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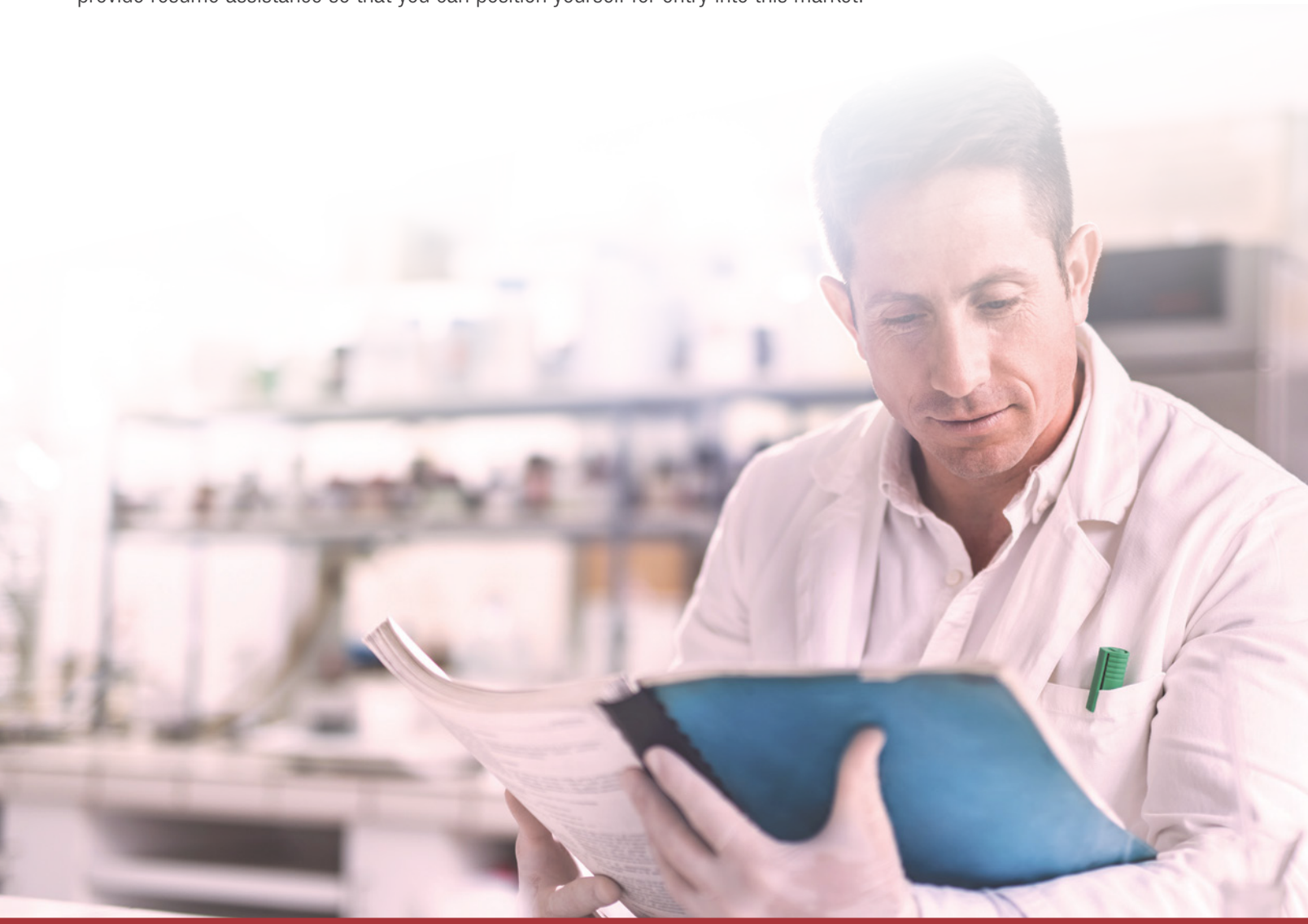


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IN MEMORIAM

ACRP Mourns Passing of Margaret F. Fay, PhD, RN, CCRC, Board of Trustees Member

The Association of Clinical Research Professionals (ACRP) was saddened by the passing in August of Margaret ("Peggy") F. Fay, PhD, RN, CCRC, Board of Trustees Member.

Dr. Fay was appointed to the Association Board of Trustees in June 2016. She was also the 2015 recipient of ACRP's Innovation in Clinical Research Award.

"Peggy was a pioneer in the world of clinical research and was personally dedicated to ACRP's mission," said ACRP Executive Director Jim Kremidas. "Her creativity and expertise were assets to our Board of Trustees. She will be missed by the industry and the many who loved her."

Dr. Fay has more than 38 years of progressive research and management experience in academic, hospital, corporate, and independently owned research site organizations. She served as a clinical study coordinator, an auditor for human and animal research, a clinical research associate, medical liaison, site director, and researcher.

In her most recent role as Global Director, Clinical Research Monitor for Medtronic, Peggy was responsible for 220 research professionals serving 10 individual businesses, and more than 400 clinical trials across the globe. She was a consultant to the research industry and served as an advisor, content expert, and medical writer for various pharmaceutical and medical device companies. She is the inventor of four patents, two in the area of micro current technology and two in the field of risk-based clinical trial conduct.

ACRP

FOR LEARNING FOR LISTENING FOR LIFE

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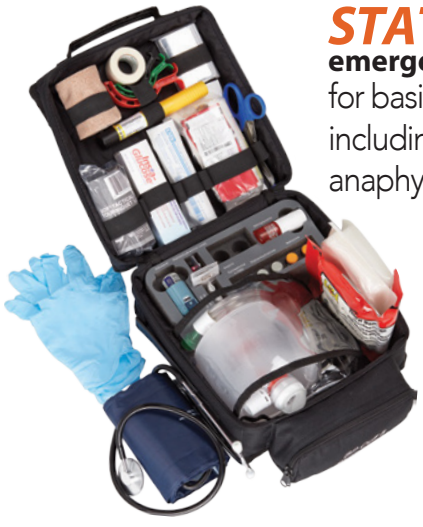

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GUEST EDITOR'S MESSAGE

Glenda Guest, CCRA, RQAP-GCP, TIACR

[DOI: 10.14524/CR-17-4039]

Regulations and Compliance: *The Climb is Worth It*

I admit it. Over the span of more than 20 years as a clinical research professional, I have become what I affectionately refer to as a "Regulatory Geek." While I learned the criticality of compliance with regulatory requirements early in my career as a research monitor, my appreciation and understanding of the concept evolved as I progressed through the ranks to my current role, which is focused on specialty auditing and advanced training. My volunteer efforts on behalf of the clinical research enterprise via my involvement with ACRP have also broadened my regulatory perspective.

I believe that there are more similarities than differences in the conduct of research, whether it is a drug or a device product, or a U.S.-based study versus one conducted outside the U.S.

When I joined ACRP's Regulatory Affairs Committee several years ago, I had no idea how much it would impact my career and my desire to see global regulatory harmonization become a reality. Those who know me via my volunteer efforts for ACRP recognize my passion for standardization and harmonization. I believe that there are more similarities than differences in the conduct of research, whether it is a drug or a device product, or a U.S.-based study versus one conducted outside the U.S. Embracing this assumption enables one to focus on the critical differences, while maximizing the similarities via efforts at standardization and harmonization.

Seeing these efforts through to completion in the form of regulations and compliance expectations that benefit the entirety of our global enterprise can often seem like a long and uphill struggle, but the climb is worth it.

In Search of Harmony

One arena in which to observe this could be the standardization of select case report forms (CRFs). For example, nearly all studies require the collection of concomitant medication data. Can we not use a standard form for all studies—omitting those fields not necessary for our product—rather than requiring sites/monitors/data management teams to accommodate slight study-specific differences with a completely different layout and form for each type of product and each sponsor?

Adoption of a standard form, with some fields "not applicable" for certain studies, would very likely foster greater accuracy, less missing data, and fewer queries, which equates to saved time and costs associated with query resolution. Even if the industry were to accept just two such CRFs (Drug Concomitant Medications and Device Concomitant Medications), it would be a step in the right direction.

As the world becomes a more global marketplace, it seems logical to me that harmonization of global regulatory requirements would be a natural evolution, as well. Cross-country acceptance of product approval data with fewer requirements for "country-specific" studies, other than those designed to address population-specific product interactions, could reduce burdens on both industry and regulatory authorities around the globe. As you will appreciate from the contents of this issue, it is rewarding to see recent progress in this area.

As the world becomes a more global marketplace, it seems logical to me that harmonization of global regulatory requirements would be a natural evolution, as well.

What's Ahead…

The International Council for Harmonization (ICH) E6 Good Clinical Practice (GCP) Guideline is a good example of a global harmonization effort. As a widely accepted global standard, the guideline has resulted in increased global harmonization for decades, and the recent, much-needed E6(R2) Addendum addresses global trends of risk-based oversight as well as technological evolution of data recording methods around the world.

While ICH E6(R2) has yet to be formally adopted by the U.S. Food and Drug Administration as of this writing, and though it will remain a "guidance" rather than a "regulation" in the U.S., this standard IS the regulatory expectation in many countries around the world. Jan S. Peterson's article in this issue about getting onboard with these revisions clearly demonstrates the hurdles to identifying a harmonized path, and yet the desirability of such a path as noted in the ever-expanding number of countries endorsing the E6(R2) Guideline.

Also in this issue, Miguel A. Willis shares an update on medical device clinical research in Latin America, and points out that although the leading countries in the region still have divergent clinical trial procedures, ICH GCP is deeply incorporated in the requirements and other standards (such as ISO 14155) are quickly adopted.

Next, Norbert Clemens' article describing the changes and challenges of the European Union Medical Device Regulation, which is to transition into full force by May 26, 2020, is exciting with regard to harmonization because of the possibility for submission of a single application for a clinical investigation involving multiple Member States established by 2027. Additionally, the requirement for Unique Device Identification (UDI) similar to U.S. requirements should enable better global oversight of device performance, monitoring of adverse experiences, and identification of safety trends in devices of a similar type, which reaches beyond the borders of (and databases of) any one country or region.

Nadina Jose, Roshan Padbidri, and Suzette Cody address a topic of growing interest in the research community as well, regarding how we detect, correct, and improve our risk-based decisions when unanticipated risks occur. Their "Tale of Two Studies" informs us of issues and outcomes from unanticipated and unmitigated risks, some of which appear to have been exasperated by a reduced monitoring frequency approach (e.g., risk-based decision to reduce onsite visits).

These authors also touch on one of the cornerstones to quality and risk reduction—workforce development. As we shift from 100% source data verification and frequent face-to-face interaction with a site team to a more targeted and less frequent approach to monitoring visits, we need to modernize old training paradigms. Reduced "face time," coupled with increased reliance on technology, will require changing attitudes, refocusing on standardized training, increasing reliance on utilizing technology-savvy resources, and modernizing old training paradigms to ensure a well-prepared workforce performs in a quality manner.

Meanwhile, the absence of consistent, competency-based training for all members of the clinical research team is cited as a barrier in clinical trial conduct by Linda S. Behar-Horenstein, Wajeeh Bajwa, H. Robert Kolb, and Alyona Pridhidko in their article on "A Mixed Method Approach to Assessing Good Clinical Practice Computerized Online Learning."

This concept is further brought home by Kelly Cairns in her article regarding the role of obtaining *and maintaining* certification as a marker of workforce quality. I would like to stress the fact that ACRP Certification is an ongoing process, and that achieving it is not easy; that is why, as a hiring manager, ACRP Certification is valuable beyond all others I have seen.

However, one must maintain his or her certification in order to claim the credential. I consider this requirement a compliance issue. Whether you are a CPI®, CCRC®, or CCRA®, or you obtain the newest "non-role based" ACRP Certified Professional (ACRP-CP®) designation, if you claim ACRP Certification because you once achieved it, you are falsely representing your credentials if you continue to use the designation without having *maintained* it. I have cited this during audits and I have a reason for doing so; maintenance involves continually learning and updating your skills.

In this ever-changing global environment, we need to keep current. Certification is a symbol of baseline quality to me, and maintenance is an assurance of ongoing efforts to remain current with trends and best practices, as well as the changing regulatory environment.

Conclusion

It has been an honor and pleasure to work with my colleagues in research in preparing this issue for you, and I hope you find the information helpful.

Glenda Guest, CCRA, RQAP-GCP, TIACR, (gmg@ncra.com) is vice president of NCRA (Norwich Clinical Research Associates, Inc.) in New York, a member of the Association Board of Trustees for ACRP, and former chair of the ACRP Regulatory Affairs Committee.

EXECUTIVE DIRECTOR'S MESSAGE
Jim Kremidas

[DOI: 10.14524/CR-17-4040]

Stop the Presses! We've Got Exciting News!

Jim Kremidas (jkremidas@acrpnet.org) is the Executive Director of ACRP.

You are holding the final printed issue of *Clinical Researcher.* As an ACRP Member, you will continue receiving the articles, columns, and peer-reviewed content you so highly value; but starting with the December issue, we are enhancing the journal to make it more relevant to your needs today.

Here's Why…

We are building community in clinical research by providing platforms to foster the exchange of ideas and information among clinical research professionals.

The clinical research community has long relied on *Clinical Researcher,* and *The Monitor* before it, as the go-to resource for community perspectives, innovative ideas, best practices, and beyond.

However, we can do more. We can do more to help you keep pace with the rapid evolution in the clinical research enterprise by evolving ourselves—by providing you with the content you value more often and more quickly.

Our goal is to continue building the competencies needed by the clinical research community and keep you informed through an enhanced *Clinical Researcher* that provides faster updates on changes affecting you, the ability to dive deeper into any given topic, and greater opportunities for interactivity, engagement, and dialogue. We can only capitalize on this opportunity by embracing the digital tools available today and into the future.

With this change, we are positioned to bring you more content at a faster pace; you will be connected with more voices from the field, more insights and perspectives, and more regulatory developments, news, and trends impacting clinical trials.

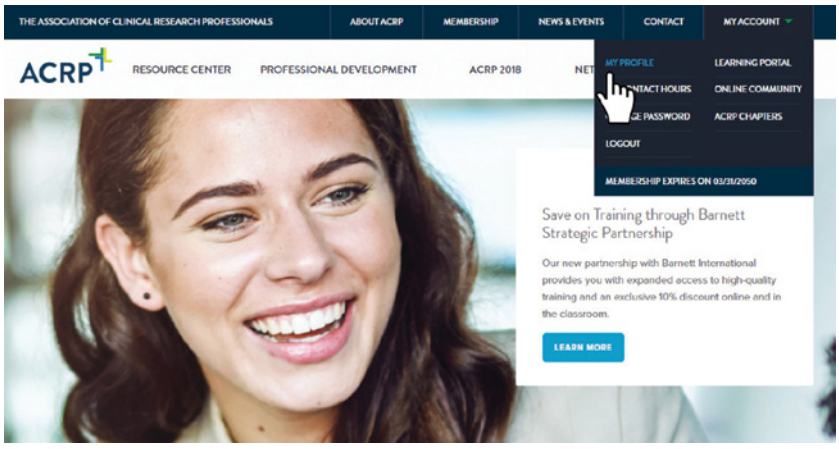
We will also publish more frequently; you will receive 10 issues of *Clinical Researcher* each year, rather than six. Additionally, you will have access to more Home Study contact hours/education credits.

Further, we are better positioned to build community by integrating the digital tools that will enable *Clinical Researcher*'s evolution toward a more "social" conduit of community engagement.

This change is also in support of efforts to provide a more "green" method of providing the information you need. However, you will still have the opportunity to print Home Study articles in PDF form if you like.

We have a lot more great news to share in the coming months as we prepare to make 2018 the best yet, but we are excited to get a jump on the year by implementing this change in December.

Thank you for your continued support of ACRP and our mission to promote excellence in clinical research.



How Will I Receive *Clinical Researcher*?

As an ACRP member, you can access *Clinical Researcher* at any time by visiting **acrpnet.org/clinicalresearcher**. Separate articles and columns have already been posted from print issues dating back to February 2016, and full-issue PDFs of all issues dating back to April 2014 (when the journal was renamed) are available for download.

You will continue receiving "issue alert" e-mails when issues are posted online. To ensure you receive these and other critical ACRP communications, please take a few minutes to update your e-mail subscriptions by following these steps:

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CHAIR'S MESSAGE

Jeff Kingsley, DO, MBA, CPI, FACRP

[DOI: 10.14524/CR-17-4041]

Good Intentions May Still Go Astray on the Regulatory Pathway

The more things change, the more they stay the same. Three years ago, I wrote a column for the *Clinical Researcher* titled "Global Regulatory Insights: Why Do We Have Regulatory Compliance Professionals?" Three years later, the U.S. Food and Drug Administration (FDA) has become more open and communicative, and regulatory bodies are acknowledging that change is needed. However, research continues to get harder as this pendulum continues to swing further toward constraint.

The regulatory framework is a patchwork of law, regulation, and guidance that has come from dozens or hundreds of federal, state, and local government offices; each has the best of intentions, but combined, they form a thicket of unintended consequences. Our regulatory compliance professionals are as needed today to help us navigate this maze as they were the last time I broached this topic.

Nothing's as Simple as it Seems

In the U.S., the Federal Food, Drug, and Cosmetic Act (FD&C Act) is a federal law enacted by Congress giving the FDA its power. Congress delegated to FDA the ability to create regulations within the confines of the FD&C Act, and those *regulations* are treated as law. FDA *guidance,* however, describes the agency's current thinking on a regulatory issue. Guidance is not law, but to be safe, everyone treats guidance as law anyway.

Well, here's an example of where things get more convoluted. There are laws governing how businesses can interact and associate. These govern, for example, the transactions that can take place between a pharmaceutical company, a hospital system, and a clinical investigator; and they govern what structures will have to be in place in order for these transactions to occur.

Then there are laws—such as the Health Insurance Portability and Accountability Act Privacy Rule, the Anti-Kickback Statute, and the Stark Law—that also have influence over what can and cannot happen, or more appropriately, under what circumstances and structures the relationship can happen.

Then there are the FDA regulations, which are the same as law, and the Office of Inspector General (OIG) regulations, which are the same as law. And then there's guidance that comes out of the FDA, but also out of the National Institutes of Health and the Office for Civil Rights, along with dozens or hundreds of other offices.

