify for other trials after completion, so we have had longstanding relationships. Their eagerness to help others find relief by donating their time as subjects was very impressive. I still have mementos given to me by some very special pediatric subjects.

It was a difficult decision, but I decided to make the leap from study coordinator to CRA (monitor) more than eight years ago. I do not regret this decision, and find myself again loving to mentor other CRAs who share my passion in this industry.

I have monitored Phase II through Phase IV trials in various therapeutic areas such as hepatitis, COPD, hepatocellular carcinoma, and others. Sponsors can be demanding…eager to launch a potentially beneficial drug, and in some cases, a life-saving or life-changing one. Travel can be grueling, trip reports can become novels, sites can have challenges, subject recruitment may be lagging, days can be long, and weeks can be longer. Then, as you collapse onto the sofa for a little television relaxation, a commercial will appear and you smile…knowing that your work helped that drug reach the market. Somehow, that helps you get out and handle another day.

To Imagine the Future of Clinical Research

Elizabeth Blair Weeks-Rowe, LVN, CCRA

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There are endless possibilities for the future of clinical research, but the assurance of continued innovation requires reflection on our past experiences to map a pathway forward.

In 2000, I started working as a study coordinator. We were entrenched in paper documents such as case report forms (CRFs), patient diaries, and questionnaires. Electronic data capture (EDC) or electronic CRFs had barely made an impact, and required a separate computer to access the platform. However, innovation will not yield, and as my career progressed to a monitoring position, nearly 30% of the studies likewise progressed to using eCRFs, with electronic query generation following suit.

Despite the naysayers who considered the technology more difficult (for both patient and caregiver), patient-reported outcomes collected in diaries and quality-of-life questionnaires were slowly being replaced by personal data assistants and interactive voice response systems to report data. In truth, these devices made a once-challenging data collection process more cohesive. They increased patient awareness of, and engagement with, personal health outcomes.

However, the most startling change, and one that I never would have imagined, was the transition to risk-based monitoring. Our industry has progressed from 100% CRF/source data review, conducted almost exclusively onsite, to the risk-based model of remote and targeted monitoring practices, which integrates the hybrid of remote EDC/source review and targeted review of critical endpoint data (onsite) into the monitoring process. Not only has this dramatically reduced the need for onsite monitoring visits, but it has been vetted by regulatory agencies and embraced by our industry.

Technology-driven data practices are at the heart of all of these changes. Computers and the Internet have made the research process more efficient, which aligns with the current research environment; and therein lays the dilemma. Will this dependence on machines make us that much more obsolete? Will there be a future in which computers/robots replace some or all clinical research positions? Despite speculation, I don't count this as a possibility.

The Human Touch

My career and the studies I have worked on have benefitted immeasurably from the influence of technology. I can only imagine an exciting future in which technology further enables more optimal performance—augmenting our responsibilities, as opposed to excluding us from fulfilling them.

No matter how seemingly sentient a device and no matter how advanced the programming to mimic human interaction, there is no substitute for authentic human interaction; productive dialogue between people is vital to working together to discover cures for disease. These are the fundamentals of clinical research.

When I think of the future of research, and the impacts of technology on science yet to come, science fiction elements like sentient computer systems and avatars spring to mind. Though based on fantasy, some themes are rooted in truth; and in that spirit, the following potentially exciting and perhaps not-so-unrealistic possibilities are what I envision for the future of clinical research.

- When shifting matter becomes a reality, automobile and airplane transportation may be replaced with transporters (as seen on *Star Trek*). Monitors will no longer have to wait in airport rental car lines, or battle rush hour traffic or flight delays. Investigators will never have to deal with jet lag or the time wasted in transit to attend a critical meeting. At precisely 10 minutes before said meeting or monitoring visit, one would simply punch coordinates into the console, step onto the platform, and materialize at the destination. Think of the environmental and economic benefits of this mode of travel; and there is only a 2% chance that your molecules won't reassemble in their original arrangement.
- The future may bring sentient computer programs to help prevent and correct data error. Imagine an electronic medical record or eCRF-based computer program with the capability to perform internal, thoughtful review of data entry; a process involving review of real-time data entry and cumulative/comparative review of existing data. Through interactive voice software, the computer would to notify the user of discrepancies and assist in resolving the issues. For example, while a study nurse enters a patient's demographic information, the computer is reviewing the screening lab results and notices that the patient's date of birth, as entered by the nurse, does not match the date of birth on the lab report. The nurse checks the entry, finds the entry that is in error, and corrects it immediately. There is no obnoxious error message that comes later; there are no redundant, duplicate system queries. There is only a pleasant computer voice advising the nurse of the error and how to correct it.
- Though a computer cannot replace a clinical research associate (CRA) or a member of the study team, in the future a computer could conceivably provide adjuvant support in the event the individual was not available. The typical "Out of Office" e-mail notification or voicemail message informs the caller that we are out of the office, without providing any problem-solving assistance to individuals seeking us. In the future, an interactive hologram could conceivably replace such notifications, transmitting a personal message targeted to the individual's query or need. The hologram would not only inform them of the person's absence, but address the reason for the contact, and provide relevant information or data. Imagine a project manager contacting a CRA to get site enrollment information, but the CRA is out of the office. However, the CRA has programmed the hologram to provide the project manager with the exact site enrollment information required, saving time and avoiding needless frustration. Further, interactive holograms or avatars could be used to complete weekly site contacts for traveling CRAs. The avatar or hologram would "transmit" to a site, providing recruitment updates, enrollment reminders, and important study information.
- For study coordinators, investigators, or CRAs at large academic or health organizations, a lot of time is spent traveling from one part of the campus to the other. However, in the future, a hover board, or hover bike, could potentially provide a rapid means of transport across campus to complete whatever tasks patient care or study procedures dictate. It would save time and resources, though the institution would need to provide hover board insurance and instruction.
- The last innovation I see for the immediate future of clinical research is already happening. I was set to visit a research site for a pre-study visit, but my flight was cancelled due to inclement weather. When I called to reschedule the meeting, the study nurse offered to conduct the pre-study visit via FaceTime, including all study discussions and facility tours. Though it was not a possibility due to the sponsor's requirements, it was something the site was starting to do more frequently, and a practice I anticipate will become more widely accepted in the near future. Video or FaceTime tours to confirm equipment and facilities, and to facilitate investigator and CRA discussion once impossible due to schedule or time zone conflict, would be a cost effective alternative.

To quote a cliché, the future is now in clinical research, and our willingness to integrate technology into our pursuit of disease treatment will ensure a brighter future for the patients we protect.

Our willingness to integrate technology into our pursuit of disease treatment will ensure a brighter future for the patients we protect.

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Merrie Lou Nagel, RN, BSN, CCRC

Rochester, New York

"Clinical research remains the number one way to explore new avenues for disease treatment and management. I am proud to help ensure the rights of human research participants."

