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The Technology Issue: *New Tools to Tackle Old Problems*

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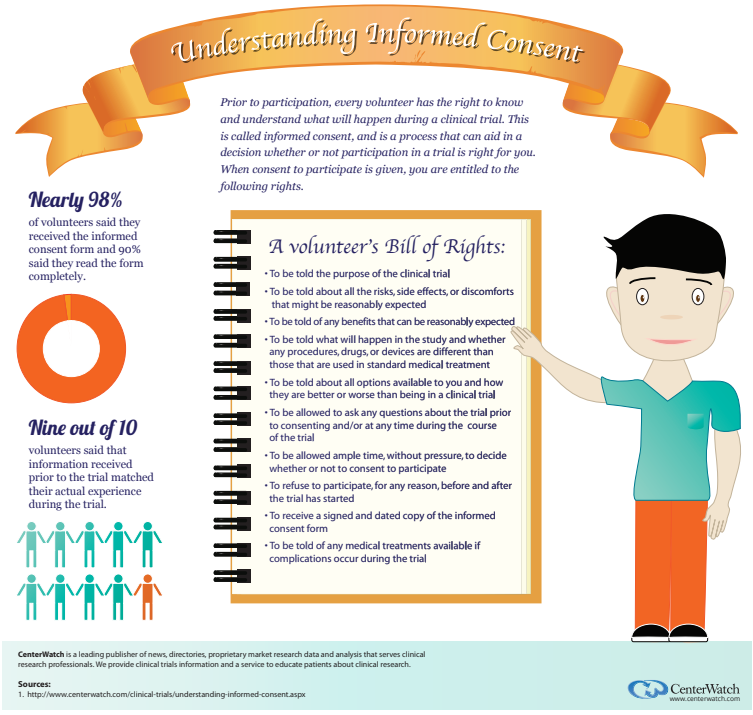
A pioneer in publishing clinical trials information, CenterWatch was the first to publish detailed information about clinical trials that could be freely accessed by patients and their advocates. Today, we have the largest online database of actively recruiting, industry-sponsored clinical trials.



CenterWatch has a unique position in patient education, and garnering interest in clinical trials.

Patient Enrollment Services:

- **Clinical Trials Listing Service™** is the leading online resource for patients seeking actively recruiting clinical trials, having reached more than 25 million potential study volunteers since launching over 20 years ago. Today, this service averages a total of 2.5+ million patient visitors annually, and contains thousands of active global clinical trial listings with a range of exclusive outreach efforts. Such efforts include collaborative partnerships with leading clinical trial services and health associations designed to maximize traffic to your clinical trial listings.
- The **Patient Notification Service** sends email notifications which precisely match subscribers to relevant clinical trials based on their medical conditions and geographic location.

Patient Education:

- The **Volunteering for a Clinical Trial brochure** is an IRB-approved, quick-reference guide for potential volunteers interested in participating in a research study. It includes an overview of the clinical trials process and answers some of the most commonly asked questions about volunteering for a clinical trial.
- **Understanding the Informed Consent Process** is an IRB-approved brochure that provides study volunteers with important information regarding the informed consent process, including facts and information about the volunteer's "Bill of Rights."
- **Infographics** offer graphic visual representations of information, data, or knowledge presented in a format that is easy to understand at a glance, and help patients understand the full scope of the clinical trials enterprise ranging from clinical trial participation, patient attrition rates, and informed consent to business aspects and much more.

Part of CenterWatch's mission is to provide patients with access to essential health and educational resources to learn more about clinical research and participation as well as other organizations that offer information and support for a range of medical conditions.

Visit **CenterWatch.com**, call **(617) 948-5100,** or email **sales@centerwatch.com** for more information.