We can layer on top of all that the International Council for Harmonization's tenets for Good Clinical Practice, as well as state and local laws.

Seeing the Forest for the Trees

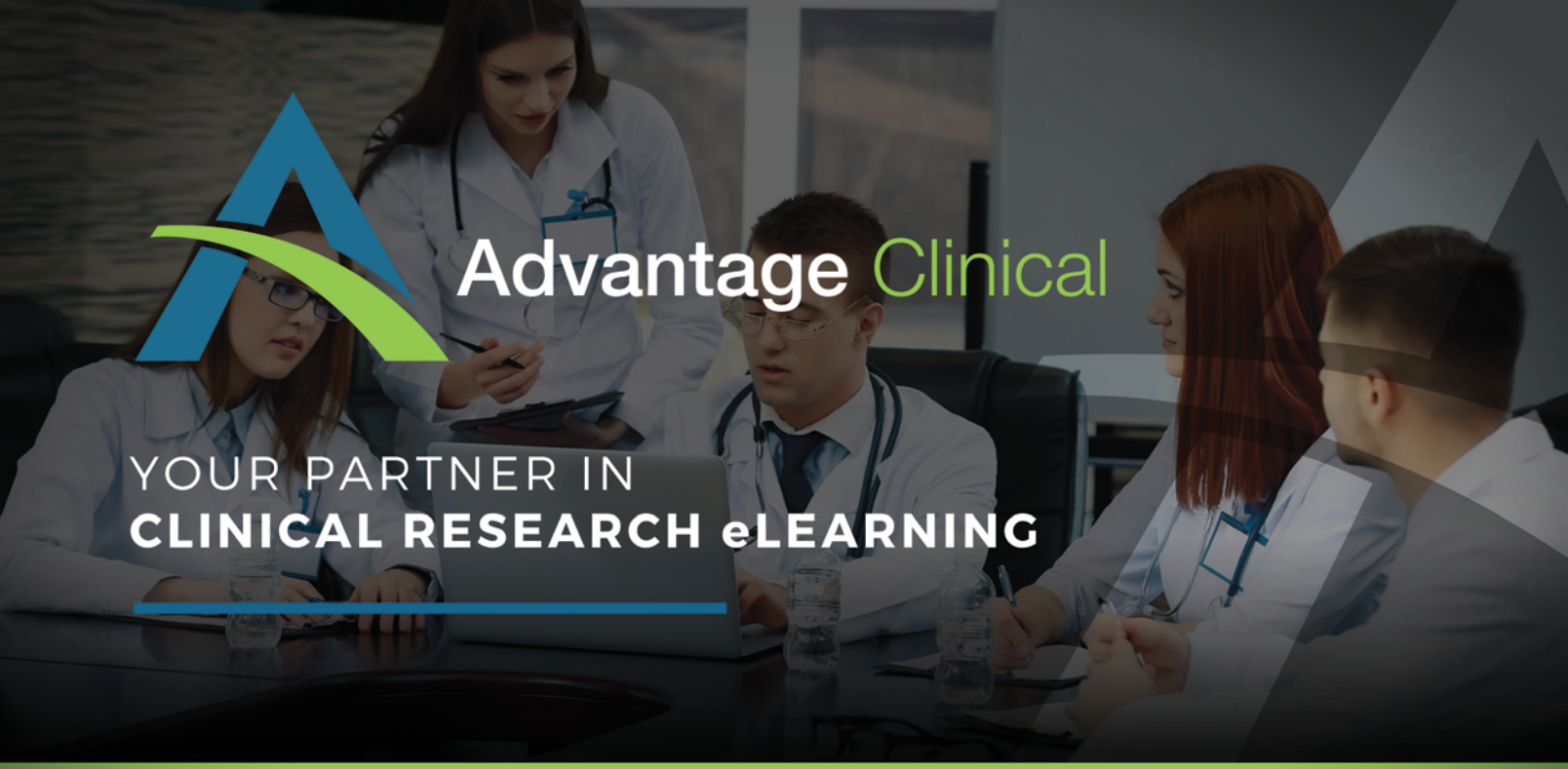
This situation has led to an industry of regulatory compliance and healthcare regulatory attorneys to navigate the tangled forest of expectations. I visualize a serene meadow in the midst of the wild woods, where we can successfully conduct research, improve healthcare, and transact business. Finding that *tiny* area of overlap where we're in compliance with all these laws, regulations, and guidances can be tough—and sometimes, impossible.

All these laws, regulations, and guidances are built with the best of intentions, and they all end with unintended consequences. Then we create more laws to try and take care of the unintended consequences.

The OIG Safe Harbor Regulation would be an example. Within the U.S. Department of Health and Human Services (HHS) is the Office for Human Research Protections (OHRP), and within OHRP is the Secretary's Advisory Committee on Human Research Protections (SACHRP). Posted on the HHS website, the SACHRP readily acknowledges the confusion that has been created by the overlap of unintended consequences. Within its meeting minutes there are numerous references regarding guidances that have resulted in "much debate and confusion throughout the research community." But with the best of intentions.

All these laws, regulations, and guidances are built with the best of intentions, and they all end with unintended consequences. Then we create more laws to try and take care of the unintended consequences.

Jeff Kingsley, DO, MBA, CPI, FACRP, (jkingsley@iacthealth.com) is chief executive officer of IACT Health in Columbus, Ga., and Chair of the 2017 Association Board of Trustees for ACRP.



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Getting on Board with ICH GCP E6(R2): Impact on Study Quality and Operations

PEER REVIEWED | Jan S. Peterson, MS, CCRA, RAC, MICR, ASQ CBA

[DOI: 10.14524/CR-17-0032]

It took 20 years for the International Council for Harmonization's (ICH's) 1996 ICH E6(R1) Guideline for Good Clinical Practice (GCP) to reach the maturity needed for significant amendment. An earlier attempt by the U.S. Food and Drug Administration (FDA) in 1977 to institute similar provisions by regulation was basically unsuccessful, but lessons learned help develop the original ICH GCP document during the 1990s.

The ICH GCP E6(R2) update finalized in 2016 was prepared as an integrated addendum with insertions designed to keep the original structure intact. These changes incorporated recent methodologies focused on risk-based approaches to quality, improved language to accommodate the digital age, and additional clarifications for sponsor and investigator responsibilities.

With clinical research under increasing pressure for safety, quality, and cost improvements, ICH is proposing additional changes to GCP even as implementation of the new E6(R2) version is just getting under way.

So Long Ago—A [Not-So] Brief History

Nearly 20 years before the ICH published its original E6(R1) GCP guideline in 1996, the FDA had published a series of proposed regulations about clinical research. In retrospect, these would constitute much of what appeared later in ICH GCP. FDA's objective was to assure the quality and integrity of the research activities subject to the agency's jurisdiction, but the implications were more widespread; the FDA proposals included separate, but coordinated, regulations for sponsors and monitors, institutional review boards (IRBs), and clinical investigators.[1–3]

At the time, pharmaceutical industry representatives and many researchers voiced strong opposition to what FDA proposed. Citing the potential for enormous cost increases for compliance and a slowing of research progress, they lobbied successfully to halt implementation of most of the proposed regulations. Of the original proposals, only the IRB regulations were successfully rewritten and issued in final form in 1981.[4]

FDA still regulated drug trials and the approval process in the U.S., but even with incremental regulatory improvements over time, what were to be considered broadly acceptable practices for clinical trials remained unsettled. Study sponsors and their consultants were on their own to create internal, often proprietary, procedures. Worldwide, except for the ethical considerations for informed consent published following World War II,[5,6] there were no competent health authorities using an agreed-upon set of guidelines for the conduct of clinical trials.

Pharmaceutical companies were keenly interested in using a commonly accepted framework to gain marketing approvals in various national markets. This was because it was often a requirement to conduct essentially the same clinical trial in multiple countries to gain local product approvals. Thus, when ICH was created in 1990 (it was known originally as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use), it was a joint effort by regulators and trade

associations in Europe, Japan, and the U.S. to create a commonly accepted set of guidelines—a "harmonized" voluntary consensus standard—for drug marketing approvals. By then, FDA had incorporated some of the earlier proposed regulations piecemeal into other rules and regulations, but the original cohesive arrangement had been lost.

Senior FDA regulators were an integral part of the ICH E6 development, and were well aware of the earlier proposed rules containing language about the responsibilities for sponsors, monitors, IRBs, and clinical investigators. Rather than attempt another comprehensive regulatory approach such as had been started 20 years earlier, FDA decided to adopt the ICH GCP E6(R1) guideline, which agency representatives helped write, as an official "guidance document" in 1997.[7] The GCP guidance was not enforceable in the manner of other regulations in the U.S., but it provided the industry and regulators with a clearer picture of what constituted acceptable practices.

Jumping Forward

The E6(R1) GCP guideline from 1996 turned out to be one of the most durable of international voluntary consensus standards, absorbing 20 years of intensive use before resigning to a second edition. An entire industry of clinical investigators, sponsors, monitors, coordinators, nurses, IRB/institutional ethics committee members, trainers, consultants, auditors, government regulators, and other research staff members around the world interpreted and used the E6(R1) guideline, devised relevant procedures, built training programs (including the professional certification programs sponsored by the Association of Clinical Research Professionals, the Society of Clinical Research Associates, and others), received and documented their training, and managed thousands of clinical trials built largely around use of the ICH GCP guideline.

Regulatory authorities of many countries (ICH members in particular) adopted the original GCP guidelines in a formal manner without modification, while some others (e.g., India) adapted them significantly to align with local laws and subsequently published their own versions.[8]

With the experience of widespread use under evolving conditions, some misinterpretations of GCP were observed to have a negative impact on quality and trial costs. By 2014, ICH created an Expert Working Group (EWG) to update the GCP guideline. The clinical research world was evolving quickly, and revisions were needed due to globalization, increasing study complexities, and technological capabilities.[9] The EWG gathered representatives from European Union (EU) regulatory authorities, the European Federation of Pharmaceutical Industries and Associations, FDA, the Pharmaceutical Research and Manufacturers of America, the Ministry of Health, Labor, and Welfare (MHLW) in Japan, the Japan Pharmaceutical Manufacturers Association, Health Canada, and Swissmedic, and benefitted from additional resources from other organizations.

The EWG made use of recent changes to clinical research procedures and quality practices (e.g., published position papers and studies, other consensus standards and guidance documents) to help prepare the GCP update.[10–17] Goals included improved harmonization of practices with proactive quality management approaches and risk-based monitoring (RBM), and integration across other ICH documents. These harmonized practices were expected to relieve impediments to innovation while maintaining protection of trial participants and data quality.[9]

Consistency of approaches and clarification of earlier GCP misinterpretations were also expected to improve clinical drug development time and costs. The EWG used an "integrated addendum" approach to GCP document modifications, making changes to the original version as insertions while retaining the original E6(R1) outline structure.

The ICH EWG completed its first draft by June 2015, and the document was sent out for comments to ICH members and the public. The final text (called Step 4 in the approval process) of the E6(R2) update was approved by ICH and published on November 9, 2016.[18]

Here We Are

The implementation stage (Step 5) for the E6(R2) update is under way. Officially, the European Medicines Agency's Committee for Medicinal Products for Human Use stepped up first and announced adoption of E6(R2) on December 15, 2016, with an effective date for the EU on June 14, 2017.[19] Health Canada adopted the E6(R2) update next on May 25,

With clinical research under increasing pressure for safety, quality, and cost improvements, ICH is proposing additional changes to GCP even as implementation of the new E6(R2) version is just getting under way.

Rather than attempt another comprehensive regulatory approach such as had been started 20 years earlier, FDA decided to adopt the ICH GCP E6(R1) guideline, which agency representatives helped write, as an official "guidance document" in 1997.

2017, announcing that full implementation would occur in April 2018.[20] Japan's MHLW/Pharmaceutical and Medical Devices Agency, Swissmedic, and the FDA have not yet announced official adoption or effective dates.

The ICH membership's expansion beyond the original tripartite group (the EU, Japan, and the U.S.) brought in regulatory members from Canada, Switzerland, Brazil, China, and the Republic of Korea. An expanding list of 23 official ICH observers now includes authorities from India, Cuba, Mexico, Singapore, South Africa, Kazakhstan, Russia, Chinese Taipei, and Australia, plus several regional organizations (e.g., the Asia-Pacific Economic Cooperation forum, the Association of Southeast Asian Nations) and other international organizations (e.g., the World Health Organization, International Federation of Pharmaceutical Manufacturers, Council for International Organizations of Medical Sciences, United States Pharmacopeia, International Pharmaceutical Excipients Council). This means the E6(R2) update and related ICH harmonization documents will have a growing impact on an even larger part of the world's healthcare industry as more stakeholders participate in developing and endorsing ICH guidelines.

The E6(R2) Impact on Study Quality and Operations—Focus on Changes

The E6(R2) GCP update is already creating a flurry of new interpretations and additional training curricula by consultants, institutions, sponsors, and contract research organizations (CROs). As the RBM adoption trend continues and sites and sponsors gain an increased understanding of the tenets of RBM,[21] it should be noted that risk-based approaches to quality emphasized in the E6(R2) update are not new. These approaches have been established in other recognized quality standards, including the International Organization for Standardization's ISO 9001:2015 (Quality management systems—Requirements) and ISO 31000:2009 (Risk management—Principles and guidelines), as well as regulatory positions in various countries.[10,11,13] ICH also has indicated that use and interpretation of the E6(R2) guideline should not be made in isolation from other ICH documents.[9,18]

The following GCP changes in E6(R2) are likely to have the greatest impact on existing operations performed by sponsors, CROs, and clinical sites:

- **Certified copies [Section 1.63]:** The medium is no longer the message. In the world of electronic data, if you have a validated process to generate copies that make an accurate and complete copy, the copy you create can be considered certified. You have to take the non-trivial step to assure the process for making copies is validated, but when this is properly documented, a significant tool is at your disposal.
- **Monitoring plans and monitoring [Sections 1.64 and 5.18.7]:** Having a plan is not new, nor is centralized monitoring, but E6(R2) now mentions "centralized" monitoring frequently, so the emphasis is new. A focus on critical data and processes is specified, which relates to RBM methods.
- **Monitoring reports [Section 5.18.6(e)]:** Since centralized monitoring is emphasized, document that activity just as you would onsite visits.
- **All trial information [Section 2.10]:** Clarifies that "all" applies to paper and electronic records.
- **Investigator responsibilities [Sections 4.2.5 and 4.2.6]:** Delegation without supervision is not acceptable. This extends to any service provider, who must be qualified and have procedures to assure integrity of tasks and data.
- **Investigator records [Section 4.9.0]:** It is spelled out here, but you have the old ALCOA principle (saying data should be Attributable, Legible, Contemporaneous, Original, and Accurate) from the FDA with the added "C" for complete: ALCOAC. The term audit trail is added for non-paper records (but this was always a requirement in computerized clinical data systems).
- **Sponsor responsibilities—Quality management [Section 5.0]:** A clear statement is given here to let sponsors know they need to have a quality system in place, and that a risk-based approach is essential. One sentence should be memorized: "The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected." From this statement, the basic ideas of risk-based approaches and RBM will follow.

The subsections outline the importance of risk-based thinking throughout the clinical trial process—from inception and protocol development, where risk identification may begin, through the evaluation, control, communication, review, and reporting of risks and how they are addressed.

- **Sponsor responsibilities—CRO oversight [Section 5.2.2]:** Sponsors remain responsible for oversight and documenting tasks they delegate to others (parallel to investigator responsibilities under Section 4.2.6).
- **Sponsor responsibilities—Monitoring [Section 5.18.3]:** Risk-based approaches to RBM are emphasized and can be flexible; centralized (or remote) monitoring methods for data quality issues can be effective.[12,16,17]
- **Sponsor responsibilities—Monitoring and noncompliance [Section 5.20.1]:** Consider that "noncompliance" has to "significantly affect" or have "potential to significantly affect" human subject protections or data reliability to require an active response; noncompliance means sponsors should take appropriate action when needed.
- **Essential documents [Section 8.1]:** Sponsors and investigators must manage essential documents in a manner that permits search and retrieval regardless of storage format. It is possible that the essential documents list is incomplete for some trials, which may need supplemental materials included, or that some documents maybe less relevant for a given trial. This is another risk-based decision to consider. Documents generated by the investigator/institution must remain under their control, and not be subject to exclusive control by the sponsor.

Wrapping Up

The recent ICH GCP E6(R2) update is not the end of this story. While implementation and training for the E6(R2) GCP update is under way now, more changes are in the works down the road. ICH has planned the modernization of the 1997 ICH E8 guideline (General considerations for clinical trials) and simultaneously is proposing a subsequent "renovation" of E6(R2).[22] These changes are expected to add flexibility for the range of clinical trial types that can be accommodated under GCP, including "real world" data from electronic health records, registries, and other sources not previously recognized as suitable for analysis in the manner of traditionally controlled clinical trials.

The preliminary plans for this work are set to begin late in 2017 or in 2018. The ICH effort may include developing a new ICH E6 "overarching principles" guideline, with a series of Annex documents focused on traditional interventional trials, nontraditional interventional trials, and other nontraditional trial designs. Like most consensus standards, significant revisions take time, but safety and quality standards remains paramount.

Editorial

As the E6 renovation project gets under way, perhaps ICH will reconsider the guideline title as well. I have often observed that clinical investigators primarily responsible for the execution of a research protocol misunderstand the term or the responsibilities involved with "good clinical practice" as we use it.

Perhaps the GCP term is confused with the ordinary care investigators would deliver to their patients, since of course they trained for years to provide "good"—if not superior—care, the service they provide is "clinical," and they are in medical "practice." This may not be so surprising knowing that, on an annual basis, a high proportion of clinical investigators are research-naïve. Perhaps because of their initial research experience and training—or lack thereof—in leading a clinical research protocol, many first-time investigators never return to utilize or improve upon their new skills.

Regulatory inspections seem to support this idea, since year after year, the most common citations issued to investigators are for not following the protocol. To help everyone recognize the important difference between their clinical skills and the research activities they undertake, I'm hoping that the title "good clinical practice" (GCP) gets updated to "good clinical research practice" (GCRP), in recognition that this activity is clearly not at all like providing good patient care.

The recent ICH GCP E6(R2) update is not the end of this story. While implementation and training for the E6(R2) GCP update is under way now, more changes are in the works down the road.