YOU ARE 1 IN A MILLION

I have been a registered nurse for 40 years. I bring my ability to help patients understand and manage their disease entities to the research arena. I am able to truly inform patients about what to expect during a clinical trial and help them to navigate the "system." For the last five or so years, I have been involved with industry-sponsored clinical drug trials searching for medications to ameliorate the oral mucositis associated with the chemo/radiation treatment of head and neck cancers. I also was part of a study that looked at the effects of separating the prostate from the rectum during the radiation treatment of prostate cancer. The investigational product remained in place during the entire seven-week treatment and self-absorbed within three months of application. The bowel-related side effects of prostate irradiation were greatly reduced. The product has gone on to receive Food and Drug Administration approval for prostate cancer, and is being used in the treatment of our patients. Our principal investigator is interested in exploring that product's use in separating the left breast tissue from the heart–in the treatment of breast cancer.

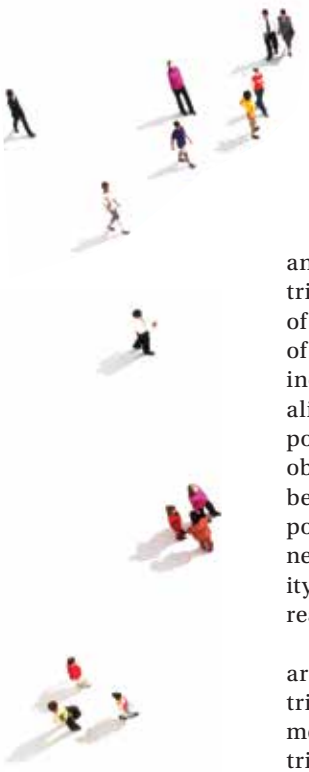
What Does the Future of Phase III Clinical Trials Look Like in a Population Health Model?

PEER REVIEWED
Kathleen M. Aguilar, MPH
Erika Shah, MS
Kelly J. Ko, PhD
[DOI: 10.14524/CR-15-0032]

Population health management strategies can change the way clinical care reaches patients. These approaches take into account the interaction among health outcomes, determinants, and policy interventions to impact the health of both individuals and communities.[1,2] By including population-level components like health assessments, health promotion, and outcome management, an effective population health model can ensure specific individuals receive appropriate care while improving the health status of the community. Population health management, therefore, has become an appealing strategy for an increasing number of health systems, insurers, employers, and public policy stakeholders.

The shift toward population health may influence clinical research in several meaningful ways. First, research agendas may be refocused to investigate the effectiveness of population health interventions and multilevel determinants of health status.[3,4] Second, the scope of information available for research purpose may be expanded. In particular, population health management often involves leveraging technology and electronic data to track patients and outcomes.[5,6] Information accumulated in these databases may also have applications for observational studies, such as patient registries.

However, it is unclear exactly which population health trends will impact clinical trials. The Institute of Medicine (IOM) recently published a report detailing the need for "disruptive innovation" in the clinical trials infrastructure, particularly to reduce the separation between healthcare delivery



and research.[7] The authors maintain that clinical trials will continue to be essential in the process of developing new therapies or new knowledge of existing therapies, thus calling for a need to increase their efficiency, effectiveness, and generalizability to treatment populations. In this regard, population health management may support this objective by facilitating improved integration between clinical care and trials. Furthermore, population health management may also lead to new trial opportunities due to increased availability of patient information and novel approaches to reaching study participants.

The purpose of the project described in this article was to explore the future of Phase III clinical trials in the context of a population health management framework. We focus specifically on Phase III trials and not the broader topic of clinical research, since initial assumptions regarding the outlook of Phase III trials are less defined than Phase IV trials, registries, or other types of observational studies. That being said, the trends identified here may also affect clinical research more broadly.

By including population-level components like health assessments, health promotion, and outcome management, an effective population health model can ensure specific individuals receive appropriate care while improving the health status of the community.

METHODS

The study approach consisted of three phases. The first phase of this study included a nonsystematic review of evidence that may be accessed in real-world situations, including but not limited to scholarly publications. This evidence review was undertaken by three trained health services researchers. Initially, PubMed was searched using terminology related to trials and population health. A targeted review was then conducted for select studies that appeared particularly relevant. In addition, a focused web search including key healthcare research websites and general web searches were undertaken to identify other appropriate web-only (not peer-reviewed) publications and references. Findings from the evidence review were summarized and seven distinct trends were identified.

For the second phase of the study, eight healthcare professionals from a variety of backgrounds were identified and asked to participate in an electronic survey. These individuals were selected to provide insight on the future of clinical trials from the perspectives of healthcare professionals, clinical researchers, the pharmaceutical industry, academic institutions, state government, and other commercial interests. The survey consisted of 10 questions designed to assess respondents' knowledge and opinions regarding potential trends affecting the future of clinical trials. These questions were based on information gleaned from the evidence review. In addition to covering predefined topics, panelists were encouraged to comment on any other trends that may have been overlooked. Survey results were aggregated to present descriptive trends only, as no additional statistical analysis was performed.

For the final phase of the study, an expert panel meeting comprised of the healthcare professionals who participated in the survey was convened. Based on results from the survey and evidence review, a discussion guide was developed to help structure the meeting to be an opportunity for respondents to elaborate on survey responses and share other perspectives on how a population health framework may impact the future of clinical trials.

The expert panel meeting was moderated by two health services researchers over a period of several hours. The panel was held on the first day of the annual Cerner Health Conference in Kansas City, Mo., and panelists were offered complimentary registration in exchange for their participation. No other compensation was provided.

RESULTS

Evidence Review

Our literature review suggests there is no clear consensus on how the extant clinical trial process can be upgraded to fit within a population health framework. However, we did identify seven trends that may influence the future of clinical trials (see Table 1):

- **Virtual Trials.** To reduce the burden of study visits, virtual trials use web services and/or telemonitoring to carry out most or all of the research. For example, in Pfizer's REMOTE trial, participants were recruited via the web, screened for eligibility using web-based questionnaires, and entered a run-in phase requiring electronic diaries.[8] Despite initial recruitment challenges, a revamped REMOTE 2.0 trial is being planned in Europe.[9] Furthermore, with increased use of smart phones and remote health monitoring devices (e.g., Fitbit activity trackers and, more recently, the Apple Watch), virtual trials may be a promising strategy.[10]
- **Genomics.** Although not a novel concept, genomics may have increasing prominence for clinical trials with the shift toward personalized medicine, which requires development of therapies and diagnostic tests targeting specific genetic characteristics.[8] Clinical trials that investigate these biomarkers generally employ innovative study designs to identify sufficient patients and capture relevant data.[11]

TABLE 1: Trends Affecting the Outlook of Clinical Trials Identified by the Evidence Review