CenterWatch

Clinical Researcher™
The Authority in Ethical, Responsible Clinical Research

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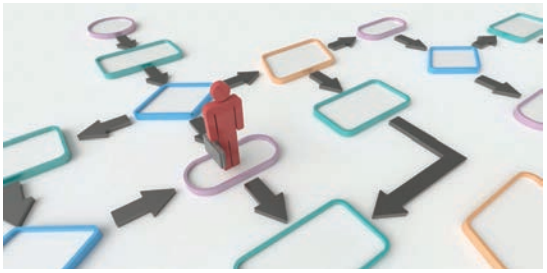

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FOR LEARNING FOR LISTENING FOR LIFE

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GUEST EDITOR'S MESSAGE

Paula Smailes, RN, MSN, CCRC, CCRP

[DOI: 10.14524/CR-16-4024]

Keeping Up with Clinical Research Technologies

While it can be exciting to see how technology makes positive impacts professionally, in our line of work we also need to think about how technologies are regulated and how they can affect human subjects.

Paula Smailes, RN, MSN, CCRC, CCRP, (Paula.Smailes@osumc.edu) is a systems analyst at The Ohio State University Wexner Medical Center, a visiting professor at Chamberlain College of Nursing, and a member of the ACRP Editorial Advisory Board.

We are constantly exposed to technological advances in our personal and professional lives, from the latest gadgets to social media, and one of the biggest struggles is how to keep up with these advances. It can be a challenge to know how to use the newest "techy" versions and adjust to the workflows they change. Another consideration is that new technologies can initially be expensive until they become more mainstream. The goal of this issue of *Clinical Researcher* is to help you keep pace with technological trends happening in the research enterprise.

While it can be exciting to see how technology makes positive impacts professionally, in our line of work we also need to think about how technologies are regulated and how they can affect human subjects protections. Technologies may solve old problems, but the reality is that they create new ones, too.

Despite presenting myriad obstacles and challenges, technological advances are making our clinical research workflows more efficient and cost-effective. Paper case report forms (CRFs) have been turning into electronic CRFs (eCRFs). Because of eCRFs, onsite monitoring has segued into remote, risk-based monitoring (RBM).

We have also seen the traditional paper source for data transition into electronic source (eSource), which is accelerating the adoption of electronic medical records by healthcare organizations, thanks to government trends that promote their use.

Let's Get Technical

Our issue this time around touches on each of these timely topics just mentioned. Leading off the lineup of articles in the pages ahead is "Maximize Your EHR Systems for Clinical Trials Operations," in which David Vulcano and colleagues provide an overview of the use of electronic health records (EHRs) in clinical research for supporting clinical research in terms of patient safety, research billing compliance, accreditation, and Health Insurance Portability and Accountability Act privacy, among other considerations. The ability of EHRs to capture trial metrics and their evolving functionality for research recruitment are also noted, along with implementation tips and ways to build an external support network.

Elsewhere in this issue, in "The Rise of Electronic Data Capture [EDC] and its Greatest Obstacle," Colton Castle discusses the many benefits of EDC for use in trials. While EDC's valuable qualities are noteworthy, challenges remain that have inhibited its use in as many settings as would seem ideal. Although not focusing on technology per se, Shilpa Patkar and Jeroze Dalal further elaborate on potential stumbling blocks to improved trial conduct in "Challenges to Implementation of Risk-Based Monitoring," by outlining the optimization of limited monitoring resources while maintaining the expected standards for patient safety and data integrity.

Meanwhile, Priya Temkar acknowledges various technological aspects of improved monitoring practices in "Site Monitoring an Expensive Affair? Not Any More…," but gives further insight on the use of monitoring support teams to strengthen site management and ensure all-time audit readiness of clinical trial systems. In "eSource and Risk-Based Monitoring: A Favorable Union in Clinical Trials," Neha Sharma also discusses the efficiencies of RBM, explores how eSource provides a solution to labor-intensive source data verification practices and accelerates data review, and offers some factors to consider for eSource deployment.

Also in the mix for this issue, the authors of "Implementation of a Research Participant Satisfaction Survey at an Academic Medical Center" outline their use of an electronic survey to gather feedback from research subjects. While surveys of this nature have commonly been done on paper, an electronic version provides greater potential for using the feedback in various forms of aggregate data, and results can be analyzed by study, by investigator, by department, or on an enterprise-wide basis.