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ACRP MEMBER PROFILE: **CHRISTINA L. NANCE**

TITLE:

Christina L. Nance, PhD, CPI, FAACI

Assistant Professor, Pediatrics/ Pathology/Immunology/ School of Tropical Medicine

Baylor College of Medicine

Texas Children's Hospital

Adjunct Assistant Professor, Epidemiology, Human Genetics & Environmental Sciences

University of Texas Health Sciences-Houston

HOMETOWN:

St. Louis, Mo.

LIVE NOW:

Houston, Texas

Why did you enter the clinical research field?

By training, I am a translational scientist in the fields of immunological/allergy/infectious disease (primary immunodeficiencies, food allergy, and HIV). My first exposure in the clinical research field was my translational medicine project on the development of a natural therapeutic agent for HIV treatment. I then moved the therapeutic agent from "bench to bedside" as my first experience ever in clinical trials.

What is your favorite part of research?

The jigsaw puzzle. The challenge as the principal investigator of fitting/timing all the pieces of the clinical trial together.

What is your least favorite part?

When you are so close to interlocking ALL the pieces and that ONE piece of the clinical trial "falls out."

People would be surprised to know that:

I singularly developed every component of my first Phase I clinical trial from scratch, inclusive of the complete Investigational New Drug application to the Food and Drug Administration and multicenter trial sites. It should have been titled "trial by fire"!

Professional heroes:

The "virus hunters" at the Centers for Disease Control and Prevention.

Hobbies:

Traveling, singing (cantor and choir), and reading.

Reason for joining ACRP:

Upon being immersed in the clinical trial field, I realized that this was a very key part of my life goals. I joined ACRP to advance my skills in the field, as this is where the experts would be to guide me.

Christine Senn, PhD, CCRC, CPI

[DOI: 10.14524/CR-17-4042]

A Q&A with **Samuel Whitaker,** Chief Technology Officer for Bracket

Editor's Note: Bracket is a company focusing on clinical research data services and technology based in Wayne, Pa.

Christine Senn, PhD, CCRC, CPI, (csenn@iacthealth.com) is the chief implementation officer and a member of the Quality Assurance and Compliance Committee with IACT Health in Columbus, Ga.

Q: There are many initiatives to make clinical research more efficient through technology. What initiatives are you most excited about?

A: My move to Bracket has allowed me to strategically shift gears as an innovator. I am most excited about disrupting established clinical technologies and paradigms in traditional product sets (such as electronic patient-reported outcomes, electronic clinical outcome assessment, randomization and trial supply management, electronic data capture, etc.) with the work I do at Bracket.

Steve Jobs didn't invent the MP3 player; he perfected the design in the iPod and went on to completely change the way music was consumed with the creation of iTunes. I believe that there are similar opportunities in the field of clinical research. I aim to replicate this model of disruption in clinical technologies, and to dedicate time and energy to correcting pain points and improving what those in the industry work with on a daily basis.

My hope is that introducing disruptive technology will drive the entire industry to evolve and place a higher focus on improving outcomes for sponsors and patients.

Q: I have always been intrigued by how people got into clinical research, but everybody's path is different. What was your journey?

A: When I started college at the University of Pennsylvania, my ambition was to go to medical school. Throughout my undergraduate career, I worked at the Hospital of the University of Pennsylvania, essentially as a junior site coordinator. The experience I had working at the hospital set the foundation for my interests and pursuits later in life. I helped to support several clinical studies in the Department of Obstetrics and Gynecology, primarily managing the transcription of paper diaries to their electronic forms and administering patient payments.

I didn't end up going to medical school like I had originally set out to do, but I still worked on the periphery when I was an investment banking analyst. From there, I went on to work in acquisitions and product management. My journey eventually led me to the field of clinical research when I decided that I wanted to make use of my unique skillset to serve patient communities.

Q: You founded Greenphire, a vendor for sites to pay subject stipends. How did you identify this need in clinical research, and how did you go about solving this industry pain?

A: Before I founded Greenphire, I was working as a product manager for a payment technology company. My ambition at the time was to start my own company, and my goal was to find a situation in which I could apply my knowledge of payment technology in a unique way—to an industry that had not yet experienced innovative payment solutions. Exploring the field of clinical research was the first idea that came to mind as a result of my experience in college and my proximity to my wife's work and experiences.

Over the years, our iterative approach to software development yielded a market-leading solution set that was uniquely designed to solve the pain points of our clients and those at the site and patient level. In my role at Bracket, I'm tasked with addressing larger and more global pain points throughout the clinical trial environment, which we do by optimizing clients' experiences with our unique solutions.

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Medical Devices Research in Latin America

PEER REVIEWED | Miguel A. Willis, PhD | Anne Blanchard, CCRA

[DOI: 10.14524/CR-17-0031]

Latin America comprises the region stretching from the southern border of the United States all the way south to Antarctica (see Figure 1). Anyone who travels the territory will encounter a great range of idiosyncratic diversity, but also cultural and linguistic similarities.

Spanish (spoken in most of the region's countries) and Portuguese (especially prevalent in Brazil) are the most widespread languages among the population, although there are some countries where the official language is French, English, or Dutch. Although this trend represents an advantage for researchers in the region, as study documents in the same language can be used in several countries, there are some idioms specific to each country that should be considered.

Although the 20 sovereign states and several territories of Latin America come in all shapes and sizes, one of the most outstanding characteristics of the region is that its people clutter in and around a few major cities (see Table 1), resulting in densely populated areas. For example, Argentina nucleates more than half its population around the metropolitan areas of its principal cities of Buenos Aires, Córdoba, and Rosario, whereas Brazil concentrates Argentina's entire population and triples the Chilean population in only four of its main cities—Sao Paulo, Rio de Janeiro, Velho Horizonte, and Fortaleza. The same trends apply to México, with its principal city being México City, but the country's several other densely populated cities include Guadalajara and Monterrey.

Regulatory Landscape

In general, Latin America has more than 13,000 ongoing pharmaceutical and medical device clinical trials, according to ClinicalTrials.gov, but as of July 11, 2017, the majority were being conducted in Brazil, México, Argentina, Chile, and Colombia (see Table 2). Although pharmaceutical trials dominate the scene, medical device studies are increasingly common as more researchers and institutions see such studies as career and economic opportunities to work on cutting-edge technologies and treatments.

Meanwhile, although the region has experienced or rapidly maturing competent authorities (see Table 2) and efforts have been made at harmonizing the regulatory environment across various borders, the leading countries in the region for

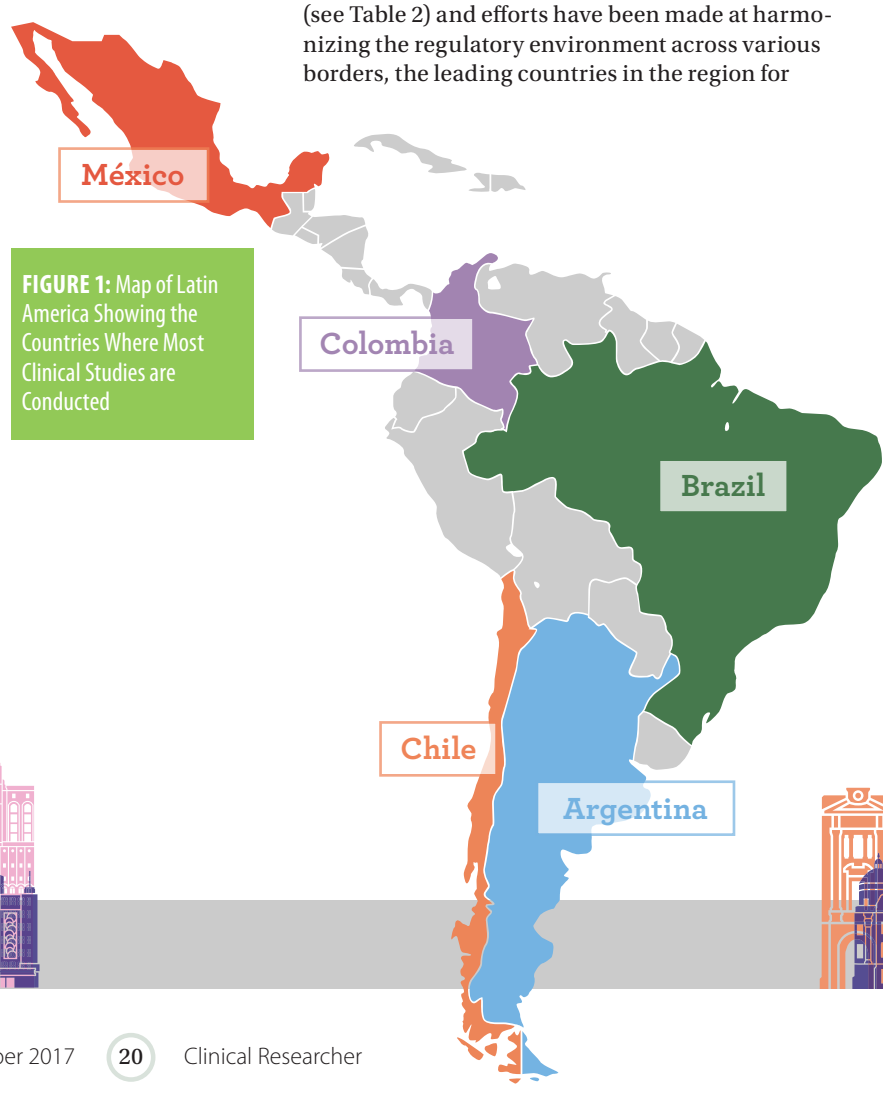


FIGURE 1: Map of Latin America Showing the Countries Where Most Clinical Studies are Conducted

clinical studies still have many divergent procedures. On the positive side, the tenets of the International Council for Harmonization's Guideline for Good Clinical Practice (GCP) have been incorporated deeply in the region, and other standards like ISO 14155 from the International Organization for Standardization are quickly being adopted.

The divergent procedures and requirements of different countries impact directly on the regulatory timeline expectations for setting up clinical studies (see Figure 2). All countries require local adaptation of trial-related documents, and this means certified translation to local languages of all critical documents. Although this by itself does not present a challenge, sponsors should have all critical documents ready for translations as soon as possible, or unnecessary delays may arise. Also, although the official language of most Latin American countries is Spanish (excluding Brazil for the purposes of this paper), companies managing translations should be deeply aware of local idioms and/or use local translators to avoid misuse of terms.

In most Latin American countries, study protocols and other critical documents must go through both institutional review board (IRB) and competent authority review and approval. (In Chile, the competent authority is only notified about studies, and in cases of postmarketing studies in Argentina, the same holds true.) The expectation of two levels of review impacts timelines and additional submission efforts, so a smart and clear regulatory strategy must be laid out when approaching IRBs and competent authorities. Brazil has, by far, the longest regulatory timelines; in addition to IRB and competent authority evaluations, submission of study details must be made to CONEP (the National Ethics Committee), although the competent authority and CONEP reviews can be done in parallel.

TABLE 1: Population Concentration in Latin America's Principal Cities (in millions)

Argentina Population: 43.4M	Buenos Aires Metropolitan Region	≈20M
	Córdoba	≈1.5M
	Rosario	≈1.4M
Brazil Population: 191M	Sao Paulo Metropolitan Area	≈21.9M
	Rio de Janeiro	≈12.1M
	Belho Horizonte	≈5.7M
	Fortaleza	≈2.5M
Chile Population: 16.6M	Santiago Metropolitan Area	≈6.3M
Colombia Population: 48.7M	Bogota	≈8M
	Medellin	≈2.5M
	Barranquilla	≈1.2M
México Population: 123.2M	México City Metropolitan Area	≈20.1M
	Guadalajara	≈4.4M
	Monterrey	≈4.1M

TABLE 2: Competent Authorities by Country and Number of Studies Being Conducted per Country (as of July 11, 2017)

Country	Competent Authority	Clinical Trials
Brazil	**ANVISA** www.anvisa.gov.br/eng/index.htm	5,773
México	**COFEPRIS** www.cofepris.gob.mx	2,832
Argentina	**ANMAT** www.anmat.gov.ar	2,225
Chile	**Instituto de Salud Publica de Chile** www.ispch.cl/dispositivos-medicos	1,272
Colombia	**INVIMA** www.invima.gov.co	1,038
Costa Rica	**Ministerio de Salud (MoH)** www.ministeriodesalud.go.cr	149
Uruguay	**Ministerio de Salud Pública** www.msp.gub.uy	59

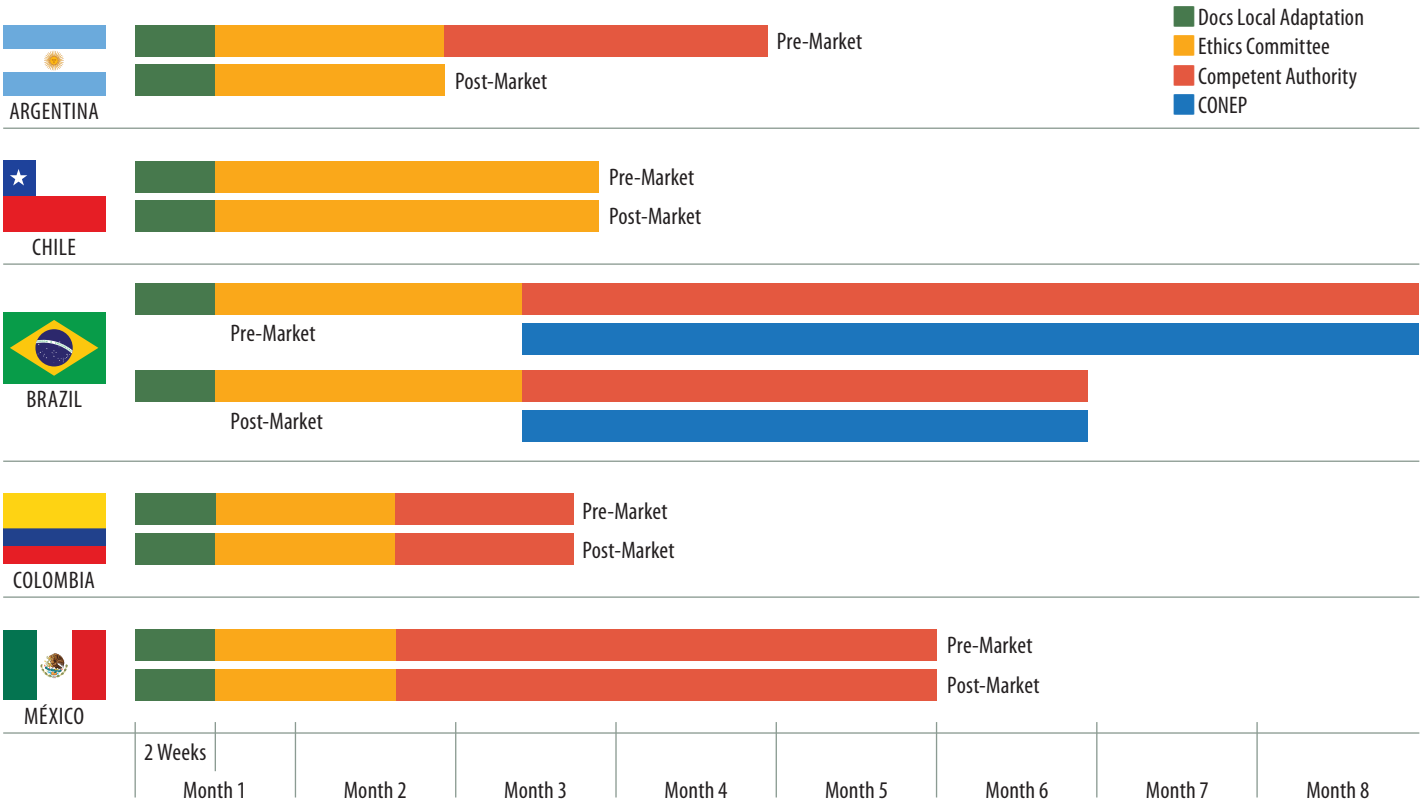
In Argentina, core regulations and IRB/ethics committee (EC) procedures are mostly oriented toward pharmacological studies, though device studies can also be performed—even if the regulations for them could stand clarification and refinement. Argentina remains an ideal setting for postmarketing research studies in relation to timelines, since these can be implemented with EC approval and with no need to notify ANMAT if importation is required.

Brazil, as stated above, has the longest regulatory timelines, but since 2015 ANVISA has been issuing new regulations specific to medical device studies, aiming to accelerate approvals. ANVISA demands the language of trial documents to be Brazilian Portuguese, and there are few exemptions when submitting for approval.

Chile currently has one of the simplest regulatory setups for medical devices, as once an IRB/EC

The expectation of two levels of review impacts timelines and additional submission efforts, so a smart and clear regulatory strategy must be laid out when approaching IRBs and competent authorities.

FIGURE 2: Regulatory Timelines in Latin America



Research sponsors may find in the region a convergence of the different variables that allow for designing a study strategy that meets the goals of timeliness, cost effectiveness, recruitment potential, and other critical factors.

approves the study, the competent authority is only to be informed and importation is authorized with no subsequent need of approvals.

In Colombia, there are no specific regulations for devices, and the Ministry of Health (INVIMA) acknowledges the same type of requirements that would apply to pharmacological research according to the research phase. Trying to obviate the regulations on the grounds there is no specific device-oriented regulation without adequate justification can lead to setbacks and delays. Investigational sites implementing medical device interventional studies must be certified for GCP by INVIMA.

México has specific regulations for medical devices, but the requirements are very similar to those for pharmacological studies. As medical device research is not very widespread in México, finding the right site to launch a study might represent a challenge, although the latest trends indicate increasing levels of activity in this arena.

Research Resources, Facilities, and Capabilities

The operations of healthcare systems in Latin American countries vary greatly (see Table 3), and even show extremes ranging from costly healthcare treatment in Chile to free public health coverage in Argentina that is also taken advantage of by citizens of neighboring countries by crossing the border for treatment. The region's densely populated cities offer access to treatments whose complexity ranges from simple to high-end levels in facilities with technical capabilities and numbers of hospital beds similar or even higher than those seen in developed countries.