Trend	Description
Virtual Trials	Web services and/or telemonitoring used to replace "live" study visits
Genomics	Focus on therapies and diagnostic tests targeted toward specific genetic characteristics
Contract Research Organization (CRO) Partnerships	Increased collaboration with CROs to execute complex trials
Globalization	Increased execution of trials outside Western countries
Translational Research	Improving the speed at which healthcare discoveries are applied to clinical practice
Data Analytics	Leveraging increased amount of clinical information for advanced data modeling
Crowd-Sourcing	Support of clinical trials by patient advocates or groups of patients, rather than industry sponsors

- **Contract Research Organizations (CROs).** While CROs have been utilized heavily for the last several years to execute complex trials quickly and at lower costs, study sponsors will have to collaborate with CROs in a much more strategic manner.[12] Management of the relationships between industry sponsors, CROs, and study sites will likely be increasingly dependent on real-time data and technology.[13] By leveraging their expertise and relationships, CROs may be able to execute trials more effectively and at a lower cost than industry sponsors.
- **Globalization.** According to one study, approximately one out of every three clinical trials is now being conducted in developing countries.[14] The expansion of research in these locations is due to multiple factors, including costs of trials in Western countries and challenges to accruing sufficient sample size.[15] Globalization of trials is providing these populations with an opportunity to participate in research and access therapies that would otherwise be unavailable. Additionally, this benefits research efforts by increasing the heterogeneity of study populations, allowing results to be more generalizable.
- **Translational Research.** Improving the speed at which healthcare discoveries are applied to meet clinical needs and improve patient care is a priority for the National Institutes of Health.[16] According to some estimates, the average time for an innovation in research to reach clinical practice is 17 years.[17] Given the length of time between discovery and application, investment is being made in shortening this duration.[14]
- **Data Analytics.** Advanced data modeling is required to effectively leverage the increasing amount of participant-related information that is available due to greater use of technology, especially electronic healthcare records (EHRs). For example, analytics can help researchers better define study designs and outcomes to reduce the occurrence of false negative trials.[15] Additionally, some clinical trials may be supplemented or even replaced by data collected from networked groups of patients.[8]
- **Crowd-Sourcing.** The drug development process may be increasingly influenced by patient advocates and clinical trials that are supported by groups of patients, rather than industry sponsors.[8] Often referred to as crowd-sourcing, this bottom-up approach may be especially beneficial for advancing the study of rare diseases and orphan drugs that have traditionally struggled with funding and recruitment.[18–20] Social media may be key in helping facilitate crowd-sourcing by connecting groups of people with common interests in the clinical trial process.

SURVEY FINDINGS

Respondents to the survey rated all of the trends identified in the evidence review as being at least slightly important to the future of clinical trials (see Figure 1). The most highly rated trends were also those most familiar to the panelists: genomics, data analytics, translational research, and CRO partnerships. The average importance rating was lowest for crowd-sourcing and virtual trials.

Based on results from the survey and evidence review, a discussion guide was developed to help structure the meeting to be an opportunity for respondents to elaborate on survey responses and share other perspectives on how a population health framework may impact the future of clinical trials.

FIGURE 1: In your opinion, how important are the following trends in relation to Phase III clinical trials?

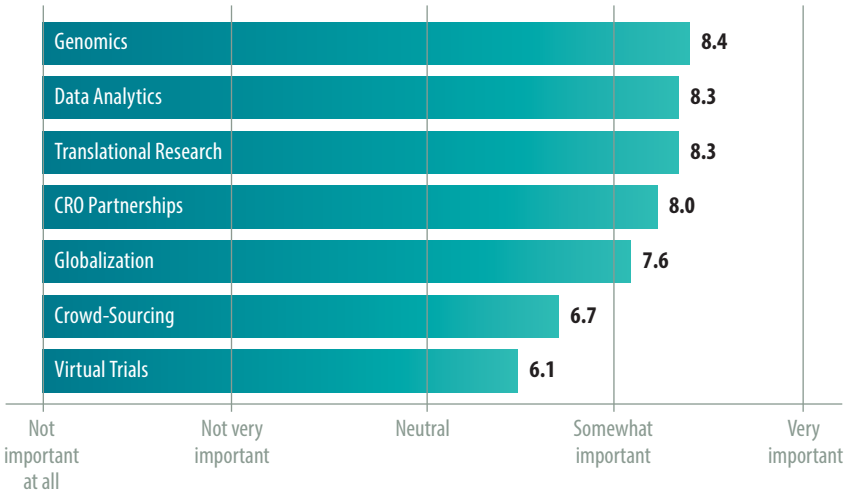
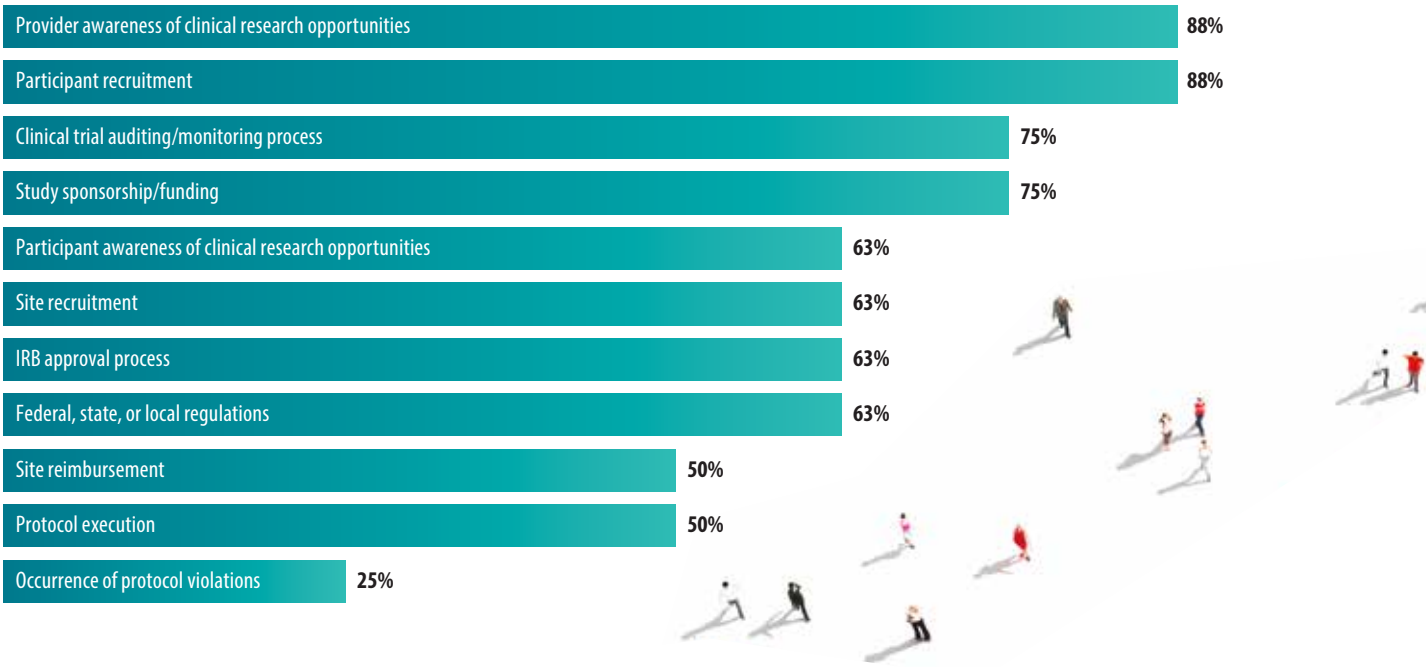


FIGURE 2: In your opinion, what aspects of Phase III clinical trials are likely to change in the next five to 10 years?