Moving at the Speed of Change

As a clinical research professional who currently works in information technology, I confess that I get easily overwhelmed by the constant influx of new changes. When this happens, I am careful to remind myself that it is important to keep the end goal in mind. These new technologies will ultimately make our jobs easier, and who doesn't want that?

Mastering Regulations in Research

What inspired your interest in the field of regulatory science?

My experience as a clinical research professional greatly influenced my interest in regulatory science. With a background in human subjects protections and experience working on Phase II-IV drug studies, I developed an appreciation for how regulatory science impacts the development of new treatment options. Research at all development stages requires proper oversight, design, and management to ensure risks are minimized and benefits are maximized, all while working to bring new treatment options to the market in a timely fashion. This is a daunting task that relies heavily on the conceptions of regulatory science. With an MS in Regulatory Science from the University of Maryland School of Pharmacy, I hope to bridge my interest in human subjects research with areas of regulatory science to ultimately improve protections for subjects and patients.

What interested you most about the MS in Regulatory Science program at the University of Maryland School of Pharmacy?

I came from a social behavioral background with my first graduate degree in applied psychological research. As I progressed in my career, I found myself in a predominantly biomedical setting working on clinical drug studies and felt I needed to expand my understanding of regulatory science to really grow in my chosen career. The courses offered in this master's program were a perfect complement to my experience and previous academic work. The program covers drug development from the preclinical stages to clinical trials, and even postapproval. The program also appealed to me because it would allow me to expand my knowledge in areas of drug development and regulation, while still being able to work full time in the field. Having worked predominantly on studies in the clinical trial phases, I often wondered how we got to this point—what came before the clinical trial, and what will come after. This program has allowed me to bridge those gaps and better appreciate the process, as well as to apply what I learned to my daily work.

What are your thoughts about the coursework offered through the program?

I have really enjoyed the coursework and, in particular, the lectures, which are presented by top experts in the field, including individuals in academia, industry, and government, who provide a wealth of knowledge. Having such experts as lecturers is, without a doubt, one of the program's major strengths. The program is also clearly designed with the working professional in mind, allowing access to lectures and course materials over several weeks. The coursework truly enabled me to explore areas of regulatory science in which I had very little knowledge before starting the program, and the lectures often piqued my interest in areas that I never would have even considered previously. The group projects also offered a valuable opportunity for me to learn from other professionals in the field.

"This is an exclusively online program designed for working professionals. For me, this was an ideal set up, as it allowed me to do my coursework in the evenings while maintaining a high level of commitment to my job and family."

Applications for the Fall 2016 semester are due July 15. Visit www.pharmacy.umaryland.edu/regulatoryscience to learn more.

Jessica Rowe, MA, CCRP, is a student in the University of Maryland School of Pharmacy's MS in Regulatory Science Program and a research quality improvement specialist in the Office of Research and Scholarship at the University of Maryland School of Nursing.

BY THE NUMBERS

Zeroing in on technology trends and innovations that are expected to make a difference in the functioning of the clinical research enterprise.

Can Twitter boost enrollment in studies? University of Pennsylvania researchers analyzed a randomly chosen sample of **1,516** tweets out of a total of **15,346** unique tweets that contained "lung cancer" in January 2015, and found that nearly **18%** of them were about clinical trials.

Source: Newswise, www.newswise.com/articles/view/649023/?sc=mwhp

A team of researchers has been awarded **$1.9 million** from the National Institutes of Health to develop an interactive software tool for giving patients a better understanding of how their electronic health record information could be used in research, so that patients can better provide an informed consent.

Source: EurekAlert!, www.eurekalert.org/pub_releases/2016-03/iu-rtf030916.php

Is the search for new medicines becoming unsustainably expensive despite huge technological advances because researchers are using the wrong methods? Experts say the chance of discovering an effective drug is so sensitive to the validity of the experimental methods that small changes in validity can have a bigger effect than running **10** or even **100** times more experiments.

Source: EurekAlert!, www.eurekalert.org/pub_releases/2016-02/uoo-ddc021216.php

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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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Jim Kremidas

[DOI: 10.14524/CR-16-4023]

For Learning. For Listening. For Life.