Latin American physicians are highly respected members of their communities, and

TABLE 3: Health Indicators in Latin America Compared to North American and European Countries

Country	Hospital Bed Density (Beds/1,000 Population)*	Physician Density (Physicians/1,000 Population)*	Life Expectancy (Years)*	Health Expenditures (% of GDP*+ $/capita**)
Argentina	4.7	3.86	Total: 77.1 Male: 74 Female: 80.4	4.8 %* $1,137**
Brazil	2.3	1.89	Total: 73.8 Male: 70.2 Female: 77.5	8.3 %* $1,318**
Chile	2.1	1.02	Total: 78.8 Male: 75.7 Female: 81.9	7.8 %* $1,749**
Colombia	1.5	1.47	Total: 75.7 Male: 72.6 Female: 79	7.2 %* $962**
México	1.5	2.1	Total: 75.9 Male: 73.1 Female: 78.8	6.3 %* $1,122**
Canada	2.7	2.07	Total: 81.9 Male: 79.2 Female: 84,6	10.4 %* $4,641**
United States	2.9	2.45	Total: 79.8 Male: 77.5 Female: 82.1	17,1 % *$9,403**
United Kingdom	2.9	2.81	Total: 80.7 Male: 78.5 Female: 83	9,1 % *$3,377**
Denmark	3.5	3.49	Total: 79.4 Male: 77 Female: 82	10.8 % $4,782**

**CIA World Facts*
***World Health Organization*

often have trustful relationship with their patients, especially in Argentina, Chile, and Brazil. Most of them have educational backgrounds and clinical expertise comparable to physicians in the U.S. and Europe, as it is common for them to have trained abroad in an effort to stand out. On the other hand, medical school training in Argentina is free, which generates conditions of high physician density in a very competitive environment. On the opposite end of the spectrum, becoming a physician in Chile is very expensive, and only students earning the highest grades have the opportunity to be trained, so this creates a similar environment in which they need to be outstanding just to survive in their careers.

Regarding costs for conducting a clinical study, sponsors should estimate that in Latin America in general, total costs for professional services will be around 25% less than in the U.S. Regulatory setup costs will be outweighed by the recruitment potential of sites, if they are chosen with care.

Conclusions

Latin America is a promising region for clinical studies, given that it presents the key characteristics for a successful study. We mean this in terms of densely populated cities and subjects with access to medical attention ranging from low- to high-complexity treatment and procedures, and highly trained physicians in high-end facilities with research backgrounds and experience.

Further, research sponsors may find in the region a convergence of the different variables that allow for designing a study strategy that meets the goals of timeliness, cost effectiveness, recruitment potential, and other critical factors. So, for example, if you are looking for short regulatory timelines, Chile will fit best. On the other hand, if you need high recruitment levels and are willing to endure long regulatory timelines, Brazil is the place to land. If you need both acceptable timelines and recruitment in premarketing studies, Argentina can offer both, and may be your best choice for postmarketing studies overall. Multinational strategies could also be a wise approach in the region, depending on the study needs.

The key element to success in the region is choosing the right partner with which to team up to guide the project through the legal and regulatory hurdles, while maintaining a close and transparent rapport with the study sponsor team.

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Resources

Central Intelligence Agency: https://www.cia.gov/library/publications/the-world-factbook/

ClinicalTrials.gov: www.clinicaltrials.gov

World Health Organization: www.who.int

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ICH E6(R2): What Does Third-Party Oversight Mean for Investigators, Sponsors, and CROs?

Over the past 20 years, the outsourcing of research and development (R&D) has become increasingly prevalent. The regulatory impact of this trend is reflected in the ICH Guideline E6(R2) from the International Council for Harmonization, in that several addenda have been made under the "Investigator" and "Sponsor" sections of the guideline. In this column, we will examine these updates and suggest ways that investigators, sponsors, and contract research organizations (CROs) can implement these changes.

Investigator Oversight of Third Parties

ICH E6(R2) addresses investigator oversight responsibilities of third parties in Addendum 4.2.6:

> "If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated."

To comply with this new requirement, investigators/institutions should retain in their files evidence that the third parties are qualified to assume responsibilities for the specific study and the contractual agreements with the third parties. Where the third parties are individuals, these should be listed in the site's delegation of authority log. Where the third parties are entities (e.g., a pharmacy), a responsible party of that entity should be listed in the site's delegation of authority log, and the entity should maintain its own internal delegation of authority log.

It is also essential that the third parties receive and document any study-specific training that is pertinent to their roles. Furthermore, it is not adequate for investigators/institutions to assume that the services performed by the third parties and the data generated will meet integrity expectations. The investigator/institution should put in place a process for assuring themselves of this throughout the study, and should retain evidence that the process has been followed.

In some cases, the investigator will contract with the third party, while in other cases the institution will assume the obligation. Even if the institution holds the contract, the investigator is ultimately accountable for the quality of the services being provided by any third parties on their studies.

Sponsor Oversight of CROs

Now let's turn to sponsor oversight of CROs. Just as in the prior version of ICH E6, Section 5.2 of ICH E6(R2) addresses the fact that sponsors may transfer responsibilities to CROs, that this transfer should be in writing, and that any responsibilities not specifically transferred are retained by the sponsor. In addition, this section states that where responsibilities are delegated to CROs, the CROs are responsible for complying with all ICH requirements related to those sponsor responsibilities.

What is different in ICH E6(R2) is the additional requirement under section 5.2.2 that, "The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s)."

Let's examine the first part of this sentence. Similar to Addendum 4.2.6 in the "Investigator" section of the guideline, it is not sufficient for sponsors to assume that because they have subcontracted services, the services performed by their third parties are being performed according to the guideline. Sponsors need to ensure that there is appropriate oversight, and the evidence of the oversight needs to be retained.

When inspecting sponsors, regulators are increasingly assessing the sponsor's oversight of the CROs it utilizes. The types of evidence that regulators look for include the following:

1. Selection and qualification of the CRO to ensure that the CRO that has been selected meets the requirements of the sponsor
2. A contractual agreement that makes clear exactly which tasks have been delegated to the CRO
3. Ongoing oversight of the CRO to confirm throughout the study that the CRO continues to meet the sponsor's requirements

Ongoing oversight has been handled differently across sponsors, ranging from a hands-off approach to one that can feel like micromanagement to the CRO. The challenge is finding a middle ground where the sponsor has sufficient data to be confident that it has a finger on the pulse of the services being provided by the CRO.

Many sponsors have traditionally relied on a quality plan or agreement to document quality expectations to be met by the CRO. Such plans or agreements may include, but are not limited to, reports required of the CRO, criteria for and/or frequency of communications with the sponsor, and details on the handling of escalations (e.g., regarding quality issues). However, these types of quality plans/agreements have typically been more reactive than proactive, in that their focus has been more on issue management, audits, and inspections than on proactive risk management.

Enhanced Oversight by Collaborative Quality Risk Management

ICH E6(R2) provides the perfect platform for enhancing sponsor oversight. The guideline invites sponsors to partner with their CROs early on to proactively identify the critical data and processes associated with their protocol, to assess the associated risks that will inform the cross-functional monitoring strategy, and to perform ongoing risk management throughout the study. If these steps are performed in a collaborative and transparent manner, sponsors will benefit by having the data they need to feel confident they have adequate oversight of their CROs. It will also reassure them that the CRO is not just informing them of issues once they have occurred, but is also actively engaged in preventing the issues from occurring in the first place.

Technology can also significantly assist in enabling sponsor oversight. By using "Key Risk Indicator" dashboards and sharing the data with their sponsors, CROs can provide real-time data and evidence of proactive risk management on the study.

Impact on CRO Interactions

For quality risk management to be effective, it needs to include all functions involved in a study—beginning with investigator site selection and covering all interactions among the functions, all the way to the generation of the clinical study report. For example, data reviews by data management units will inform the monitoring performed at the investigator site and vice versa. This cross-functional approach allows the sponsor to have a holistic picture of the state of quality for the duration of the study.

As a result, if study functions are outsourced to different CROs, those CROs will need to become more comfortable sharing data from their quality risk management activities with other CROs contracted to perform different functions on the study. This might include data that a CRO previously considered proprietary (whether shared directly or indirectly through the sponsor), which will likely impact the current outsourcing model that minimizes interactions among the CROs supporting a given study.

Oversight of CRO Subcontractors

Now let's turn to the second part of Addendum 5.2.2: "The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s)."

In the past, it was thought to be acceptable for a sponsor not to intervene to a great extent in CRO subcontractor arrangements, since the contract was between the CRO and its subcontractor. Most sponsors limited their oversight to assuring themselves through audits that their CROs had a process in place for qualifying their subcontractors, while some went further by requiring their CROs to seek sponsor pre-approval of their third parties. This level of oversight is no longer adequate, as responsibility has been put squarely on sponsors to ensure oversight of functions that their CROs subcontract.

What does this mean? Sponsors will most likely require that all subcontractors be pre-approved by them, and they will expect to be provided with more details on the results of the qualifications performed by their CROs. They will also want evidence that the CROs are actively managing their subcontractors throughout their studies. In addition, more sponsors will likely be inserting third-party beneficiary language into agreements with their CROs, to allow the sponsors to have more direct oversight of these subcontractors.

Conclusion

Given the increasing prevalence of outsourcing in R&D, it is not surprising that ICH E6(R2) has addressed in more detail third-party oversight expectations of both investigators and sponsors. The addenda will result in a number of changes in contractual agreements as well as investigator, sponsor, and CRO processes that will enable effective quality risk management critical to the protection of human subjects and reliability of trial results.

What is different in ICH E6(R2) is the additional requirement under section 5.2.2 that, "The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s)."

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The New European Medical Device Regulation 2017/745: **Main Changes and Challenges**

The new European Medical Device Regulation 2017/745 (MDR)[1] and the European Union (EU) *In Vitro* Diagnostic Medical Devices Regulation 2017/746 (IVDR)[2] passed in the European Parliament on April 5, 2017. The MDR was published in the *Official Journal of the European Union* on May 5, 2017, and entered into force on May 25, 2017.

PEER REVIEWED
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GUIDE TO ABBREVIATIONS USED IN THIS ARTICLE	
AIMDD	Active Implantable Medical Devices Directive
CER	Clinical Evaluation Reports
EEC	European Economic Community
EU	European Union
EUDAMED	European Database on Medical Devices
GCP	Good Clinical Practice
HRI	Human Readable Interpretation
IVD	*In Vitro* Diagnostic
IVDR	*In Vitro* Diagnostic Medical Devices Regulation
ISO	International Organization for Standardization
MDD	Medical Device Directive
MDR	Medical Device Regulation
NB	Notified Body
PMCF	Post-Market Clinical Follow-Up
PIP	Poly Implant Prothèse
UDI	Unique Device Identification
UDI-DI	Unique Device Identification Device Identifiers

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This article focuses solely on the impact of the MDR on clinical evaluations and clinical investigations. The new MDR will repeal two directives that are currently in place:

- Medical Device Directive (MDD 93/42/EEC)
- Active Implantable Medical Devices Directive (AIMDD 90/385/EEC)

These directives have been labeled as "New Approach Legislation," with the aim to protect public health mainly based on self-regulation by the industry. Legislation valid in all 28 Member States of the EU is either imposed through directives addressed to national authorities, who must take action to make them part of national law, or through regulations; as soon as they are passed, they have binding legal force throughout every Member State, on par with national laws.

Background

The medical device industry and market has steadily grown over the past decades, with a vast variety of sophisticated and advanced products in the pipeline. Due to this fact, the European Commission and EU Parliament decided to adapt the existing legislation (initially installed in 1990 and 1993, with amendments in 2003 and 2007) to the significant technological and scientific progress occurring in this sector in the past 20 years.

Furthermore, the European Commission argues: "Problems with diverging interpretation of the current Directives as well as the incident concerning fraudulent production of the Poly Implant Prothèse (PIP) silicone breast implants in 2012 highlighted weaknesses in the legal system in place at the time and damaged the confidence of patients, consumers and healthcare professionals in the safety of medical devices."[3]

One of the key objectives of the new MDR is to ensure a consistently high level of health and safety protection for EU citizens using these products. Making clinical investigation and evaluation requirements more stringent is aimed at improving health and safety through transparency and traceability.

The MDR consists of 10 chapters with 123 articles and 17 annexes (see Table 1), and covers clinical evaluations and clinical investigations with medical devices in the EU, depending on any type of sponsor (industry, noncommercial, academia). It will fully apply from May 26, 2020, and manufacturers have the duration of the three-year transition period to update their technical documentation and processes to meet the new requirements.

TABLE 1: What's Found in the New Medical Device Regulation

Location	Content	Articles
Chapter I	Scope and definitions	1 to 4
Chapter II	Making available on the market and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement	5 to 24
Chapter III	Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices	25 to 34
Chapter IV	Notified bodies	35 to 50
Chapter V	Classification and conformity assessment	51 to 60
Chapter VI	Clinical evaluation and clinical investigations	61 to 82
Chapter VII	Post-market surveillance, vigilance, and market surveillance	83 to 100
Chapter VIII	Cooperation between Member States, Medical Device Coordination Group, expert laboratories, expert panels, and device registers	101 to 108
Chapter IX	Confidentiality, data protection, funding, and penalties	109 to 113
Chapter X	Final provisions	114 to 123
Annex I	General safety and performance requirements	
Annex II	Technical documentation	
Annex III	Technical documentation on post-market surveillance	
Annex IV	EU declaration of conformity	
Annex V	CE marking of conformity	
Annex VI	Information to be submitted upon the registration of devices and economic operators in accordance with articles 29(4) and 31, core data elements to be provided to the UDI database together with the UDI-DI in accordance with articles 28 and 29, and the UDI system	
Annex VII	Requirements to be met by notified bodies	
Annex VIII	Classification rules	
Annex IX	Conformity assessment based on quality management system and on assessment of technical documentation	
Annex X	Conformity assessment based on type-examination	
Annex XI	Conformity assessment based on product conformity verification	
Annex XII	Certificates issued by a notified body	
Annex XIII	Procedure for custom-made devices	
Annex XIV	Clinical evaluation and post-market clinical follow-up	
Annex XV	Clinical investigations	
Annex XVI	List of groups of products without an intended medical purpose referred to in article 1(2)	
Annex XVII	Correlation table	

Article 120 of the MDR states a number of transitional provisions, and should be referred to for more detail. Certificates issued to the MDD and AIMDD during the transition period will remain valid for the entire period indicated on the certificate.

The medical device industry and market has steadily grown over the past decades, with a vast variety of sophisticated and advanced products in the pipeline.

What's New in the MDR?

Main changes introduced by the MDR are (some are described in more detail below):

- Clinical investigations and evaluations are regulated in more than 20 articles of the MDR
  - Clinical evidence: Sufficient high-quality data to allow a qualified assessment of whether the device achieves the intended clinical benefit(s) and safety, when used as intended.
  - Clinical evaluation: Systematic and planned process to continuously generate, collect, analyze, and assess the clinical data pertaining to a device.
- The technical documentation (Annex II) must be updated continuously
- Labeling requirements have been massively increased
- Notified bodies (NBs), manufacturers, and importers will have to be registered (MDR certificate)
- Installation of a scrutiny procedure for NBs (class IIb and III devices)
- A Unique Device Identification (UDI) will be required
- Extension of the EUDAMED Database
  - Access to competent authorities, manufacturers, NBs, and the public.
  - Display of certificates, vigilance reports, clinical investigations, PMCFs.
- Harmonized evaluation of high-risk devices

Clinical Evaluations

Demonstration of clinical evidence is not a new requirement. Under the aforementioned MDDs, lower risk devices were required to have clinical evaluation reports (CERs) and higher risk devices had to present clinical data. CERs are still required (Annex XIV, Part A) but the content is changing. In addition to CERs, a public summary of safety and clinical performance (Article 32) is now required for certain types and classes of devices. This summary is expected to consider diagnostic or therapeutic options addressed in the CER and diagnostic/therapeutic alternatives.

The following text is an extract of section 1, Part A of Annex XIV (Clinical evaluation):

To plan, continuously conduct and document a clinical evaluation, manufacturers shall:

(a) establish and update a clinical evaluation plan, which shall include at least:

- an identification of the general safety and performance requirements that require support from relevant clinical data;
- a specification of the intended purpose of the device;
- a clear specification of intended target groups with clear indications and contraindications;
- a detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters;
- a specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects;
- an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device;
- an indication how benefit-risk issues relating to specific components such as use of pharmaceutical, non-viable animal or human tissues are to be addressed; and
- a clinical development plan indicating progression from exploratory investigations (such as first-in-human studies), feasibility studies, and pilot studies to confirmatory investigations (such as pivotal clinical investigations), and a PMCF as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria

Class III and implantable devices must have clinical data derived from clinical investigations that were conducted under the supervision of a sponsor. Those clinical studies need to follow Good Clinical Practices (GCPs), such as those outlined in ISO 14155:2011 from the International Organization for Standardization and in the Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Compliance with the Charter of Fundamental Rights of

As a result of the new MDR, many adjustments will be required in the roles and responsibilities of all involved in manufacturing and distribution of medical device products into Europe.

the European Union, which governs personal data protection, is required as well.

Currently marketed devices will not be automatically grandfathered into the new MDR without need for further clinical investigation or documentation. In the case of implantable devices and class III devices, clinical investigations shall be performed, except if (under Article 61):

- the device has been designed by modifications of a device already marketed by the same manufacturer;
- the modified device has been demonstrated to be equivalent (to be endorsed by the NB); and
- the clinical evaluation is sufficient to demonstrate conformity with the relevant safety and performance requirements.

From 2027 onward, the submission of a single application for a clinical investigation involving multiple Member States will be established (comparable to the rules for pharmaceuticals coming into force much earlier).[4]

Unique Device Identification (UDI) Requirements

There are many requirements associated with verifying a medical device product through the UDI System, including an obligation to place relevant information on the label of the device and all higher levels of packaging. In addition, UDI device identifiers (UDI-DIs) must appear on the EU Declaration of Conformity.

The European UDI System has been designed to improve the traceability of medical devices and IVDs, and to improve incident reporting and oversight by the competent authorities. UDI will be used to report serious incidents and field safety corrective actions. MEDDEV templates have been developed that will include numeric descriptions and UDI, with the task of keeping the list of UDIs up to date being the responsibility of the manufacturer. Further, manufacturers of implantable devices must provide UDIs on the devices' accompanying implant cards.