The group believed that several types of research partnerships will increase and that collaboration across sites, sponsors, and CROs will become even more essential. In addition, state, federal, and other third-party payers may have a more central role.

Respondents indicated that many aspects of the clinical trial process would change in the next five to 10 years (see Figure 2). In particular, all but one of the eight respondents signified that healthcare provider awareness of clinical research opportunities and participant recruitment would change. Other factors were also rated as likely to change, such as study sponsorship/funding (by six respondents) and institutional review board (IRB) approval process (by five respondents).

When asked what factors would influence the future conduct of clinical trials, respondents rated those related to technology as most significant (see Figure 3). Specifically, so-called "big data" usage and analytics had the highest average rating, followed by increased use of EHRs and new technology. Government legislation/regulation and healthcare reform were rated least influential.

All eight respondents indicated that privacy or other data security concerns would be barriers to changes in the clinical trial process (see Figure 4). All but one or two, respectively, also believed that lack of trial funding and regulations on clinical research were inhibiting factors. In contrast, only two rated technology adoption and access to data as barriers. Many also did not indicate the lack of awareness regarding research opportunities, by either patients or healthcare providers, to be a barrier.

EXPERT PANEL DISCUSSION

Overall, when the survey respondents were later gathered for a panel discussion, they agreed that population health will have some effect on clinical trials; however, opinions were mixed regarding the extent of impact. Although it was acknowledged that population health tools, such as outreach programs and patient dashboards, may help target specific populations, panelists indicated the population health model focuses largely on prevention and chronic conditions. Thus, it may have limited applicability for interventional trials or studies of rare diseases (although access to patient data may be used to target orphan diseases).

Findings from the evidence review were used to initiate discussion among panel members, and key findings are listed below. The group believed that several types of research partnerships will increase and that collaboration across sites, sponsors, and CROs will become even more essential. In addition, state, federal, and other third-party payers may have a more central role. Specifically, partnerships with these entities would facilitate better integration of data from multiple sources that can be leveraged for clinical trials.

Changing referral patterns may become a barrier for clinical trials. Given the emergence of accountable care organizations (ACOs) and the dynamic landscape of healthcare delivery, providers may be reluctant to share data and/or refer patients outside their own network. Thus, clinical trials may be impacted as providers become less inclined to refer patients for studies outside their network and are motivated to keep trial referrals within their organizations.

The panelists indicated new clinical trial technology may only be appropriate in specific contexts. For example, trends such as virtual trials or telehealth may be challenging for many clinical studies, especially those involving clinical or laboratory measures. Instead, these technical advances may be most beneficial in the collection of patient-reported outcomes, where participants

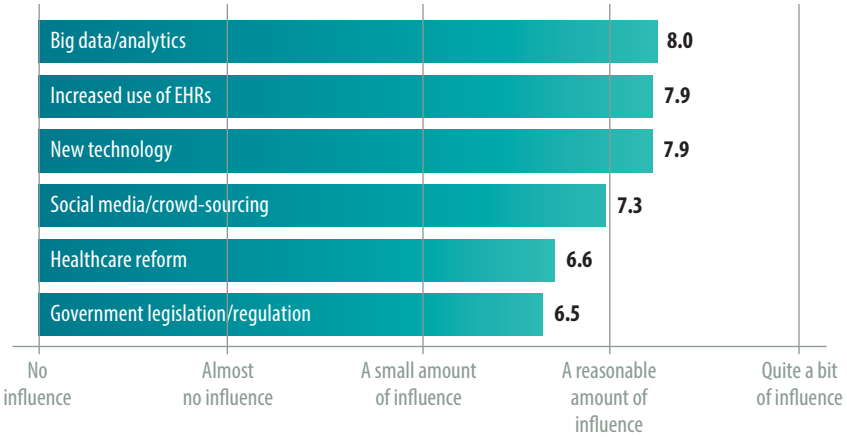
are equipped with new methods of communicating their experiences and opinions.

Leveraging technology for certain therapeutic areas and study designs holds some promise. Specifically, virtual trials may be more successful for monitoring more common and predictable conditions (e.g., diabetes), as opposed to specialty trials in areas such as oncology, which can be more complex and require more oversight. Panelists were also optimistic that technological trends, such as telehealth, could benefit rural and Medicaid populations that may otherwise lack access to clinical sites.

The panelist believed that prospective study participants will eventually be more engaged in clinical research. The concept of crowd-sourcing for clinical trials was found to be intriguing, especially as a way to gauge participation interest. Specifically, social media may also increase public awareness of, and attraction to, clinical trials, especially in terms of online patient communities that connect visitors for education and support.

The shift toward patient-centered care has implications for clinical trials. Panelists suggested that trials should also focus on individuals' health goals and autonomy. The increased use of technology across the general population is also improving how participants can access information and make more informed healthcare decisions.

FIGURE 3: In your opinion, how much influence will each of the following have on the conduct of Phase III clinical trials in the next five to 10 years?