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

If you attended our successful ACRP 2016 Meeting & Expo in Atlanta, Ga. in April, you had the chance to see the unveiling of ACRP's new logo and philosophy: For Learning. For Listening. For Life. While I believe we all shared the excitement of viewing and discussing ACRP's new look, I also believe the actions we've begun to take to support it are what are most important.

While we have a number of new offerings in the works (watch this space!), here are two that are ready to roll right now:

1. Current ACRP members now pay just $25 for live webinars that keep you up-to-date on regulatory developments, industry trends, and specialized clinical research topics.
2. We've significantly reduced pricing for classroom courses, including two of our most popular ones—"Fundamentals of Clinical Research" and "Project Management for Clinical Research Professionals."

These changes are a direct result of feedback from members like you, and are just a few examples of how we're constantly striving to better support you.

Yes, these are exciting times for us all.

The Personal Touch

I had the chance to meet hundreds of you at the annual meeting, where I could see and hear your commitment and passion. So many of our speakers—including U.S. Food and Drug Administration Commissioner Robert Califf and the innovative futurist Martine Rothblatt—emphasized the importance of the work you do to advance public health.

"What you're doing in clinical research is giving us the information and the knowledge we need to make the best decisions" when reviewing new drugs and devices, Califf said. For Rothblatt, it was more personal. "The people in this room helped to save my daughters' life," she said in the first line of her plenary address. "Thank you." Her voice crackled with emotion, and I could see its effect rippling across the packed auditorium.

Spurred by technology and increasing pressure to deliver treatments and cures more efficiently and more effectively, the clinical research landscape is fast evolving. Califf touched on it when he mentioned the rising cost of clinical research and a potentially dangerous drift toward a "one-size-fits-all" mentality. Stressing a "quality by design" approach, he noted as an example that early-phase clinical trials need to be heavily detailed, while trials further down the line sometimes have to address genomics and other biometric challenges.

At ACRP, we look forward to being an active and responsive partner as you navigate these and other new developments. We promise that we, too, are rapidly evolving to keep you on pace with change and to ensure that our collective vision—that clinical research is performed ethically, responsibly, and professionally everywhere in the world—is realized. As clinical research operations evolve and modernize, so too will ACRP.

Our Commitment

As we have for 40 years, we will continue to be here for you; to help you learn and to help you realize your true potential by providing you with unparalleled training and development opportunities.

We will continue to listen to you so that we can understand your needs and desires, so that we can better serve you, and so that you can empower us to champion your interests, perspectives, and opinions. We will continue to promote the value of certification. When you make it clear that a product, service, or even a sounding board will help you to thrive, we will do our best to provide it.

We commit to being your lifelong partner as you continue to better the lives of patients around the world and drive innovation in clinical research. Let us help you thrive throughout your entire career lifecycle.

I look forward to meeting more of you in the coming months. As always, I encourage you to contact me or any staff member so that we can answer your questions and hear your ideas for new ways to help you. ACRP will always be here for you. For learning. For listening. For life.

We promise that we are rapidly evolving to keep you on pace with change and to ensure that our collective vision—that clinical research is performed ethically, responsibly, and professionally everywhere in the world—is realized.

AT PRA, WE'RE FAMILY

A look inside PRA's "boomerang" phenomenon

Employees gather for a grand opening celebration.

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

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

Why?

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

So what makes PRA home?

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

PRA is home, and the people here are family.

Experience Nicole's CRA journey at DiscoverYourPRA.com.

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

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

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

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

For more information, please visit DiscoverYourPRA.com

PRAHEALTHSCIENCES

Six prestigious awards were announced at the ACRP 2016 Meeting & Expo in Atlanta in April

Outstanding Leadership in Clinical Research by a CRA
Outstanding Leadership in Clinical Research by a Project Manager
Outstanding Leadership in Clinical Research by a Physician
Advancing Public Awareness in Clinical Research
Innovation in Clinical Research
Exceptional Contribution to the Clinical Research Profession

Theresa Miarecki

Outstanding Leadership in Clinical Research by a CRA

This award recognizes a member who is active as a clinical research associate (CRA) and has made exceptional leadership/practice contributions that have furthered the vision and mission of ACRP—to promote excellence in clinical research.