Annex V indicates a new UDI-DI is required whenever there is a change that could lead to misidentification of the device and/or ambiguity in its traceability, such as alterations of the brand name, of the device version or model, in requirements for sterile packaging or for sterilization before use, in the quantity of devices provided in a package, in critical warnings, or in contraindications.

Core data elements must be submitted to the UDI database prior to placement of a device on the market, and the devices and the device packages must have UDIs visible via an approved UDI carrier [e.g., a bar code accompanied by Human Readable Interpretation (HRI)].

EUDAMED

Several articles in the regulation address requirements to register information electronically under EUDAMED, as part of the MDR, for the economic operators. The European database on medical devices will be transformed into a public tool. Previously, EUDAMED has been an information repository exclusively accessible to national competent authorities and the European Commission.

The new MDR is now mandating use of this web-based portal for economic operators and notified bodies to provide data related to various articles of the MDR, including clinical investigations and summaries of safety and performance for class III and implantable devices. The database is expected to be operational in May 2020, but delays may occur.

Conclusion

The new MDR imposes significant changes, including verification of the Declaration of Conformity and technical documentation, the addition of a designated person responsible for regulatory compliance, verification that UDIs are properly used, new labeling requirements, demonstration of device conformity to regulations, and involvement in post-market surveillance.

As a result of the new MDR, many adjustments will be required in the roles and responsibilities of all involved in manufacturing and distribution of medical device products into Europe, which are covered in articles 10–15 of the MDR.

Economic operators commercializing medical devices in the EU must be prepared to adopt these new rules, as "grandfathering in" will not be allowed. Each device must be certified under the new rules in the transitional time frames that have been defined: with medical device manufacturers having 36 months from May 26, 2017 to meet the new requirements.

Time is flying, therefore it is important to start planning as soon as possible to be ready for the numerous requirement changes.

References

1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
2. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
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OPERATING ASSUMPTIONS

Ronald S. Waife

The End is the Beginning

"Begin with the end in mind" is one of those classic business phrases which is no less valuable for the number of times it is ignored. Clinical research sponsors are guilty of often fatal forgetfulness of this key concept when planning the development, implementation, and use of new software applications or major organizational change.

Clinical research sponsors generally start an organizational change or a software acquisition not with the end results firmly planted in their minds, but with some "stimulus" having been applied to their backsides: a department is complaining that everybody else gets new tools except them; the competition changed its outsourcing model so the firm's executives think it should too; someone met a smooth-talking salesperson on an airplane; a vendor just announced an upgrade and it won't support the old version anymore; the firm just hired a new vice president and she prefers vendor "X" over vendor "Y." While some or all of these situations may justify change, they do not in themselves sufficiently define the "why" and "what."

Starting Isn't the Hard Part

Sponsors may also start from some business trigger which gives them the illusion that the end is in mind: we need to save headcount, so let's use electronic data capture (EDC); or we're frustrated with having multiple overlapping and out-of-date investigator databases, so let's buy a clinical trial management system (CTMS); we just acquired Teeny Biotech and we don't have anyone in-house in its therapeutic area, or our new translational medicine executive says we're going to have a flood of pharmacogenomics data coming in, so let's get one of those "data warehouses."

What's missing from these situations is sufficient consideration by the company of what the strategic benefits and daily operational impacts will be, what the software's users will have to change to use it properly, and overall what will the benefit be two years from now? What is the tie-in between the initial impetus—the needle in the backside or the business trigger—and the actual output the change will provide?

This disconnect is particularly critical in enterprise software projects or major business acquisitions, because we all know that the cost in money, time, headcount, and disruption will be high. The benefit therefore must be high as well, or the cost reduced, to be in line with the diminished (and realistic) results. The good news is that analyzing a potential project's end-user benefit compared to the initial impetus need not be fatally time-consuming, which is the usual reaction to the suggestion; however, it can save large amounts of wasted time and money.

We should recognize that it is very easy to fall into the disconnect trap. For instance, let's consider the situation where clinical operations becomes frustrated about the multiple investigator databases being used. The complaint is forwarded to the information technology department (or worse, a naïf goes to a booth at a trade show), and the answer comes back: there is no "investigator database fixer" product out there, but there are these CTMS packages and boy, they do everything. Before you know it, you are installing a multimillion-dollar application over multiple years, you've doubled the

amount of training everyone has to go through, and you have all this rich functionality, and no one can or wants to use it because it's not relevant—neither to the original trigger or to the actual user circumstances.

I would suggest that even a good understanding of how the end-user works, and what he or she needs, is not sufficient in today's business environment. We have fewer and fewer in-house staff, we are narrowing our "distinctive competencies," we have uncertain economic and reimbursement conditions, and we have unrelenting competitive pressures. All of this mitigates against expensive multiyear infrastructure projects unless we do more to predict and understand the future end-user business need. What should the future identity, purpose, and constitution of our business look like, and therefore, what changes and tools do we need to get there?

Even for projects where the pain and the solution appear more clear and pragmatic, we are usually missing a robust and detailed visualization of how a tool will be used, and without this, we will misconfigure and misspend our time and money. For instance, how does a shift to outsourcing change who the users are for a CTMS, document management system, EDC, and similar programs? How useful are e-tools if the "back end" of the workflow stays "paper-minded" in its policies and procedures, reflected in unchanged workflows, double-checks, and review practices?

And Vendors, Too

The developers of software used in clinical research are equally guilty of forgetting the context of how customers use their tools. Vendors have great opportunities to add significant value to their customers by helping sponsors see the possibilities that their tools open up, and by knowing the clinical research business as deeply and broadly as possible. This knowledge should translate into more focused and anticipatory designs, creating more powerful and efficient tools. Too often, however, vendors and contract research organizations see educating their clients as a danger to future sales, and try to over-simplify change.

Typical software development—even the industry-specific kind we in clinical research usually encounter—tends to chase after customer-driven enhancement requests that are often short-sighted for all the reasons cited above (responding to the "needle in the backside"). The result is needlessly complex software with features even the requesting sponsors may forget they wanted! More damaging than needless complexity is that the effort to chase enhancements takes money away from the literal "end"—the output, reporting, and visualization of information (which is all a tool is really good for).

This irony plagues each aspect of the research software universe. Vendors may see the whole gamut of functionality possible, but as professional engineers, they see and build it linearly (they begin at the beginning and end with the end). As a consequence, they inevitably run out of time and money before they reach the output function (reporting).

How many times do we hear vendors do their demos this way: they start with the very first point of data entry, move through to the point everyone is waiting for (getting something back for all that entry), and then they say, "well, there was no point in re-inventing a report writer, so you should use something standard and off-the-shelf." The "data out" are what matter in the actual business context, but to a software engineer it looks like a data processing problem, not a business use problem. If this were true, and off-the-shelf reporting was adequate, so too would be off-the-shelf entry—so actually, let's forget the whole thing; and yet there really is a utility for clinical research–specific software products, if built with the end in mind.

Today's software vendors need a knowledgebase and a discipline not commonly found. The need for vendor domain knowledge is greater than ever, plus an understanding and vision of where their customers are going. Certainly, sponsors have the bulk of the responsibility in teaching this, but for the vendors, the discipline is in rejecting enhancements for enhancements' sake and leading their customers toward being enabled to handle the future.

Is There an End?

Another way that clinical research sponsors get ahead of themselves is to assume that once the first wave of interest and urgency is sated, the project is done. This is hardly the case. Yes, processes may have been rewritten, software configured, and newly reorganized staff trained in their altered jobs, but the work does not, and cannot, stop there. The second and third waves of change wash over the organization as the "lower priority" staff need to be oriented, and as the new processes need to be iterated to reflect actual experiences versus the original assumptions.

It sounds like "continuous quality improvement" for those sponsors who have process improvement staff. Except, for sponsors with such staff, they themselves are moving from project to project—working continuously, perhaps, but not necessarily improving. They too get bored (or run out of resources) with the first wave of the project, and are not there to reconsider the impact and effectiveness of new work models or software applications. So, in some senses there is no end, but rather steady re-examination of purpose, needs, and solutions.

"Begin with the end in mind" is certainly the start of a solution. "Begin with an understanding of the end" is probably more profound. Identifying possible "ends" is one thing; understanding their meaning to the user and the enterprise requires more thought, breadth, and management than most sponsors or vendors are used to providing.

How useful are e-tools if the "back end" of the workflow stays "paper-minded" in its policies and procedures, reflected in unchanged workflows, double-checks, and review practices?

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Blind Spot in Clinical Trial Operations: *Who is Watching?*

PEER REVIEWED

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Who is watching when clinical trial stakeholders—the sponsors, contract research organizations (CROs), and sites involved—are spread out doing simultaneous business on multiple trials across the globe? Who is watching to make sure that every individual clinical trial project is proceeding through its milestones with every possible issue and risk properly identified and responded to?

The assumed answer is usually *everyone*—as in every stakeholder—and therein lies the problem. Everyone thinks everyone else is watching; however, the truth is, with everyone being overloaded with information, it is not humanly possible to track every issue in real time.

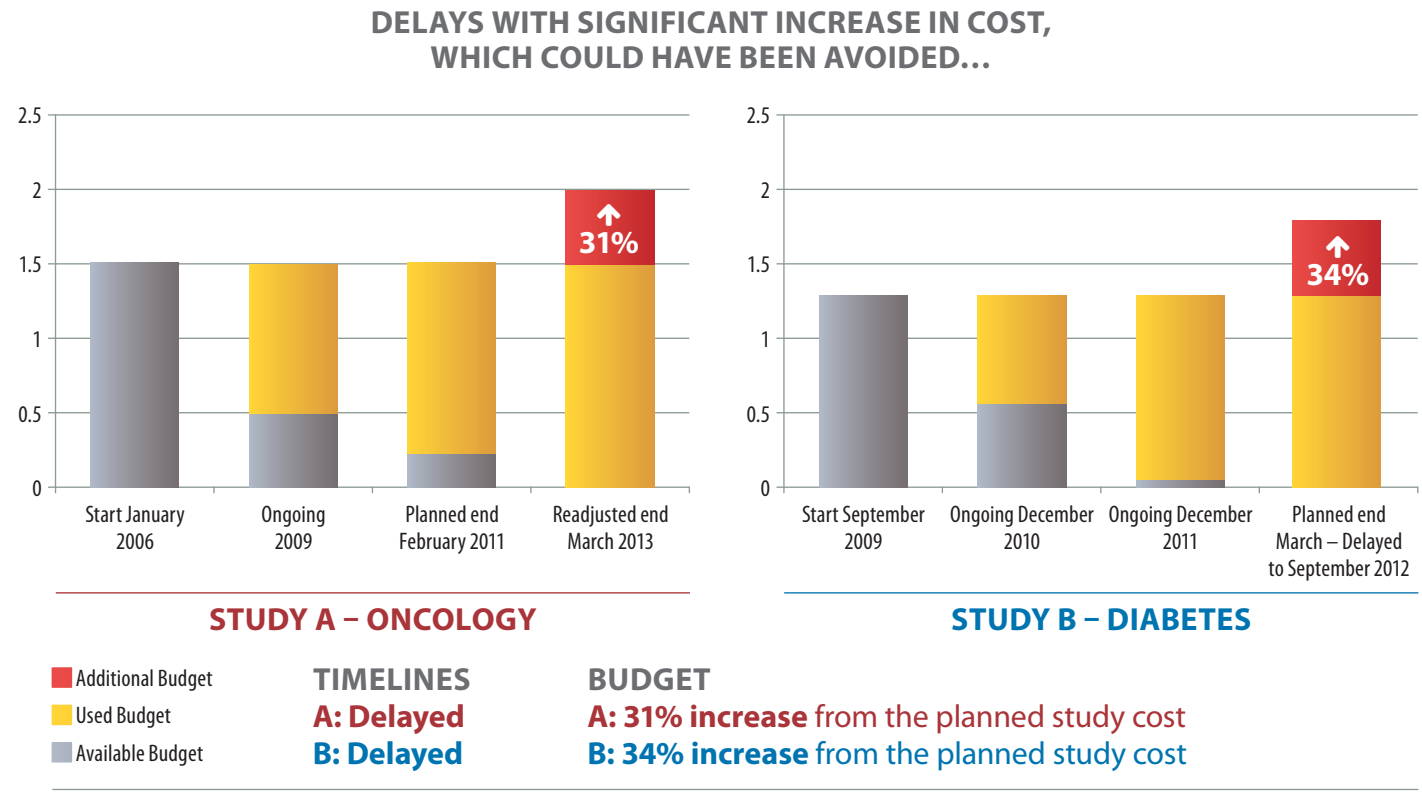
Mostly, issues are reported much later than is ideal, and with little or inadequate action taken.[1] Consequently, for example, one unattended query could become the basis for escalated data management discrepancies. Project delays and increases in projected study budget are more the norm than the exception. More important than the consequent increase in cost is the painful loss of timely access to treatment by waiting patients.

A Tale of Two Studies

Without disclosing either study's profile, we illustrate the philosophy behind "Who is Watching?" by describing the issues underlying delays in two studies. We reviewed the available data and results of interviews with the project team during the January–May period in 2012. Several unattended and unmitigated risks contributed to delays in completion and increased budgets for Study A (Oncology) and Study B (Diabetes) (see Figure 1). The issues listed below interrelate and impact each other, and many of them are broken out for examination in the sections to come:

1. Many unresolved queries[2] (Study A alone had nearly 10,000 total queries)
2. Insufficient monitoring caused by inadequate processes
3. Lack of staff training
4. Lack of documented communications among the stakeholders
5. Lack of structured handover
6. Insufficient vendor oversight
7. Insufficient contract oversight and tracking

FIGURE 1: Time and Cost Analysis



Unresolved Queries

About 40% of the queries for Study A were repetitive in nature, and about 30% were more than nine months old with no apparent documentation of reasons for the delay in being addressed. Multiple changes of project managers and local country operations teams were the immediate reasons for unresolved queries. Lack of query details in project management and communications documents with the data management vendor also helped to worsen the condition of outstanding queries.

For Studies A and B, contracts failed to adequately establish thresholds or specify how to manage the numbers and kinds of queries. Unresolved queries alone resulted in an increase in change orders that then increased the budget. Further, there were no interim face-to-face meetings or communication between the key clinical trial sites and the sponsor or monitoring staff. Reviewing the communication logs, particularly where minutes were kept, revealed that regular communications were nonexistent.

Insufficient Monitoring

Both studies lacked sufficient monitoring visits and well-defined processes. Although it is acceptable for long-term studies to have a reduced number of visits, it is essential to have processes to continue to monitor the quality of the data that the studies are generating. Since these were missing, several quality issues were overlooked, including monitoring of critical data points.

Monitoring data deficiencies were mainly due to limited onsite visits. Case report forms (CRFs) that were sent to data management did not undergo source data verification (SDV), resulting in repeated queries.

Other issues were related to delayed completion of CRF (e.g., data entry was delayed for almost one year in some cases, thus query resolution was also delayed). Changes in principal investigators in some institutes occurred without proper handover and documentation. In addition, on the specific datapoint of efficacy, the follow-up data to treatment outcomes were missing; names of concomitant medication were missing and not reconciled; and safety database reconciliation was never performed.

The resulting delayed interim analysis was costly because the needed data for planned conference publications were not available. This postponed product launches and key opinion leader engagement activities.

Although it is acceptable for long-term studies to have a reduced number of visits, it is essential to have processes to continue to monitor the quality of the data that the studies are generating.

Using innovative technology that is the personification of a well-trained, cost-oriented, and independent (human) quality checker in a complicated assembly line, but a hundred times better than any human, is no easy task.

Lack of Training

Since both were long-running studies in multiple countries in Asia, the Middle East, and Eastern Europe, several regulatory and pharmacovigilance changes occurred. Training related to new regulations, policies, and standard operating procedures (SOPs) was not implemented in real time at several clinical sites in different countries, which resulted in protocol deviations such as missed visit windows, noncompliance to study product intake, and inadequate safety reporting. Correcting these deficiencies required time-consuming and resource-intensive efforts. Lack of a proper training matrix and poor delivery of the existing training were at the root of this issue.[3]

Lack of Stakeholder Communication

Our analysis of the issues also revealed a lack of proper communication channels to not only address the issues, but to determine their severity. Had there been proper risk monitoring through quality tracking or oversight, the issues could have been identified and resolved in a timely manner.

A robust quality oversight system would have prevented the delays and increased costs experienced during both studies. By applying the spirit and concept behind the U.S. Food and Drug Administration's (FDA's) guidance on risk-based monitoring and the related European Medicines Agency's (EMA's) reflection paper, the study owner—a major pharmaceutical company—could have alleviated the situation by combining the right technology with trained personnel.

In 2012, the FDA encouraged "sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight in part by taking advantage of the innovations in modern clinical trials. The FDA asserts that [RBM] could improve sponsor oversight of clinical investigations."[4] Further, in 2013, the EMA came out with its own views on RBM for quality purposes in clinical trials, in a paper that states the purpose is "to encourage and facilitate the development of a more systematic, prioritized, risk-based approach to quality management of clinical trials, to support the principles of Good Clinical Practice and to complement existing quality practices, requirements and standards. Quality in this context is commonly defined as fitness for purpose. Clinical research is about generating information to support decision making while protecting the safety and rights of participating subjects. The quality of information generated should therefore be sufficient to support good decision making."[5]

While the intents of the FDA's guidance and EMA's reflection paper are similar, two major issues are noted with the adoption of the tenets of both documents: *interpretation and implementation*.

Depending on the functional structure of a sponsor's or CRO's project team, there is a shift from 100% SDV with frequent face-to-face interaction with a site team to a more targeted and less frequent approach to monitoring visits. The decision-making process on how to adopt the guidance hinges upon first tweaking conventional, proven, and tested processes (re-prioritizing the budgets that come with them), and then to assume that the expected outcome of the tweaked actions will yield the same result. Unfortunately, this is not the case.

Updating processes is not the only key that defines compliance with both the guidance document and the reflection paper. For the paradigm to shift, the mindset must change. Along with this change must come acceptance of the initial increase in cost to leverage new or already available technology.