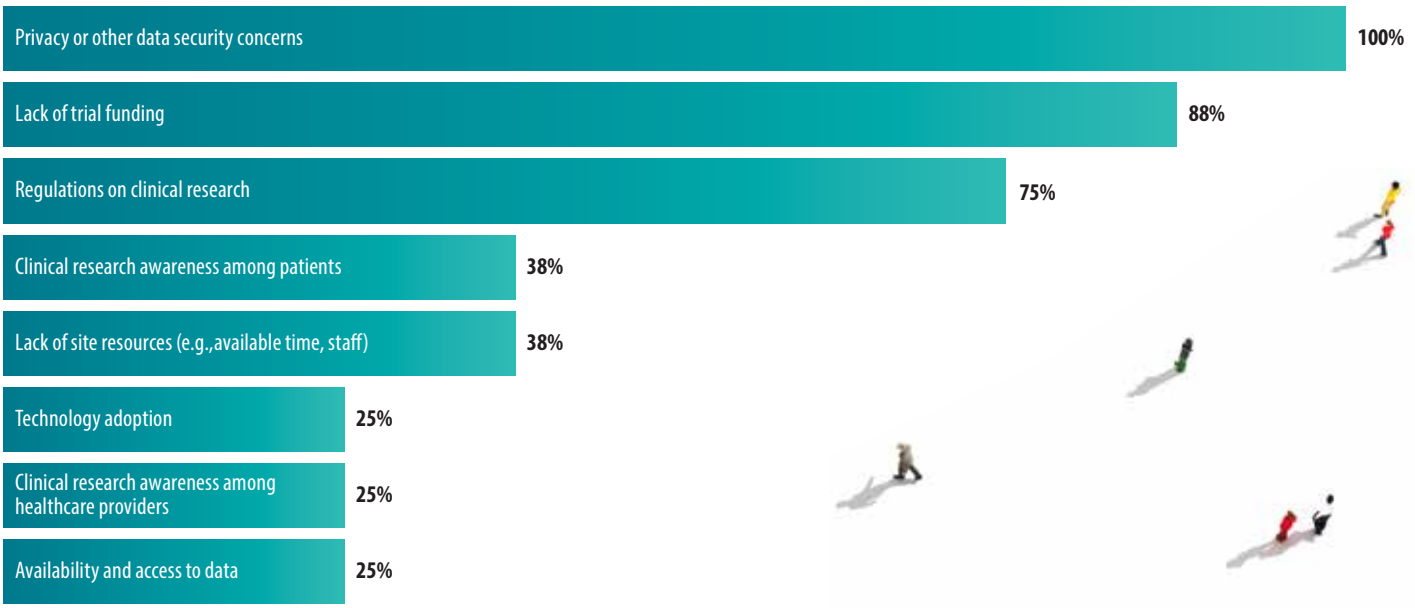


Although big data could benefit clinical trials, there are obstacles worth noting. As ACOs become more prevalent, more complex and voluminous data will be available for research purposes. However, fully leveraging this information requires a workforce capable of managing large datasets and performing sophisticated analyses. Furthermore, the integration of multiple data sources presents other challenges, such as those to data governance and quality control efforts.

CONCLUSION

The findings of our multifaceted exploration suggest changes associated with the population health framework will impact clinical trials in the next decade, and that there is an opportunity to

FIGURE 4: Which of the following are likely to inhibit changes in Phase III clinical trials in the next five to 10 years?



leverage these concepts toward the evolution of the clinical trial process. However, instead of widespread change, our findings suggest clinical trials will advance in a piecemeal fashion, with new approaches implemented only under the right circumstances; that is, for specific study outcomes, therapeutic areas, and target populations.

It is very likely that the shift toward population health will result in greater use of technology, an abundance of data on research participants, and novel approaches to executing clinical trials. While some of these trends are already in practice, further advancement requires an improved ability to leverage big data, sufficient numbers of skilled personnel, and a reimagined approach to ensuring participant protections and regulatory requirements. In this regard, an increase in collaborative partnerships across various stakeholders is likely to occur as researchers consider how to apply concepts from population health management toward innovations in the clinical trial process.

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"I have worked in research and development for 14 years. I've been certified for 10 years. I am so proud to be an associated with ACRP. I will be recognized by ACRP this year for 10 years of excellence."

I am happy to say that I love my job. I have had the chance to offer people/patients help through research that was not offered to the general public–therapies and treatment that have made a difference in so many lives.

The fact that I have had the opportunity to do work in this area of medicine is life-changing and rewarding. To know that if someone has had an improved quality of life due to the diligence of a career in research is rewarding. I have encouraged many of my coworkers to strive for excellence in becoming certified. My career has helped someone enjoy life that would have not been possible if not for their participation in a clinical trial.

Ten Years Have Got Behind Me

Gary W. Cramer

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

Celebrating my 10th anniversary on the job for ACRP at right about the same time as the Association hits its 40th anniversary has been filling my recent days with both melancholy and excitement. It makes me think of the words from "Time," a favorite Pink Floyd song: "And then one day you'll find/ten years have got behind you/ no one told you when to run/you missed the starting gun."

First, the melancholy. When I arrived on staff as a writer/editor for ACRP in February 2006, the April issue of *Clinical Researcher*'s predecessor, *The Monitor,* was being prepared in parallel with a special issue celebrating the Association's 30th anniversary. My previous few jobs had given me plenty of layperson's knowledge for writing about the work of landscape architecture professionals for a nonprofit devoted to that population, and about trends in teaching, research, and service in a higher education setting… but most certainly not about clinical research.

At first, it seemed that I would be spending most of my time putting together the *Wire* e-newsletter; writing and editing other communications for the Association; and spending "some" time copy-editing materials for the journal, which was just transitioning from publication on a quarterly to a bimonthly basis. However, with changes in personnel and in the Association's needs, the priority level of those three arenas soon got spun around nearly 180 degrees, such that, as of this 40th anniversary issue going to press, I have now been involved very closely indeed in the production of 68 straight issues of the journal. Along the way, members of the staff editorial team and the all-volunteer Editorial Advisory Board have strengthened the journal's peer-review processes and scholarly contents, adapted to new technologies for its print production and digital presentation, won some satisfying publication industry awards, and, most recently, overseen its complete renovation, rebranding, and renaming.

There's no denying that I've learned a lot about a field of research that was a total mystery to me prior to 2006. Even from the vantage point of someone who's never worked on a trial, I've come to admire anyone who devotes himself or herself to the myriad tasks that make up the ethical, responsible conduct of clinical research—both on the patient and provider sides of the research team. Among many others tied historically to the Association, I wish to thank former Editors-in-Chief Sharada Gilkey and A. Veronica (Ronnie) Precup and former Director of Marketing & Communications/current Director of Business Development Jenna Rouse for bringing me into the organization in the first place, and for their guidance and support as I grew in my role and responsibilities for ACRP.

Now for the excitement. Knowing that this issue will be unveiled during the ACRP 2016 Meeting & Expo in Atlanta, Ga. also sends my thoughts back to all the great experiences I've had because of the people I've met at the various annual conferences to which I was sent as a staff assistant. Many of those

Even from the vantage point of someone who's never worked on a trial, I've come to admire anyone who devotes himself or herself to the myriad tasks that make up the ethical, responsible conduct of clinical research—both on the patient and provider sides of the research team.

days in Boston, Denver, Tampa, Orlando, and San Antonio remain highlights of my career when I think of what we have and can accomplish together for the good of patients and their families everywhere through education and networking. I look forward to all the good things that will happen in Atlanta and beyond, after we attendees have returned to the far corners of the globe, refreshed and reinvigorated for tackling the challenges this great enterprise brings us, and ready to share that excitement with colleagues, clients, patients, and members wherever we encounter them.