Miarecki has been a clinical research professional for more than three years at Instrumentation Laboratory (IL), a global market leader in diagnostic instruments for critical care and hemostasis.

As a CRA at IL, she monitors several concurrent multisite trials for the clinical validation of laboratory and point-of-care IVD devices. She developed SIV training procedures focusing on device operation and specimen handling which have significantly improved the quality of data received from evaluation sites—leading to quicker database lock and site close-out. She also provides leadership and training to in-house and contract CRAs.

Romiya Barry

Outstanding Leadership in Clinical Research by a Project Manager

This award recognizes a member who is active as a project manager and has made exceptional contributions that have furthered the vision and mission of ACRP—to promote excellence in clinical research.

Barry has worked in the medical device field for more than 12 years focusing on clinical program management, including regulatory and commercialization strategies, analytical and usability study design, and project management of multicenter pre- and post-market trials throughout the U.S. and Europe.

At Instrumentation Laboratory Company, she led a redesign of the clinical trial operations to help meet new regulatory challenges, aligning the system to corporate initiatives within the design control Quality System. In her current role at the medical device start-up CeQur Corporation, she is managing the first multicenter study for a simple and discreet wearable insulin delivery device for patients with diabetes.

Mark Brody, MD, CPI

Outstanding Leadership in Clinical Research by a Physician

This recognizes an ACRP member who is active as a physician in clinical research and has made exceptional contributions that have furthered the vision and mission of ACRP—to promote excellence in clinical research. Brody is president and founder of Brain Matters Research, the largest private clinical research facility in the country specializing in Alzheimer's disease diagnosis, treatment, and research.

Brody is a nationally recognized expert in both Alzheimer's disease and stroke, as well as the principal investigator in numerous clinical trials seeking to prevent and treat Alzheimer's. He is in private practice in Delray Beach, Fla., specializing in memory disorders and stroke prevention. He is one of a small group of neurologists whose career spans academic and clinical practice, as well as clinical research.

Brody is also the author of *Brain Matters – The Prevention of Alzheimer's, Aging and Stroke.*

Fabian Sandoval, MD

Advancing Public Awareness in Clinical Research

Winner Sandoval was recognized as an individual who has contributed to the public's understanding of clinical research, and to the advancement of the profession.

He has more than 18 years of bench-to-bedside research experience. His diversified research career has been in academia, healthcare systems, and the public sector.

Before opening the doors to Emerson Clinical Research Institute (ECRI), Sandoval's research activities have included bench research at the National Institutes of Neurological Disorders and Stroke, where he focused his work on early onset Alzheimer's disease and Cretzfelt-Jakob disease.

Sandoval served as the supervisory research integrity and compliance officer in the Army Human Research Protections Office in the Office of the Army Surgeon General. Responsibilities included establishment and oversight of Human Research Protection Programs across Army commands. His input has been instrumental in the review, development, and selection of protocols, in addition to education and training for resident and hospital faculty.

Mark Lacy

Innovation in Clinical Research

This recognizes an ACRP member who exemplifies the spirit of creativity and innovation through adaptation, improvement, or development of new processes that result in improvement to the clinical research process.

Lacy is founder and CEO of Benchmark Research, a network of quality investigative research sites throughout the United States. His active participation with ACRP includes serving as chair of the Site Manager's Forum, chair of the Finance Committee, and a member of the Board of Trustees. In 2005, he was a recipient of the Meritorious Service Award.

In 2010, Lacy was selected by *Entrepreneur Magazine* as one of the top four "Established Entrepreneurs" for his success in growing Benchmark Research, and he was recognized in 2011 by *PharmaVoice* as one of the 100 most Inspiring People. His entrepreneurial philosophy helped him to create VaxCorps, a nationally prominent research network focusing on vaccines, of which he is the CEO.