The cost of change will not be readily visible until a few years down the line. In performing the root cause analysis and identifying the factors that contributed to the increase in cost and delay in completion of the studies mentioned earlier, it became more evident that it was only after the company decided to retrospectively review its processes and identify the gaps that things became more obvious.

The old adage of "learning from one's mistake" not only resounded clearly, but also highlighted the fact that in today's current clinical trial management environment, staying ahead and being first to market must take into account changing attitudes, refocusing on standardized training, increasing reliance on utilizing technology-savvy resources,[6] and reconfiguring budgets to include (during the start-up phase) technology that can do half the work for people who will be spending more of their time in-house or homebound versus continuing to work as "road warriors."

Quality Oversight Technology

Finding the technology these days that best suits what project teams need is like differentiating between wheat and rice noodles in a bowl of soup. Technology platforms from different vendors have major similarities in vision, and all promise to track and trend in as close to real time as possible.

Using innovative technology that is the personification of a well-trained, cost-oriented, and independent (human) quality checker in a complicated assembly line, but a hundred times better than any human, is no easy task. The sponsor is the best stakeholder to utilize such technology, since other than the patient, the sponsor is the most impacted by delayed clinical trials and consequent increase in budget allocation.

The ability of the sponsor's clinical research team to use, at any time of the day and night, their smart phones or tablets to check the status of their studies in real time is to this day still in question. The goal of being able to rely on technology to see the number of queries, or patients enrolled, or risks identified and graded, as well as the cost for each activity and the site's actual performance remains on the project team's wish list. To date, project teams are still dependent on reports being spit out by data management or study management systems purchased by their companies, or must rely on Excel spreadsheets as their backup.[7]

The questions remain: How can innovative treatments be made available faster and improve the trends toward disease management? How do we ensure that both data quality and the means of collection are reliable?

With a new political administration in the U.S. and with forecasts of deregulation in the FDA[8] leading to faster cheaper drug development, a system that functions as an independent quality and risk tracker may be needed more than ever to ensure the "no blind spots" mentality. Any risks or quality issues detected compromise clinical trial safety and efficiency without timely responses. Hence, such a system should be configured to be able to track and trend issues in as close to real time as possible. Company and site processes will need to be reviewed and enhanced to adapt to the changing landscape.

There is an opportunity for the FDA to once again focus on its mission of ensuring that patients have access to better drugs faster and at lower cost.[9] For years, the agency appeared risk averse, because it is answerable to Congress and the public when risks of adverse side effects from approved drugs become apparent.

FDA's risk aversion converts to complicated regulations that contribute to delays due to lack of resources at sites to comply with the regulations, or due to failures to fully understand the intents of the regulations on the parts of clinical trials teams. Meanwhile, as the clear victims of side effects are accounted for, those patients who have yet to access or even know of better drugs to improve their lives remain mostly unidentified. Who can quantify the loss of life or diminishment in quality of life due to delays in terms of improved treatments reaching market?

The prevailing cost of a clinical trial program for the development of a single new drug could range from millions to billions of dollars.[10] Only the big pharmaceutical companies will long be able to manage this because they have the resource, but even these firms are complaining; their investment must translate to bigger returns, thus costlier drugs.[11] The ones who are excluded from the big trials are the small, innovative pharmaceuticals and biotechnology companies, and it is difficult for them to compete due to cost; however, they could be the source of life-improving drugs and devices.

Quality and Risk Oversight Tracking (QROT)

QROT[12] is the use of Big Data analytics and patient-centric solutions that are transparent, and that promote integrity with the ultimate goal of bringing medicines swiftly to patients at affordable prices (see Figure 2). The industry's tradition of using mostly batch data transfers is not effective in helping improve data-driven decision-making abilities. With QROT, however, tracking quality and risk indicators (including financial data from enterprise solutions) in real time is very valuable in assessing cost and performance of projects any time of day or night in smart devices.

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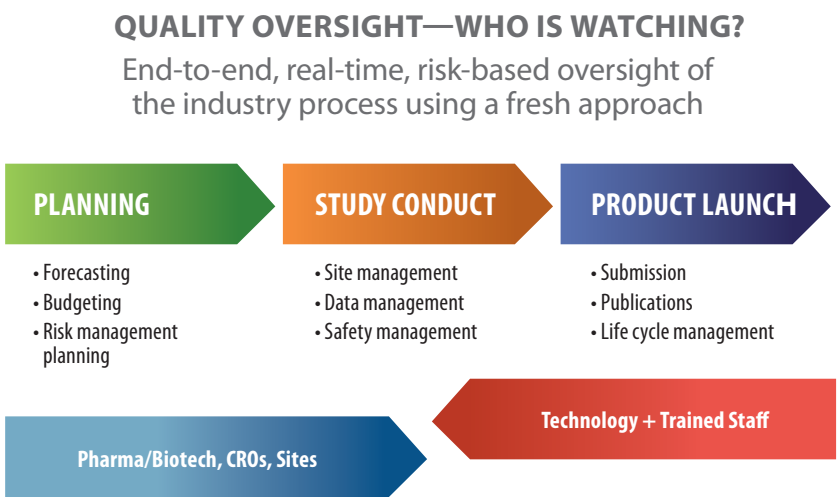
FIGURE 2: Quality and Risk Oversight Tracking



This QROT concept is further exemplified by the Quality Management Institute, which ascribes to having a "Zero Defect Attitude."[13] As applied to the process of QROT, this attitude means that having "pride of workmanship" leads to people doing things right for the client, and delivering as close to what was promised as accurately as humanly possible. Adopting a "Zero Defect Attitude" empowers project teams to focus on using solutions that can diminish possible deficiencies.

Conclusion

Relating back to the case studies presented, the lack of quality oversight resonated from all the deficiencies identified. The underlying thought that followed was the need to avoid having the same problematic issues arise again and again.

The owner of the studies eventually embarked on trying something different; using the outcomes from the root cause analysis as a tool to defend the study budgets and to secure the use of a new technology for quality risk oversight that tracked and trended data as they came in.

Two new, smaller scale studies were launched. This time, the project team used the information from the systems dashboard to closely monitor the progress of the studies. In the process of having a more robust and updated tracking of how the studies were doing, they were also able to enhance their SOPs, propose the continued use of the technology for quality risk oversight, and justify more training for their project team.

After 12 months, these two new studies had clear outcomes in terms of finishing on time and within budget, and more importantly, being available for publication per the targeted date. No more blind spots were noted after adequate tracking had been initiated.

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A Mixed Method Approach to Assessing Good Clinical Practice Computerized Online Learning

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Clinical research translation requires a trained, well-prepared workforce of clinical research professionals who can effectively conduct critical testing in clinical trials.[1] However, trials funded by industry and governmental sources have been criticized for inconsistencies in the design, execution, analysis, and reporting of clinical trial activity,[2] even as development of new drugs, devices, and behavioral interventions is one of the most highly regulated endeavors in the United States.[3]

Recently, the National Institutes of Health (NIH) mandated "all NIH-funded investigators and staff engaged in clinical trials research be trained in Good Clinical Practice (GCP)."

Management of clinical research at the site level is largely delegated to study coordinators who may manage multiple studies for principal investigators (PIs) with a high degree of autonomy. This takes place in an evolving interdisciplinary arena, where complexity is the rule rather than the exception. Importantly however, consistent requirements for providing and ensuring an appropriate level of qualifications do not exist.

A critical barrier to clinical trials is inconsistent—or even absent—competency-based training for all study personnel involved in clinical trials,[4] even as the Declaration of Helsinki opines, "medical research must be conducted by individuals with appropriate training and qualifications in clinical research."[5] While training and education of research staff is integral to the success of the team and the studies they work on, standardization of training is limited.[6]

Training for research staff often takes place within isolated academic departments, where there is variable quality in the content delivery. A competency tracking system to validate that staff have the knowledge and skills to meet data and safety standards may not be present. Further, inadequate training can lead to delayed startup, unmet enrollment goals, poor data integrity, and compromised research participant safety (e.g., during the consenting process), although clinical research professionals are held accountable for meeting these measures.

Background

Recently, the National Institutes of Health (NIH) mandated "all NIH-funded investigators and staff engaged in clinical trials research be trained in Good Clinical Practice (GCP),"[7] the tenets of which are promulgated by the International Council for Harmonization (ICH) and followed by researchers in such locations as the U.S., Canada, European Union, Japan, and Switzerland. Many programs, such as the Collaborative Institutional Training Initiative (CITI), which provides peer-reviewed, web-based educational courses in research, ethics, regulatory oversight, responsible conduct of research, research administration, and other topics pertinent to the interests of member organizations and individual learners, rely on standardized training systems; 60 of the 62 institutions supported by the NIH Clinical and Translational Science Award (CTSA) program currently use CITI training.

The nonprofit Association of Clinical Research Professionals (ACRP), meanwhile, which offers a variety of training, networking, and self-directed resources to its members and other stakeholders in the research community, has an on-demand eLearning platform designed to equip learners with the core concepts of GCP, among other topics.[8] Approximately 30% of CTSA institutions also utilize ACRP training.

CITI and ACRP platforms introduce users to the clinical research environment and regulations. Whether or not the process of obtaining competences is better achieved through online learning or structured work experience and mentoring has not been shown.[8] The purpose of the research described here was to assess the quality of online training in the ACRP and CITI learning platforms.

A randomized, mixed-method, quantitative-qualitative, sequential, explanatory design framed this study. Analysis of focus group data was used to corroborate, refute, or explain the results of the survey.

Participants and Their Preferences

Participants (interviewees) included volunteers involved in human subject research at any level at a large, public university in the southeastern U.S. that is part of the aforementioned CTSA program, without differentiation for gender and race. After institutional review board (IRB) approval, participants were recruited by placing posters on campus and sending e-mails to various mailing lists used by the research community. A total of 128 participants were needed to provide sufficient power analysis for this study.

Consenting participants accessed a CITI-developed online presentation on "GCP for Clinical Trials with Investigational Drugs and Biologics (ICH Focus)" and an ACRP-developed online presentation on "Good Clinical Practice: An Introduction to ICH GCP." Each participant was paid $100 for completing the training modules and the pre- and post-training surveys for both modules.

After first completing the randomly selected training module and survey, participants then completed the alternate training platform and survey a minimum of one week later. The Wilcoxon signed-ranks test was used to test for differences between the paired observations. Participants' responses determined their preference for one of the learning platforms on student learning

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variables including: (a) engaging, (b) ease of navigation, (c) satisfaction with scenarios, (d) content relevance, organization, and feedback, (e) hours to complete the online learning courses, (f) number of attempts to pass the module, (g) number of years engaged in research, and (h) type of responsibility. Level of significance in testing was set at $p \leq .05$.

Participants' preference for the ARCP training was statistically significant on the variables of engaging ($p \leq 0.0003$), ease of navigation ($p \leq 0.0205$), and hours to complete the course ($p \leq 0.0006$) (see Table 1). Compared to the mean of 2.3 hours for the ACRP training, it took participants a mean of 3.26 hours to complete the CITI course. Participants reported a preference for content organization and the opportunity for feedback in ACRP. Those with a preference for CITI were slightly more satisfied with the relevance of the content and expended less time in passing this course.

Focus Group Analysis

Further, 10 individuals were randomly invited from a pool of 132 participants for a focus group discussion, with nine individuals eventually participating and being compensated an additional $100. Participants' demographic information and responses to 22 survey questions were recorded in, and housed at, secure servers. Participants were asked to: (a) indicate time taken to complete the training modules, (b) preferred presentation style/method, (c) satisfaction with the material presented, and (d) satisfaction with the learning objectives.

TABLE 1: ACRP vs. CITI Learning Platforms on Student Learning Variables

Variable	ACRP Mean (Standard Deviation)	CITI Mean (Standard Deviation)	Wilcoxon Two-Sample Test p-value (Two-Sided)
Engaging	2.23 (0.84)	1.69 (0.97)	0.0003
Easy to Navigate	3.38 (0.92)	3.2 (0.65)	0.0205
Satisfaction with Scenarios	2.33 (0.54)	2.25 (0.54)	0.4265
Satisfaction with Relevance	2.41 (0.62)	2.43 (0.55)	0.9937
Satisfaction with Content	2.38 (0.58)	2.23 (0.57)	0.1338
Satisfaction with Feedback	2.21 (0.64)	2 (0.64)	0.0581
Hours to Complete	2.3 (1.25)	3.26 (1.71)	0.0006
Attempts to Pass Module	1.44 (0.62)	1.26 (0.44)	0.0961
Responsibility	1.98 (0.63)	2.1 (0.65)	0.3650

This single focus group was conducted to better understand participant experiences with the online learning platforms. Participants were all female; two African American and seven White. This methodology relies heavily on the skills of the moderator (interviewer) who: (1) introduces the topic in the same way, (2) ensures the conversation remains on track, (3) collects data related to the shared experiences among a group of participants, (4) develops an understanding regarding a phenomenon, and (5) encourages all participants to respond to questions (see Table 2).[9–12]

Three of the authors independently read the focus group transcript and formulated impressions of emergent themes. During a meeting, they reached consensus on the emergent themes and related conceptual definitions. Next, two authors selected two of the four themes and, while reading line by line, extracted selected text representative of the conceptual definition related to the theme.

These authors then audited each other's analysis to indicate agreement or disagreement with selected text. Use of the constant comparative method assisted in moving data to better fitting codes and codes to other categories or themes. This process resulted in some themes coalescing and others expanding; it involved coding, refining codes, identifying examples to support themes, making a master outline to illustrate relationships, and locating quotations to support the outline. The third author resolved any differences in opinion.

Four themes emerged, including: Self-Evaluation, Missing Components, Deviations, and Preferences (see Table 3). Self-evaluation refers to assessing personal skill level. Missing components refers to identifying content and topics not presented in the learning platforms. Deviations refers to pointing out protocol violations. Preferences refers to expressing predispositions for one of the two particular learning platforms.

Due to space limitations in the print edition of this journal, the research team's summary of the qualitative results from this portion of the overall research is shared as a supplemental document in the "Good Clinical Practice & Ethics" Interest Group hosted in the ACRP members-only Online Community (see https://www.acrpnet.org/networking/interest-groups/), and can be requested by non-members by contacting editor@acrpnet.org.

Discussion

Overall, the survey findings showed participants found the ACRP course more engaging, easier to navigate, and requiring less time to complete than the CITI course. Findings from the focus group confirmed those results.

Notably, online training accentuated the integral role of the coordinator in ensuring the quality and veracity of research, and enhanced participants' confidence levels. Also reported was how vastly different the training platforms were in terms of content relevance, organization, applicability, and assessments. Inability to have face-to-face interaction was an impediment to observation, and prevented opportunities for spontaneous peer-to-peer and peer-to-instructor interaction.

Other criticisms of the online learning platforms were that the questions and scenarios presented did not reflect the realities of day-to-day work. The findings supported the notion that the online learning platforms offered (a) no mechanism to validate staff attainment of knowledge or skills, (b) no evidence participants could consistently meet data and safety standards, and (c) no mechanism to ensure competency.

Overall, the findings highlight how obtaining competencies cannot be solely achieved through online learning. Further research is warranted, including replicating this design to see if the results are unique to our locale or if they will be similar at other CTSA institutions.

Coordinators felt vulnerable in a culture designed to protect institutions. Future research might be directed toward examining the inequalities and systems of power as they interlock with GCP regulations in a "relational, dynamic, processual, and mutually transforming character [as found] in any system of power differentials."[13]

Limitations

The researcher-constructed survey was not a validated scale. Without established psychometrics, the utility of the study findings must be considered in the context of these observations. Perhaps participants simply provided responses in terms of what they believed was essential, selected responses they thought researcher sought, or over-rated their skills. The study was carried out at single health science center, representative of only one of the 62 CTSA hubs.

TABLE 2: Focus Group Questions

1. Which platform, CITI or ACRP, best addressed your training needs?
2. Which section or module was the most important to you? Why?
3. Was there any element that was missing from either of these training modules that you feel would help you in carrying out your responsibilities as a coordinator?
4. How well did the CITI and ACRP platforms measure GCP competencies?
5. Can you recommend a platform for GCP training at the University of Florida: (a) CITI, (b) ACRP, (c) classroom, or (d) a combination? Explain why.
6. What essential skills or competencies for coordinator training and professionalization were not addressed in the GCP training program?
7. Has your confidence in your level of professionalization increased or decreased as a result of this GCP training program? Explain why.
8. How has GCP training program influenced your role as a research coordinator?
9. What aspects of the GCP training program influenced your own sense of being/becoming an ideal research coordinator?
10. As a result of the GCP training how confident are you in: (a) Identifying ethical and professional conflicts in conjunction with clinical trials and (b) Bringing observed ethical/professional conflicts within clinical trials to the attention of the PI or other designated authorities?
11. How often have you observed deviations in the last 12 months? (a) Did you bring this deviation to the PI's attention? (b) If so, did you discuss it verbally, via e-mail, or through both methods? How did the PI respond? (c) In other words, did the PI take your observation seriously and make the appropriate changes? (d) Did the PI simply acknowledge your concern, but not act on it? (e) Did the PI reject your observation of the deviation? (f) How would you handle a situation where you observe a serious deviation, but the PI does not take any action?

TABLE 3: Main Themes from Participants

Themes	Conceptual Definitions
Self-Evaluation	Assessing personal skill level
Missing Components	Identifying content and topics not presented in the learning platforms
Deviations	Pointing out protocol violations
Preferences	Expressing predispositions for particular learning platforms

Consenting participants accessed a CITI-developed online presentation on "GCP for Clinical Trials with Investigational Drugs and Biologics (ICH Focus)" and an ACRP-developed online presentation on "Good Clinical Practice: An Introduction to ICH GCP."

All nine individuals participated actively during the focus group; however, it is possible some may not have felt comfortable voicing their opinion or may have felt pressure to conform to the group's consensus opinion. Overall, the focus group findings are not generalizable. Also, the number of questions asked was restricted; the available response time for any participant to answer each question was necessarily limited in order to hear from everyone. Despite efforts made to systematize data collection through use of a standardized protocol, the potential for moderator influence cannot be determined.

The authors want readers to know that we have no potential conflict of interest with the products assessed in this study.

Conclusions

Although the CITI and ACRP platforms provide a solid introduction to the clinical research environment and regulations, they are not without advantages and disadvantages. Participants showed a clear preference for the ACRP platform, and the ACRP course took less time to complete compared to the CITI course.