Speaking of challenges, I wish I could think of some truly uplifting Pink Floyd lyrics to help close this with, but as much as it's my number one band, its catalog can be a bit depressing. So, as someone whose musical tastes have largely been fossilized since the mid-1980s, I'll turn to Howard Jones with his "Things Can Only Get Better" for inspiration: "Future dreams we have to realize/a thousand skeptic hands won't keep us from the things we plan/unless we're clinging to the things we prize."

With stacks of a decade's worth of journal issues threatening to swamp me and blocking the view from my desk of the Potomac River as it flows by the ACRP headquarters, I am happy to say that the next 10 years…the next 40 years…and beyond are looking bright.

Michael R. Hamrell, PhD, RAC, FRAPS, RQAP-GCP, CCRA

[DOI: 10.14524/CR-16-4008]

A Look Back on the Development of **Good Clinical Practice**

As we celebrate the 40th anniversary of ACRP, I thought it would be good to reflect back on the changes in tone and direction that have happened in the realm of good clinical practice (GCP)—the international quality standard for the conduct of clinical trials—over the past 40 years and more.

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A lot of significant regulations and rules have come into effect, going back at least into the 1970s.

In 1974, then-President Ford created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission was charged with making recommendations to the federal government regarding policies and rules needed to enforce human subject protection in the United States. This was a result of the fallout from the recent revelations in 1972 regarding the infamous Tuskegee study, launched in 1932, in which African American men identified as having syphilis by U.S. Public Health Service researchers were left untreated so that the natural history of the disease might be observed.

Based on the work of the National Commission, the Department of Health and Human Services revised and expanded its regulations for the protection of human subjects found in 45 CFR part 46 in the *Code of Federal Regulations* in the late 1970s and early 1980s.

In 1978, the commission's report on "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" was published. It was named the Belmont Report, for the Belmont Conference Center, where the National Commission met when first drafting the report. The Belmont Report explained the unifying ethical principles that form the basis for the commission's topic-specific reports and the regulations that incorporate its recommendations.

So, in 1976 at the birth of ACRP (then called the Associates of Clinical Pharmacology), none of the specific regulations regarding institutional review boards and informed consent that we deal with today (21 CFR §50, §56 and 45 CFR §46) were in place.

Progress, at a Slow Pace

In fact, in 1976, there were elements of GCP described in the Investigational New Drug regulations in 21 CFR §312, but no single source of information on what constituted GCP.

Furthermore, in 1977 and 1978, the U.S. Food and Drug Administration proposed regulations on obligations of sponsors, monitors, and the role of clinical investigators (in 21 CFR parts 52 and 54). These regulations were never finalized, and were withdrawn from consideration. It was not until nearly 20 years later, in 1996, that the International Conference on Harmonization came out with its consolidated guidance on GCP.

Monitoring of studies was a person-intense, paper-based process in the 1970s, and progress is still slow to come in some aspects of the profession. Certainly, communication regarding GCP, regulatory compliance, and study oversight was a lot different before the advent of personal computers, the Internet, cell phones, smart phones, e-mail, texting, Twitter, Pinterest, Facebook, and so on. Even the fax machine was not a common tool 40 years ago.

What hasn't changed over time is that much of the progress seen in the clinical research enterprise results from a shared collaboration involving the study volunteers, sponsors, medical staff, vendors, consultants, and more who together constitute the research team. However, in 1976, we did not really have contract research organizations, central labs, electronic case report forms, or many other kinds of resources, tools, and relationships that today are integral parts of clinical research. We also did not have regulations regarding privacy of medical records (e.g., the Health Insurance Portability and Accountability Act), and our understanding and reporting of adverse events was very different than today.

So, as we think back about the history of ACRP specifically, and clinical research as a whole, it is important to consider how far we have come in regulating and managing subject protection and clinical research.

RESEARCH COMPLIANCE

Brent Ibata, PhD, JD, MPH, FACHE, RAC, CCRC, CPI, CHRC

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Intellectual Property—*Protecting Patents, Trademarks, Copyrights, and Trade Secrets*

Among the enumerated powers granted to the federal government by the U.S. Constitution is the power to "promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."[1]

Intellectual property rights balance the incentive for innovative thought and creative expression with the greatest public access to the writings and discoveries that result. The form and function of the intellectual property determine the manner and duration that it may be protected. Inventors are issued patents that are generally good for 20 years. Authors and artists get copyrights that survive for the lifetime of the creator plus 70 years. Trademarks and trade secrets can theoretically last forever.

INTELLECTUAL PROPERTY

Property can be used and owned to the exclusion of others. Property includes both real property (land and buildings) and personal property (tangible and intangible). Tangible personal property can be thought of as property that you can carry in your hands, and intangible personal property you must carry in your head. Intellectual property is a sub-category of the broad category of property.

Intellectual property is usually distinct from the tangible forms of property in which it is embodied. For example, Thomas Edison's patent for a light bulb protects the design for the light bulb, and not the tangible form of the bulb that he fully intended to sell. Intellectual property is defined as the "commercially valuable product of the human intellect, in a concrete or abstract form, such as a copyrightable work, a protectable trademark, a patentable invention, or a trade secret."[2]

Intellectual property includes innovative machines, creative forms of visual and performance arts, business names and their associated good will, secret recipes, and the distinctive packaging of popular products that distinguish one from another (see Table 1). Intellectual property rights are given to the inventors, writers, and artists in exchange for their creativity and hard work. Once most forms of intellectual property are placed into commerce, their expiration dates are set.

PATENTS

There have been millions of patents granted since George Washington signed the first one in 1790. Patents are generally placed into two categories: for processes or for product. A process patent describes a "series of acts performed in order to produce a given result," while a product patent claims tangible objects and typically consist of "machines, manufacturers, or compositions of matter."[3]

TABLE 1: Intellectual Property Laws

Type	Short Title	Reference
Copyright	Copyright Act	17 U.S.C. §§ 101-1332
Patent	Patent Act	35 U.S.C. §§ 1-390
Trademark	Lanham Act	15 U.S.C. 1127
Trade Secret	Economic Espionage Act	18 U.S.C. §§ 1831-1839

Brent Ibata, PhD, JD, MPH, FACHE, RAC, CCRC, CPI, CHRC

Intellectual property rights balance the incentive for innovative thought and creative expression with the greatest public access to the writings and discoveries that result.

Section 101 of the Patent Act defines to inventors those inventions eligible for a patent:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.[4]

There are two conditions of patentability for an invention to be eligible for a patent protection: the invention must be novel (§ 102 of the Patent Act) and it must be non-obvious (§ 103 of the Patent Act). Generally, an invention that is known by others, used by others, or described in a printed publication more than one year prior to the filing of a patent application is not considered novel.

COPYRIGHTS

Section 102 of the Copyright Act defines those forms of creative expression that are eligible for copyright protections:

> Copyright protection subsists, in accordance with this title, in original works of authorship fixed in any tangible medium of expression, now known or later developed, from which they can be perceived, reproduced, or otherwise communicated, either directly or with the aid of a machine or device. Works of authorship include the following categories: (1) literary works; (2) musical works, including any accompanying words; (3) dramatic works, including any accompanying music; (4) pantomimes and choreographic works; (5) pictorial, graphic, and sculptural works; (6) motion pictures and other audiovisual works; (7) sound recordings; and (8) architectural works.[5]

The essential elements of a copyrightable work are that it must be original and it must be fixed. To be original, a work must have a modicum of creativity and not be just a copy of another's work.[6] To be fixed, "the work has to be written down, taped, filmed, or otherwise captured in some way before federal copyright protection can attach."[7]

It is a common misconception that registration and deposit of a work is a condition of obtaining a copyright. The ownership of a copyright "arises immediately upon the creation of a work, without the necessity of any governmental examination or approval."[8] Registering and depositing a work increases the ability to prove infringement—much like inventorying your personal property increases the ability to prove theft—but does little to prevent theft.

TRADEMARKS

The purpose of trademark law is to ensure that consumers can identify the source of an item or service and distinguish one source from another when they seek to purchase an item or service from one particular producer over any others. Reputation and goodwill have limited value if competitors could use the same or similar trademarks or trade dress with abandon.

A trademark includes any word, name, symbol, device, or combination thereof that is used to identify and distinguish one source of goods from those manufactured or sold by others.[9] Words, names, symbols, or devices must be distinctive before they can be recognized and protected as trademarks. For example, you cannot trademark the word "hamburger" to describe a ground beef sandwich, but you could use the name of a fruit to describe a personal computer.

Trade dress is how manufacturers package and design products with a combination of colors, designs, and graphics to distinguish their products from those of competitors. Trade dress is a form of a trademark, and may be protected if the product or packaging attributes are distinctive and non-functional (not essential to the use, purpose, cost, or quality).[10] A common example of protected trade dress is the use of pink coloring to distinguish one manufacturer of insulation materials from another.

TRADE SECRETS

Trade secrets can be the most valuable forms of intellectual property, and the most difficult to protect. A trade secret is not protected by filing an application with a governmental agency—it is protected as long as the holder acts in a manner to keep it a secret. A trade secret's value lies in the fact that it does not have a statutory expiration date where it becomes part of the public domain. Therefore, a well-kept trade secret can theoretically last forever. However, the holder of the trade secret must continuously use reasonable efforts to maintain its secrecy to maintain the claim of a trade secret.

Well-crafted confidentiality clauses in employment contracts and clinical trial agreements allow sharing of trade secrets in the ordinary course of business without forfeiting valuable intellectual property rights.

CONCLUSION

To bring all of the above into the realm of clinical research, a well-crafted clinical trial agreement protects the intellectual property rights of the parties engaged in the research. The disclosure and assignment of intellectual property rights of inventions derived from access to another party's confidential information should be clearly defined, especially when there are joint-ownership arrangements for inventions made by one party due to access to another party's trade secrets or confidential information.

Publication clauses in clinical trial agreements should allow for time to file for patent protection to preserve the novelty of a potential patent that arises during a trial. Well-crafted confidentiality clauses in employment contracts and clinical trial agreements allow sharing of trade secrets in the ordinary course of business without forfeiting valuable intellectual property rights. Timely progress from patent to market launch can only be achieved when intellectual property rights are understood, protected, and respected.

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Martin Robinson, PhD

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Forty Years in the Making—*The Remote Manager*

Forty years ago, ACRP was born, and at that time the world was a different place. In 1976, I was working in my first job in the pharmaceutical industry. I was employed in Pfizer's research and development facility for the United Kingdom, in the town of Sandwich. At the risk of sounding like a living exhibit from a museum, we kept hand-written notebooks, submitted hand-written reports, and communicated with each other by speaking face-to-face or by telephone, fax, and letter…and that was it.

I don't remember attending a single teleconference with people from another European office, and phone calls with the U.S. were an exotic activity, presumably exclusive to only the uppermost echelons of management.

The one and only laboratory computer was an imposing piece of work the size of a large row of filing cabinets, and it came equipped with an impressive array of toggle switches and flashing lights. Two computer specialists (the expression IT was still to be invented) were the sole operators, and no one else was allowed near it.

Members of the team to which I belonged were all located in the same group of offices, and my line manager sat a few desks away. We had regular meetings (all face-to-face), exchanged paperwork, and filed reports. Somehow the world worked, but looking back it is hard to imagine how, given what we can do today.

(Almost) Everything Must Change

Naturally, technology has moved on, and this has enabled an increasing number of people, including line managers, to work from home. Welcome to the advent of the remote manager. (Some managers could be "remote" in 1976, but that was more to do with a sense of aloofness!)

Remote management has several advantages:

- People don't need to relocate when changing jobs, and can chose to work in a picturesque, rural setting far away from industrial conurbations.
- There is no daily commute with all the stress that it brings and the hours that it adds to the day.
- People can manage global teams and can choose, to some extent, how they organize their hours in a day, away from the straightjacket of a "9 to 5" routine.
- Remote working is also advantageous in that businesses can reduce costs by not having to rent or buy large amounts of expensive office space.

Although technology has changed our expectations out of all recognition, allowing us to communicate pretty much with anyone at any time anywhere in the world, human nature has not evolved in 40 years. We still like to feel valued, still need someone

Although technology has changed our expectations out of all recognition, allowing us to communicate pretty much with anyone at any time anywhere in the world, human nature has not evolved in 40 years.

for a spontaneous conversation when we have a bright idea or when trouble strikes, or just to have a person nearby with whom to share a joke.

How to Compensate for Remoteness

We still need the team camaraderie that comes from working in the same location. So if you are a remote manager, what are some of the things you can do to compensate for these missing pieces?