The findings suggest that no single online training product adequately meets the guidelines set forth by ICH GCP or the intentions of NIH, in terms of developing a fully competent translational workforce. Future research should determine how competencies can be effectively and efficiently certified. Developing rubrics and criterion indicators and calibrating raters will likely be the next steps.

Acknowledgments

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PEER REVIEWED | Kelly M. Cairns, MA, BASc, APRM, CCRA
[DOI: 10.14524/CR-17-0030]

OPINION:

The Role of Certification in Developing a Quality Clinical Workforce

"Quality" is a term that is thrown around at will when speaking about clinical research—we speak of quality by design, quality systems, quality endpoints, quality management plans, quality data, quality outcomes, etc. We have been talking about quality for as long as I have been involved in clinical research, and that has been for more than 20 years.

The goal of certification is not to educate, but to provide a means by which proficiency and knowledge can be measured, hence measuring "quality."

One thing I've noticed in the clinical research enterprise is that we spend a lot of time focusing on quality goals, quality outcomes, and quality processes, yet we spend very little time focusing on "quality resources" and—in particular—"quality human resources." I would like to focus our attention in this article on the importance of the "quality clinical workforce."

As used in various situations, the word quality may convey the standard of something as measured against other things of a similar kind; the general degree of excellence of something; or a distinctive attribute or characteristic possessed by someone or something. As nebulous as these uses may be, how do we measure quality when we are speaking about the "workforce" or human resources? That is where certification comes in, as certification is a formal recognition of professionals who have demonstrated the knowledge, skills, and abilities to perform their duties by passing a certification exam based on international standards.

Further, certification is a voluntary process to recognize individuals for meeting standards in terms of their professional experience, and for achieving educational requirements before taking the exam. Certification assures the public that an individual demonstrates specific knowledge required of a practitioner at a certain level. The goal of certification is not to educate, but to provide a means by which proficiency and knowledge can be measured, hence measuring "quality."

Why Certification?

There are some obvious benefits to an individual from becoming certified (see Figure 1). Achieving certification demonstrates that you have met or exceeded the quality standards required in the industry and have validated your competence. It furthermore demonstrates a level of professionalism and indicates a commitment to quality standards.

In essence, certification defines you as a "quality resource" in your industry. As specifically considered within the clinical research enterprise, there are many pros to certification, including how it improves the conduct and public perception of research by establishing and continually raising the levels of quality to which we are held. More pointedly, sponsor companies and study sites are able to use certification as a yardstick by which they can have their quality resources assessed and measured.

Sources of Certification

Currently, there are several organizations that offer clinical research certification. To date, the Association of Clinical Research Professionals (ACRP) is the only organization that offers role-specific certification programs (through its affiliated Academy of Clinical Research Professionals) for the clinical research coordinator (CCRC®), clinical research associate (CCRA®), and principal investigator (CPI®)

In time, perhaps regulatory stakeholders around the world will also embrace certification as a quality measurement, and will deem that certification of anyone performing clinical research activities be required.

roles, as well as a general certified professional (ACRP-CP®) program since 2017 for anyone who does not neatly fall into the other roles.

Other organizations, such as the Society of Clinical Research Associates, offer more generic certifications covering multiple roles and functions. Many other organizations offer various types of role-specific certifications such as the Society for Clinical Data Management, the Society of Quality Assurance, the Clinical Research Society, and the Regulatory Affairs Professionals Society, to name a few.

Any respectable organization that offers certification will take the steps necessary to ensure that certain levels of quality have been achieved through their programs. Although ACRP may have led the way in the certification of clinical research professionals, there have been other organizations that have followed—not because any higher authority mandated it, but because their members asked them to.

In time, perhaps regulatory stakeholders around the world will also embrace certification as a quality measurement, and will deem that certification of anyone performing clinical research activities be required. This may be "pie in the sky" thinking, but it would go a long way toward making our study volunteers feel confident that they are being protected and are in "good hands."

Maintenance of Certification

For those of us who have achieved certification, equally as important is the subsequent maintenance of the designation. Throughout our careers, we want to continue to demonstrate that we are meeting or exceeding the quality standards set by the industry. Maintenance can be achieved through continuing education in both research- and healthcare-related subjects, as well as through continuing involvement in clinical research activities.

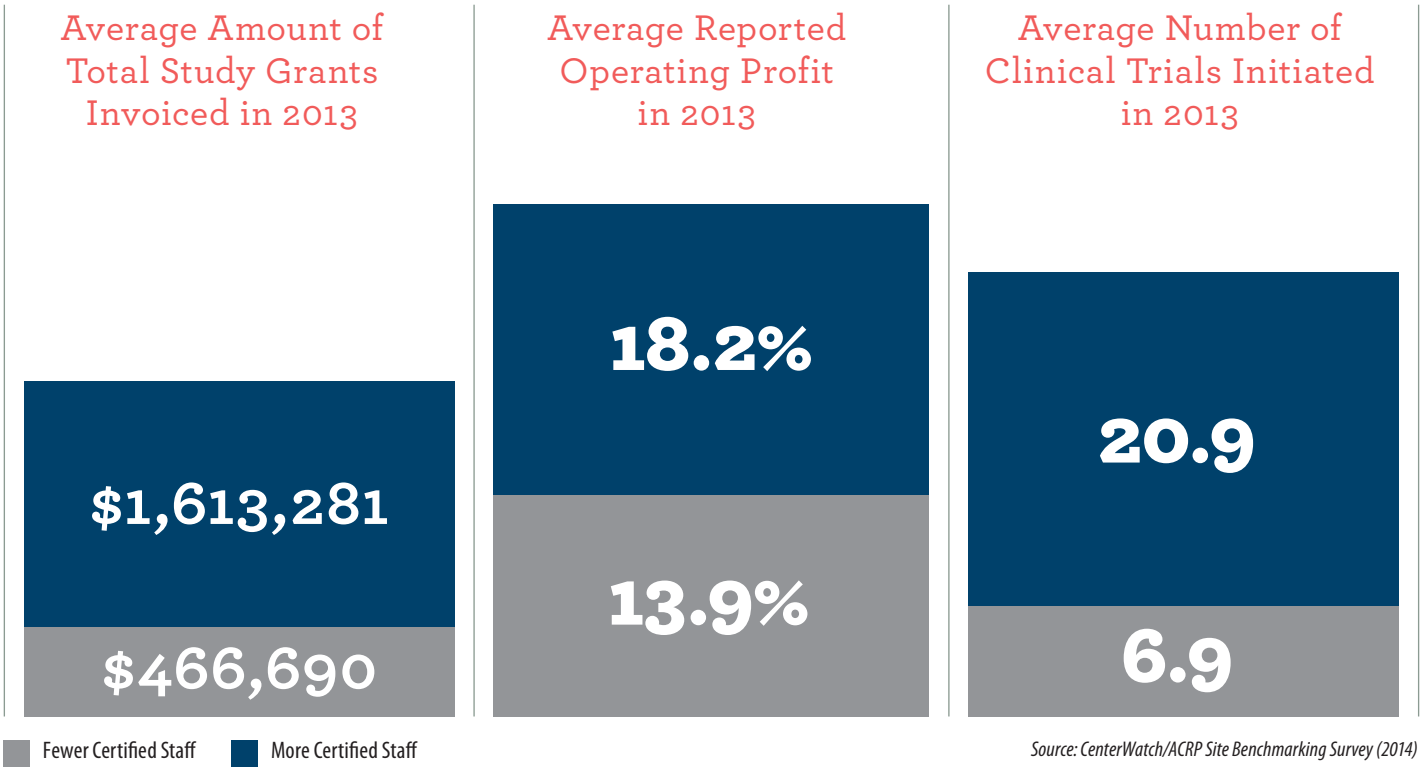
Since most individuals would prefer not to have to take a certification exam over again following a lapse in their certification status, the option for continuing education and continuing involvement is the more popular one, and the benefit to the industry is the assurance that certificants are staying abreast of the latest and greatest trends and topics in clinical research. In short, maintenance of certification validates that certificants continue to demonstrate their knowledge and skills as their careers progress (see Figure 2).

FIGURE 2: MAINTENANCE OF CERTIFICATION

FIGURE 1: REASONS BEHIND CERTIFICATION

Source: Survey of ACRP Certificants (January 2013 - April 2014)

FIGURE 3: INDICATORS OF CERTIFICATION'S CONTRIBUTIONS TO SITE PERFORMANCE



Source: CenterWatch/ACRP Site Benchmarking Survey (2014)

Linked to Fewer Protocol Deviations

CCRC® and CPI® certification have the potential to increase protocol adherence and improve clinical trial quality through links to fewer protocol deviations (*Clinical Research and Regulatory Affairs,* 2009).

Linked to More Favorable Outcomes from Regulatory Audits

A positive correlation exists between the CPI® designation and favorable outcomes (No Action Indicated) for FDA audits according to the article "CPI® Certification as Predictor of Clinical Investigators' Regulatory Compliance" (*Drug Information Journal,* 2012).

Other Considerations for Certification

As the clinical research industry has become more competitive, the need for its professionals to differentiate themselves from one another has become a more cogent reality. The use of credentials to demonstrate certification has become increasingly important when trying to promote one's curriculum vitae to the top of the pile.

Unfortunately, there has been some rather negative press regarding resume fraud, and one recent, controversial article cited that, out of more than 40,000 CRAs being captured by one recruitment firm, approximately 17% had falsified all or part of their resumes. As a hiring manager in the industry, I too have witnessed my share of "creative writing" when it comes to prospective applicants. This is where certification can play a role in ensuring that those applicants presenting with the credential of "certified" can be held accountable to a higher level, and employers can be assured of a standardized level of quality.

ACRP takes the use of its credentials very seriously, and has strict policies pertaining to the continued use of the "certification credential." Anyone who fails to maintain their certification must immediately stop using the credential to promote himself or herself. In fact, misrepresentation of one's certification status through ACRP is grounds for disciplinary action through the aforementioned Academy of Clinical Research Professionals, according to its "Code of Ethics and Professional Conduct" policy.

This, once again, points to the fact that certification is formal recognition of professionals in the industry who perform at or above a certain quality standard. Prospective employers and regulatory inspectors can search a registry to ensure that anyone using the ACRP credential is actually currently certified. Falsifying credentials is a serious blemish when it comes to tarnishing one's quality reputation, and no one wants that.

Getting back to the issue of "quality," it has been demonstrated that certification through ACRP has a positive impact on clinical trial quality surrogates, such as stated at left. From the sponsor's perspective when looking at potential sites, quality plays a role. Studies have shown that having certified staff at a site leads to fewer protocol deviations and potentially increases trial adherence, and that a positive relationship can be seen between a certified PI and more favorable audit outcomes with the U.S. Food and Drug Administration (FDA).

From a site's perspective, we can see a positive relationship between the number of certified staff and the number of study grants received, the operating profit achieved, and the number of clinical trials initiated (see Figure 3). These site performance metrics are all very important when trying to attract studies to your site; certification can therefore be seen as an investment in the professional development of a site's research personnel and the site's commitment to quality in the conduct of clinical trials. The return on investment for a site from having certified staff can be easily demonstrated.

Furthermore, certification can be used as a proxy for improved outcomes, which can be demonstrated through adherence to the protocol, compliance with the regulations, ethical practice, trial subject safety, and ultimately end-consumer safety. With respect to our quality clinical workforce, certification can be used as an acceptable method to validate that study coordinators, monitors, investigators, and other clinical research professionals have the knowledge, skills, and abilities fundamental to accomplishing their job roles.

As the arena of certification products offered through various organizations expands, there is a recognized need for more formal study of the impact on quality from the perspective of the site, the sponsor, and ultimately the patient. For now, the ship is moving in the right direction.

Conclusion

Now that we know what a quality resource is, we can measure that quality through certification. We also can demonstrate continued commitment to quality through maintenance of certification, and we are now moving to a more data-driven place whereby we can demonstrate improvements in quality through the use of "quality human resources."

Certification can be a valuable resource for a variety of stakeholders to validate that the clinical research professionals with whom they are engaging—in whatever relationship that may be (i.e., site-sponsor, sponsor-employee, site-employee, etc.)—have the knowledge, skills, and abilities fundamental to their role, and that they truly are a quality human resource and part of the "quality clinical workforce."

In a recent CenterWatch publication, ACRP Executive Director Jim Kremidas stated, "If you get your hair cut, the barber cutting your hair must have a license. In many parts of the world, if you join a clinical trial, the study coordinator doesn't need a license or to even be credentialed." He has a very good point; does it seem right that we place so little value on quality when it comes to clinical research?

To be sure, there are certain jurisdictions around the globe where qualifications for clinical research are taken more seriously. In some countries, for example, study coordinators must hold at least a bachelor's degree, but this is not universal. Unfortunately, we have a long way to go to standardize these requirements on a global scale.

Ultimately, if we want to improve the quality of research, then industry needs to come together to make sure we have competent "quality resources" and a "quality workforce" conducting our clinical trials. There is an ever-increasing wealth of evidence as to why we need these quality human resources—among it, the fact that the equivalent of a bad haircut in clinical research can be deadly.

> As the clinical research industry has become more competitive, the need for its professionals to differentiate themselves from one another has become a more cogent reality.

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ACRP MEMBER PROFILE: **SHIRLEY TRAINOR-THOMAS**

TITLE:

Shirley Trainor-Thomas, MHSA

Chief Strategy Officer, GuideStar

HOMETOWN:

Charleston, S.C.

LIVE NOW:

Charleston, S.C.

Why did you enter the clinical research field?

Like many, I fell into the clinical research space. Most of my career has been in healthcare management, and I paid little to no attention to clinical trial activity. So, it's ironic that my focus now is on educating healthcare leaders about the benefits of having a clinical trials program and guiding them on how to operate one as a business.

I am not a clinician, but function on the business and marketing side of clinical research, and believe that clinical trials should be available to patients at their local healthcare facilities. I also believe if the proper structure exists to support physicians, more would become involved.

I have become passionate about enlightening healthcare leaders about the strategic, financial, and quality benefits trials bring to a healthcare organization; but more importantly, about the impact offering trials at a local level makes on the future of healthcare.

What is your favorite part of research?

I always take delight in seeing the eyes of a hospital or health system CEO light up the moment the benefits of clinical trials "click" with them. They become excited and supportive—especially in these days of tightening belts—and it's nice to see some administrators ramping up research efforts because they believe in it from both the altruistic and business perspectives. They also get excited about the possibility of participating in trials that can change the current standard of care.

Personal or professional heroes:

Amelia Earhart, because of her adventurist spirit.

Margaret Thatcher, because of her ability to command and her absolute determination.

My grandmother, because she taught me to be strong and always find a reason to laugh.

Favorite quote:

Do right. Do your best. Treat others as you want to be treated. – Lou Holtz

Hobbies:

Boating, fishing, and golf (because, you know, I live in Charleston!).

People would be surprised to know that:

My undergraduate degree is in Journalism. I certainly didn't take a normal path to clinical research!

Reason for joining ACRP:

I joined ACRP because I saw a wave of positive change, with a strengthened commitment to a broadened population—not just the clinicians, but to those who have been in the clinical trial industry in supportive roles.

My life philosophy:

Humor, honesty, and undying hope are essential tools of life.

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Regulations, Competent Authorities, and Compliance in the News

FDA'S GOTTLIEB PROMISES AGENCY WILL HELP SPEED CLINICAL TRIALS

It's not going to be business as usual at the U.S. Food and Drug Administration (FDA) going forward, new Commissioner Scott Gottlieb told attendees of the RAPS (Regulatory Affairs Professionals Society) 2017 Regulatory Convergence conference on September 11.

There are many areas where the agency wants to increase its activity, Gottlieb said. For example, the agency needs to more proactively work with all stakeholders in clinical trials to get them to cooperate with one another and better share information. The FDA is pushing many new initiatives Gottlieb believes will speed trials and improve efficiency and efficacy. Members of clinical research teams can look for a number of agency guidances and open meetings on a variety of topics over the next 12 months, Gottlieb advised.

FDA is also committed to modernizing how it collects trial information, supporting intelligent use of adaptive approaches that can help to identify patients less likely to suffer adverse events during or after a trial, and that promote "seamless" trials. In the latter, Phase I, II, and III trials are hewn into a single trial with connective breaks in-between the project's transitional movement through the trial process.

(Source: ACRP Blog, https://www.acrpnet.org/2017/09/11/fdas-gottlieb-promises-agency-will-help-speed-clinical-trials/)

EUROPEAN MEDICINES AGENCY RELEASES FIRST-IN-HUMAN TRIAL GUIDELINES

The European Medicines Agency (EMA) recently unveiled a guidance for first-in-human clinical trials designed to help stakeholders identify and address risks for trial participants.

"Participants in these trials, often healthy volunteers, face an element of risk as the ability of researchers to predict the effects of a new medicine on people is limited before it is actually studied in humans," EMA said in a press release accompanying the new guidance.

The revision, years in the making, is also designed to recognize the increasing complexity of clinical trial protocols over the past decade. Studies now often include different subsections within a single clinical trial protocol that are aimed as assessing such factors as single- and multiple-ascending doses, food-drug interactions, or a drug's effect on members of different age groups, EMA noted.

(Source: ACRP Blog, https://www.acrpnet.org/2017/08/09/european-medicines-agency-releases-first-human-trial-guidelines/)

FDA OFFERS TIPS ON WHAT TRIGGERS INSPECTIONS

Clinical trial sponsors, clinical investigators, and institutional review boards often struggle to understand what most often triggers a U.S. Food and Drug Administration (FDA) inspection—especially one that is unannounced.

The prospect of an unannounced FDA inspection can loom over a clinical trial site. While the vast majority of inspections are prescheduled, FDA is more likely to arrive without warning if the inspection was assigned as a result of information that raises concern about the site, such as about the adequacy of its subject protection measures, or issues with data integrity, and/or a history of problems with the inspected party, FDA officials say.

FDA inspections of entities involved in clinical trials are considered bioresearch monitoring (BIMO) inspections, to differentiate them from the manufacturing inspections more commonly conducted by FDA inspectors. FDA BIMO inspections are usually preannounced.

In most cases, the FDA investigator contacts the site and suggests a date for the inspection, rather than offering to schedule it. This usually occurs about five days prior to the date the FDA investigator has chosen to start the inspection. In other words, they won't call until they're about ready to move.