1. Set up weekly one-to-ones with each team member. Make sure to set aside enough time for each person and respect time zones. Be flexible and take turns with team members in time zones with large differences (e.g., more than eight hours) from your own to speak in each other's "normal working hours." Ensure you make time to give each team member the big picture and discuss with them how their goals and objectives fit into the wider context. Avoid postponing and changing the times of one-to-ones unless absolutely necessary; it can be demotivating for your team members if their weekly catch-ups are constantly being rearranged.
2. Use video wherever possible. Various pieces of research have shown that more than 50% of communication is nonverbal. You and your team members will be in a much better position to gauge each other's' reactions. Seeing each other also helps build rapport. There are a number of free or inexpensive video platforms available.
3. Work extra hard at building rapport with each individual team member. This will help when it comes to problem solving or getting a piece of urgent work done. Take time for a bit of small talk at the start of a call with a team member. Naturally, in circumstances where there is a crisis or a major challenge, then a bit of social chit-chat may have to be set aside.
4. Avoid overuse of e-mail. It is easy to get into the habit of sitting all day at your computer writing and firing off messages. Instead, pick up the phone or make a video call. If you do need to write an e-mail, make sure the message is succinct and clear. Use warmth and humor where appropriate.
5. Let your team know on a weekly basis the windows of time when you will be available for them to call you if they have an issue a question or need advice. Make sure you keep this availability calendar up to date if it changes during the week.
6. One of the hardest things for a remote manager is gauging each team member's workload. Make sure you spend enough time getting a good picture for whether a person is overloaded or under-utilized. Take time to agree on priorities and set goals. It is very important to trust remote team members. Micromanaging can be very demotivating for the team and exhausting for the manager, so avoid it.
7. Make sure you show appreciation for team members when they have done outstanding work. A thank you goes a long way.
8. Make technology work for you. There are a number of cloud-based project management platforms that can be used to share documents, exchange ideas, and track progress. Sometimes, team chatrooms can be helpful in sharing information and facilitating team discussions.
9. If it is at all possible and there is the budget for it, try and get the team together physically in the same place, even if it is only once a year. It is remarkable how meeting face-to-face makes people warm to each other and makes future communication and teamwork so much easier.

Conclusion

Remote workforces were nearly unthinkable even 20 years ago. With all the advantages that technology can bring, it remains important that it be used wisely. There must be an adequate trade-off between the benefits of remote management in cost saving and having a flexible, global workforce versus the drawbacks of lack of face-to-face communication and interaction. By implementing good remote management practice, you can build a cohesive, motivated, and productive team.

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Bonnie Miller's recipe for success begins with hard work, risk-taking, and a heaping scoop of good humor

This global and dynamic field includes constantly changing regulations, laws, economies, science, medicine, technology, and medical needs. It's rich with opportunities and roles for both newly transitioning professionals and those already in the field.

Q: Please share a bit about your background—when did you first became interested in research and what brought you to your current position?

A: Years ago, during my ADN training, I collected data from medical charts for a prenatal nutrition study. Later, my staff nursing career exposed me to clinical trials. I also earned a certificate in business management and participated in a university program teaching research methods to nurses while working and earning my BSN.

While completing a master's in nursing administration studies, I held research assistant jobs for behavioral studies, worked as study coordinator, and contributed to a proposed model for staff nurse compensation framework linked to practice excellence, experience, and education. This was published in a nursing journal.

After graduation, I had lunch with a study buddy who managed a hospital clinical research unit and a clinical research associate (CRA) who was monitoring one of the trials. Next thing I knew, I was at the library looking up clinical research, and then on a plane to interview with a pharmaceutical company for a CRA position. I didn't end up working for that company, but did attend a study coordinator networking meeting soon after, and was hired as a CRA in the local office of a global contract research organization.

My key expertise is in clinical operations, good clinical practices, standard operating procedures, infrastructure, training, and mentoring. I have held a variety of traditional and newly created roles with biotech, pharma, and device sponsors, as well as with vendors, a medical center, and educational institutions.

I was encouraged by a mentor to earn a Training Certificate, and awhile back I partnered with a local university to build a clinical trials certificate program. I continue to teach part-time in two local university hybrid online/classroom clinical research certificate programs. This is important to me, because not only do I love to teach and teaching keeps me on my toes, but I'm investing in the next generation.

I'm also a study subject as a long-term participant in the Nurses' Health Study and a few genomic sampling studies. These experiences provide an important perspective to me when writing or reviewing an informed consent form, and for personalizing the value of study participation to the potential benefit of others.

Q: How about your involvement in ACRP? When did you first get involved, and what type of benefits have you reaped from being a member? What about your involvement with the local chapter? How has this affected you professionally?

A: ACRP is my primary professional affiliation because it offers the most opportunities at local and global levels. These include maintaining my knowledge in this fast-changing field, building my career, contributing to the course of the profession, developing long-lasting friendships and professional relationships with experts, and having a lot of fun.

I began attending my local Northern California Chapter events several years ago, volunteered on committees, agreed to a three-year succession plan as vice president with the current president, and I'm now in my third and final two-year term as president.

I have also contributed at the global level to ACRP's mission, including on the Professional Development Committee, for which I led the "CRA Pathways" working group. We also mapped the professional development offerings for target level of expertise. I was on the first and then last year's updated version of panel webinars on "Entering the Clinical Research Field," as well as part of last year's "Experienced Clinical Researchers—What is Next in Your Career Growth?" webinar, both available as free replays.

I just completed my third and final year leading the Chapter Chairs/Presidents group, and now serve on the Chapters Advisory Committee. This role collaborates with ACRP staff and Chapter leaders to align and support the work being done on various strategic goals.

Q: What advice do you have for clinical research professionals in terms of how to advance their careers, and what do you see as currently being the biggest challenge for clinical research professionals? Any advice on how to approach or overcome barriers?

A: This global and dynamic field includes constantly changing regulations, laws, economies, science, medicine, technology, and medical needs. It's rich with opportunities and roles for both newly transitioning professionals and those already in the field.

At intervals, assess your current path to benchmark, confirm, or recalibrate it to meet your goals. Assess your direct or transferrable skills and experience and what your comfort/risk zone is, consider where you'd like to be in the future, and research the opportunities and what's needed to get there. Identify your target work and consider creating the job to fit an unmet need and how you can fill it.

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

A: The best advice I can give someone is to always stay connected to what is going on outside his or her current role. What I mean by that is, no matter how happy you are in your career, I believe you should continue to educate and network and to stay close to the world beyond your immediate job duties.

The best place to start, in my opinion, is ACRP! Read the *Clinical Researcher,* sign up for events, volunteer. I work very closely with employers in this industry, and very often they are interested in what candidates are doing to better themselves OUTSIDE the workplace. Of course, it does not hurt to get to know a variety of people, and ACRP events offer up a fantastic opportunity to network and learn about people and the jobs they do.

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

A: I'm doing exactly what I need to be doing right now. I enjoy working with bright, funny, and kind colleagues to investigate meeting unmet medical needs and contribute to better quality of life or cures for patients; and to train the next generation to continue the mission.

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

A: I suggest the following:

- Keep the end in mind. The purpose of clinical research is to meet unmet medical needs, contribute to better quality of life or cures for patients, and always to preserve patients' safety, rights, and welfare. I'm proud to have contributed to products that were approved and today meet previously unmet medical needs.
- Join and contribute to your professional organization for benefits beyond what you can anticipate.
- Stay agile and flexible in your career by networking and being a lifelong learner.

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- We do whatever is necessary to accommodate our subjects' school and/or work schedule, which maximizes compliance and retention.
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