(Source: ACRP Blog, https://www.acrpnet.org/2017/08/30/fda-offers-tips-triggers-inspections/)

SHOULD PHYSICIANS BE SOLELY RESPONSIBLE FOR INFORMED CONSENT? ONE STATE THINKS SO

A recent Pennsylvania Supreme Court decision has ruled that physicians, not their delegates, should obtain consent for "… administering an experimental medication or device" (40 P.S. § 1303.504). It is unclear how this will impact obtaining consent in a research setting. ACRP reached out to Glenda Guest, vice president of Norwich Clinical Research Associates (NCRA) and member of the ACRP Association Board of Trustees, who offered some initial thoughts.

According to Guest, this ruling will have a major impact on how physicians across Pennsylvania obtain informed consent from their patients. In *Shinal v. Toms M.D.*, 2017 WL 2655387 (Pa. June 20, 2017), the court ruled 4-3 that only physicians, not members of their staff, may obtain informed consent from patients before performing medical procedures.

Similar to the California Research Subject Bill of Rights requirement, the situation in Pennsylvania is another example of state-specific laws of which researchers must be aware because the laws are more restrictive than federal regulations regarding clinical trial informed consent. The decision could be overturned in future court decisions regarding the case, but right now, if one is conducting research in the Commonwealth of Pennsylvania, it appears that you must comply with this requirement. The Pennsylvania Supreme Court decision is not specific to only clinical research informed consent—it covers treatments specified in the Medical Care Availability and Reduction of Error (MCARE) Act—but it does include studies of experimental medications and devices.

The MCARE Act is being interpreted differently between the litigating parties in this case. The major issue appears to be whether a physician may rely on qualified staff to communicate information to patients as part of the informed consent process, in addition to their personal obligation to discuss the procedures and consent with the subject.

(Source: ACRP Blog, https://www.acrpnet.org/2017/08/11/physicians-solely-responsible-informed-consent-one-state-thinks/)

FDA WARNS AGAINST WELL-INTENTIONED BACKDATING

You may have the best motive and intent in the world when you backdate a clinical trial document. You may also still have a problem with the U.S. Food and Drug Administration (FDA).

Example: A subject signs the wrong informed consent form (ICF) during a screening visit. The study coordinator later realizes that a signed copy of the correct form is not among the subject's source materials, and asks the subject to fax him a signed copy of the correct ICF signature page. A fax of the ICF signature page dated November 15 is filed in the subject's source; however, the fax header shows that the fax actually arrived several days later and yet the study coordinator's signature is also dated November 15.

When a visiting clinical research associate asks about the discrepancy, the study coordinator explains that he did not really sign the ICF on November 15, but thought he should backdate the fax copy to the same date that the subject signed. Eventually, the study coordinator is able to get both his and the patient's signature on an original copy of the correct ICF with the same date.

Should the study coordinator have not signed off on the fax copy and, instead, documented the situation in the source and reported the discrepancy to the institutional review board? The FDA's short answer? Yes.

(Source: ACRP Blog, https://www.acrpnet.org/2017/08/23/fda-warns-well-intentioned-backdating/)

PROPOSED NEW JERSEY RULE COULD HAVE CHILLING EFFECT ON CLINICAL TRIALS

A proposed new rule could have a chilling impact on clinical trial research in the state of New Jersey. It's no stretch to imagine similar bills cropping up in other states. The rule would set a $10,000 cap on the amount a prescriber can accept from manufacturers in a calendar year for bona fide services. Fair market payments for speaking engagements at continuing education events are excluded from this cap.

"As written, this rule could have the unintended consequence of doing more harm than good," says Jim Kremidas, Executive Director of the Association of Clinical Research Professionals (ACRP). "New Jersey lawmakers may be trying to ensure prescribers are not influenced inappropriately by payments from pharmaceutical companies, but this law could have unintended consequences on the advancement of medicine." Emphasizing that research must be "pristine," Kremidas worries that the current rule, as written, would hamper important clinical trials across the state.

Visit the full posting at the link below, where guest blogger and former Chair of the ACRP Board of Trustees David M. Vulcano, LCSW, MBA, CIP, RAC, offers his perspective on the topic, based on his experience as a healthcare executive for clinical research with the Clinical Services Group of HCA (Hospital Corporation of America) in Nashville, Tenn.

(Source: ACRP Blog, https://www.acrpnet.org/2017/09/08/proposed-new-jersey-rule-chilling-effect-clinical-trials/)

[DOI: 10.14524/CR-17-4038]

ACRP's Career Development Resources—Looking Beyond Competency Development

Beth D. Harper, BSOT, MBA

As a former volunteer and now the newly appointed Workforce Innovation Officer, I am pleased to continue to support ACRP's ongoing efforts to further enhance the quality and competency of the clinical research workforce. From informal activities to formal, industry-wide programs, ACRP is involved in a wide variety of initiatives about which I will be providing updates in the coming months. In the meantime, I wanted to take this opportunity to re-cap many of the existing resources of which you can take advantage for enhancing your career.

From informal activities to formal, industry-wide programs, ACRP is involved in a wide variety of initiatives about which I will be providing updates in the coming months.

What's on Tap

If you've been a member long enough, you are no doubt familiar with our general educational programs and webinars, our award-winning *Clinical Researcher* journal, the annual Meeting & Expo (formerly known as the Global Conference & Exhibition), and chapter events which provide ample opportunities for ongoing continuing education on a wide range of topics. Many of these programs and resources have been mapped to the Joint Task Force (JTF) for Clinical Trial Competency Framework domains to facilitate your ability to strengthen your knowledge, skills, and abilities across the eight competency categories:

- Scientific Concepts and Research Design
- Ethical and Participant Safety Considerations
- Medicines Development and Regulation
- Clinical Trials Operations (Good Clinical Practices)
- Study and Site Management
- Data Management and Informatics
- Leadership and Professionalism
- Communication and Teamwork

The competency framework provides an excellent guidepost for prioritizing the content areas that you need to focus on as your career evolves. The framework has recently been updated, as more academic programs and other stakeholder groups gain experience with the framework and identify areas for refinement. To keep up with the progress of these refinements, be sure to periodically check out the JTF website: *https://www.clinicaltrialcompetency.org/news-updates/*.

Beyond curiosity about developing competencies, many of the questions we receive are more related to the practical aspects of career development, such as job searching, resume enhancement, salary negotiations, formal academic degrees, career mapping, mentorship opportunities, and more. Let's take a brief walk through ACRP's website to orient you to where you can find all of the available resources surrounding these topics.

Career Development Webinars

Archived and upcoming webinars will continue to focus on the logistics of career development. Recent topics cover a broad range of topics, including but not limited to:

- Evolving Roles of Clinical Research Associates (CRAs)—How to Successfully Elevate Performance in a Transitioning Environment
- Career Compass: Steer Your Clinical Research Career by Leveraging Real-World Trends
- Beat the Heat—Stay Cool in Your Next Interview
- Negotiation: The Why and The How
- Reinvent Your Job: Extend Your Worth and Job Satisfaction
- The 5 "Cs" of a Successful Mentoring Program

As a member, you are entitled to a substantial discount for the webinars (fee of $25 for members vs. $75 for nonmembers per webinar). If you have an idea for a future webinar and/or would like to contribute as a subject matter expert, please contact Jill Chapman, our Senior Manager of Training and Development, at *JChapman@acrpnet.org*.

You can access the current and recorded webinars in the "Training Programs" area under the "Professional Development" tab at *www.acrpnet.org*. You can also search for specific topics as well as download a directory of all training programs at this portion of the website.

Online Conference Library

Career development sessions are always the highlight of the ACRP Meeting & Expo. In case you missed one of the recent annual events, or a particular session at an event, the Online Conference Library of recorded conference sessions currently includes most, but not all, of the sessions delivered at the 2015 (Salt Lake City), 2016 (Atlanta), and 2017 (Seattle) gatherings. Topics from recent years included sessions such as:

- So You Want to Be an Independent Consultant
- Fast Track to Success for New Clinical Research Coordinators
- CRAs in 2010 and 2020: CRA Career Ladder Survey II
- A Creative Solution to Staffing in a Competitive Hiring Environment
- Manage Your Career or Someone Else Will

Pricing for the recorded presentations varies based on the volume of presentations purchased. You can peruse the Online Conference Library at *http://acrp.digitellinc.com/acrp/*.

Mentorship Programs

Mentor Match is a new program that provides ACRP Members the opportunity to serve in both the capacity of mentor and mentee. The program is about growing professionally and networking with fellow ACRP members; it is not about finding a job. Mentor Match is available free to ACRP members. To learn more, visit *https://www.acrpnet.org/membership/mentor-match/*.

Career Center

The ACRP Career Center is all about bringing together employers and talent. For your chance to get discovered, post your resume and/or search for open jobs (in the U.S.) at *https://www.acrpnet.org/professional-development/career-center/*.

Even if you aren't currently looking for a new job, you can get a sense of the ever-expanding range of career opportunities by exploring the job postings, which may inspire you to advance your career path in ways never previously imagined.

Clinical Researcher—December 2017 Careers Issue

Back by popular demand next issue in ACRP's *Clinical Researcher* journal will be our periodic focus on career challenges and opportunities. This issue will cover a broad range of hot topics facing professionals in roles across the clinical research enterprise. Until then, be sure to check out the December 2016 issue on trends in workforce development by visiting *https://www.acrpnet.org/resources/clinical-researcher/*; it spotlights why workforce development is important and why it should be an ongoing priority for all clinical research professionals.

Most online articles and columns from past issues of *Clinical Researcher* can be seen as separate postings and/or through full-issue, downloadable PDFs by ACRP members only; however, the December 2017 issue will be open online to the general public.

Career and Salary Benchmark Survey

Last, but not least, be on the lookout in October for our next biennial salary survey, which we implement in partnership with CenterWatch to provide you the opportunity to contribute anonymous data that support the industry's leading benchmark report on clinical research professional salaries. The 2017 report should be available early in 2018, and members will receive information on the discounted price to purchase the report. You can still purchase the previous benchmark report for a discount at the CenterWatch store by visiting *https://store.centerwatch.com/p-456-2015-career-and-salary-benchmark-reports.aspx.*

In Closing

Make the most of your ACRP membership by taking full advantage of all these career development resources. Please feel free to reach out to us with other ideas and ways that we can help support your ongoing professional development.

Beyond curiosity about developing competencies, many of the questions we receive are more related to the practical aspects of career development, such as job searching, resume enhancement, salary negotiations, formal academic degrees, career mapping, mentorship opportunities, and more.

Beth D. Harper, BSOT, MBA, (beth.harper@acrpnet.org) was appointed ACRP's new Workforce Innovation Officer in July 2017.

The Latest News from the World of Workforce Innovation

LEVERAGE BUDGETING AS OPPORTUNITY TO BOOST COMPETITIVE EDGE

Believe it or not, a sponsor who pushes back on a site's budget requests might be doing the site's leaders a favor. "In some cases, it can show that the site has hidden inefficiencies that make it charge [above the going rate] for a trial or specific piece of a trial," says Jennifer Goldfarb, MSN, RN, CCRP, senior director of the Clinical Research Support Office at Children's Hospital of Philadelphia.

Example: A site in good conscience might seek $300 per blood draw as part of its budget request. Most sponsors would balk at that dollar figure. However, neither side is engaging in gamesmanship. Instead, the site has just learned through its budgeting that its costs are probably out of whack. "It might take them $300 per blood draw, but it probably shouldn't," Goldfarb says. Thus, "Budgeting presents an opportunity [for sites] to look at their own operational efficiencies."

In addition, working up a study budget effectively should help the site identify questions its leaders need to ask the sponsor. "It's not up to the sponsor to tell you what you need to do to get something done," Goldfarb says.

(Source: ACRP Blog, https://www.acrpnet.org/2017/08/28/leverage-budgeting-opportunity-boost-competitive-edge/)

DOCTORS REMAIN KEY TO BOOSTING CLINICAL TRIAL PARTICIPATION

More than 80% of people are likely to participate in a clinical trial if it is recommended by their doctor. The bad news? Less than 20% say their doctor has ever broached the subject, according to a new survey conducted by Zogby Analytics. While the latter figure is discouraging, it's worth nothing that it's up from 9% in 2013.

The study, funded in part by the Association of Clinical Research Organizations (ACRO), surveyed 1,000 adults nationwide in July 2017 and further found that an overwhelming majority (86%) of respondents believe that doctors should discuss clinical trials with patients as part of standard care.

The survey suggests patients are open to participating in trials. Three-quarters of survey respondents feel that participating is as important to public health as giving blood. Additionally, more than half believe that the federal government should provide tax incentives—as many other countries do—for trials run in the U.S.

(Source: ACRP Blog, https://www.acrpnet.org/2017/09/06/doctors-remain-key-boosting-clinical-trial-participation/)

FOCUS ON PATIENT-CENTRIC INFORMED CONSENT YIELDS DIVIDENDS

Long-time pediatric trial professional Halle Showalter Salas is "firmly convinced" that patient-centric informed consent improves compliance and retention throughout a clinical trial. She spent more than seven years as a research and family liaison and vice chair of the institutional review board (IRB) at Seattle Children's Hospital. Currently, she's senior internal consultant for employer market strategy with Premera Blue Cross.

In the end, a better informed consent process comes down to establishing relationships with patients and their broader support group, Salas says, adding that in her days at the IRB, they labeled the approach "participant-centric," because in some cases the focus may be on a subject's family or other helpers during the informed consent process. "We try to make sure the patient's whole journey is taken into account," she says. That means assessing who will help them to make their participation a success.

The strongest patient relationships begin with honesty. For example, "We're very careful to make sure a patient understands it when [the fact is] a trial may not directly help them," Salas says. They'll point out that the trial is an option or a choice to potentially help someone else, without pressing the point too hard.

(Source: ACRP Blog, https://www.acrpnet.org/2017/09/08/focus-patient-centric-informed-consent-yields-dividends/)

FXM RESEARCH

IT'S NOT JUST CLINICAL RESEARCH!

IT'S CLINICAL RESEARCH EXCELLENCE... SUSTAINED!

Founded in the year 2000, **FXM Research** is a privately owned and operated Clinical Research Site that conducts phase II, III, and IV clinical research trials specializing in Dermatology. Throughout the years, our ability to deliver aggressive, time bound enrollment goals, while providing trustworthy data to Pharmaceutical companies and CROs, has earned **FXM Research** a great deal of notoriety and fame within the Dermatology research industry.

Today, FXM Research's success is widely regarded throughout our four operating branches: **FXM Research Corp.**, based in Miami, Florida and home of our headquarters, **FXM Research Miramar**, located in the city of Miramar, Florida and **FXM Research International**, including two branches in Belize City, Central America.

OUR MISSION

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

- We specialize in conducting phase II, III, and IV Dermatology Clinical Trials.
- Our primary concerns are subject safety and adherence to the protocol.
- Turnover time for Regulatory Documents, budgets, and contracts is usually 24 to 48 hours.

OUR SUCCESS

- We offer experienced, trained, and bilingual personnel (English and Spanish), who interact with our subjects, sponsors, and CROs as a cohesive team.
- Our Principal Investigators are Board Certified Dermatologists and Certified Clinical Research Investigators with many years of extensive experience. They are located onsite and are available full-time.
- Most subjects are recruited from the office of our PI's private practice, and/or FXM Research's extensive clinical database. We draw heavily from a Spanish speaking population, a group often under-represented in clinical trials. We also have continuing extensive experience with a pediatric population.
- We do whatever is necessary to accommodate our subjects' school and/or work schedule, which maximizes compliance and retention.
- We are confident that we can surpass sponsors expectations relating to cost, subject enrollment/retention, and the quality of our work.

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HOME STUDY TEST

Earn 3.0 Continuing Education Credits

Three articles from this issue of *Clinical Researcher* will be selected as the basis for a Home Study test that contains 30 questions. For your convenience, the selected articles and test questions will be combined and posted online in the form of a printable PDF at **https://www.acrpnet.org/professional-development/training/home-study/** in October 2017, and *the test will be active until October 31, 2018.* This activity is anticipated to take three hours.

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

ACRP DISCLOSURE STATEMENT

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

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

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

CONTINUING EDUCATION INFORMATION

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

Contact Hours

The Association of Clinical Research Professionals (ACRP) provides 3.0 contact hours for the completion of this educational activity. These contact hours can be used to meet the certifications maintenance requirement. (ACRP-2017-HMS-010)

Continuing Nursing Education

The California Board of Registered Nursing (Provider Number 11147) approves the Association of Clinical Research Professionals (ACRP) as a provider of continuing nursing education. This activity provides 3.0 nursing education credits. (Program Number 11147-2017-HMS-010)

Continuing Medical Education

The Association of Clinical Research Professionals (ACRP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Association of Clinical Research Professionals designates this enduring material for a maximum of 3.0 AMA PRA Category 1 Credits™. Each physician should claim only the credit commensurate with the extent of their participation in the activity.

It's not a corporation, *it's a community*

At PRA, "remote" doesn't mean alone.

These micro-community events, happening in various cities across the U.S., bring some of our remote employees together to connect and build relationships.

We're a global organization of more than 13,000 people. Many employees work in our offices around the world, but many others make up a special group – our remote employees. For some people, the thought of being a remote employee is daunting. It's easy to feel isolated and not part of a community. At PRA, we're working to change that.

Remote workers are often only engaged if they live near an office. There's no opportunity to meet new people by the coffee maker or to get to know someone based on how they've decorated their cubicle. That's not how we do things at PRA. As a company, we understand the importance of creating relationships not just from behind a computer screen or on the other end of an e-mail. Even more, so do our employees.

We want each employee to be a fully engaged and valued member of the PRA team and embracing the spirit of what it means to be part of PRA. But, large corporate events can be uncomfortable for remote employees when everyone else seems to already know one another. So, our employees are coming together for smaller, informal, micro-community events where they can meet other PRA employees in their area. Remote employees can connect and build camaraderie with the coworkers they may not have the opportunity to meet otherwise. These micro-community events, happening in various cities across the U.S., bring some of our remote employees together to connect and build relationships.

Our PRA community spans the globe, and we're making sure that every single employee feels like an important part of it.

Explore our open job opportunities at DiscoverYourPRA.com

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