Robert O'Connor, MS, CCRA

Exceptional Contribution to the Clinical Research Profession

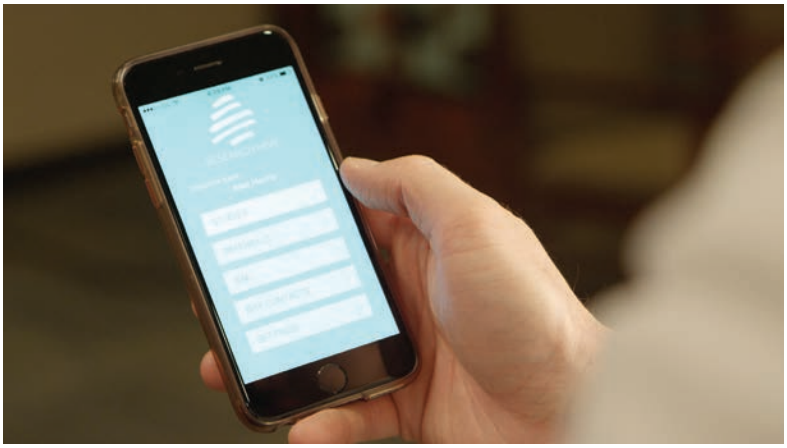
This recognizes thought leaders, innovators, and/or subject-matter experts who have made a significant positive impact on the clinical research profession or furthered the mission and vision of ACRP.

O'Connor is a senior clinical scientist and clinical investigator in the Global Clinical Sciences Department at The Procter & Gamble Company.

He has extensive experience in clinical research education and training, having been at least partly responsible for training clinical research professionals at three companies in good clinical practices and monitoring. He has been an adjunct professor in the Clinical Research Certificate Program offered at the University of Cincinnati since 2008, where he teaches face-to-face, online, and hybrid courses on regulations of clinical trials and clinical trial execution. In doing so, he has educated more than 150 students in the field of clinical research. He was also influential in getting a research ethics class added to the curriculum at the University of Cincinnati, Blue Ash campus.

Big buzz surrounds Research Hive

Innovative mobile app plays a key role



"...our weekly referral rate increased over 70% above our pre-Research Hive levels."

Let's face it: clinical research coordinators (CRCs) can make or break any trial. Beginning with the site selection visit, the coordinator is carrying a large load. Tasked to learn new trial procedures, vendors, and schedules, they must also explain these details to patients and their team. Tight timelines and pressure from all sides wreak havoc during startup and recruitment, especially when managing multiple protocols. CRCs must play the role of symphony conductor (or circus ringleader), with tools that haven't changed for decades. Intent upon creating a solution, a team of coordinators developed Research Hive.

Research Hive is an innovative recruitment and retention platform.

At the core it is a straight-forward mobile app, developed to help coordinators. Neil Schmitz, head of product development, shared the initial vision: "We developed Research Hive to improve team communication and give sites all study details in one familiar place; their smartphone. We knew recruitment would improve if we could give a team real-time access to critical study information. It had to be fast to review the study criteria and then refer a patient, so that was our focus."

Download on the App Store

GET IT ON Google play

From a quality site to #1 in the world.

A high-enrolling Cardiology practice in Houston saw room for improvement because the majority of recruitment came from half of the investigators. When the site was selected to participate in a global trial (12,000 target enrollment), they decided to use Research Hive, and the impact was immediate. "We were getting referrals from the doctors who were previously not referring, even while they were rounding in the hospital. They stopped asking us to fill them in on study details in the hallway. It was great!" When enrollment closed, the site earned special distinction as #1 enrolling site world-wide.

Top retina site sees dramatic results.

A dynamic, industry-leading site with 11 investigators, 12 locations, and over 40 ongoing trials sought to improve their recruitment process. "Our clinic EMR was not the solution, neither was text or email." They discovered Research Hive, and the results were stunning. "We were hoping to get flexible and secure communication and tracking of referrals within our team. We got that, but were surprised to watch our weekly referral rate increase over 70% above our pre-Research Hive levels."

A perfect fit.

"Research Hive was designed with the coordinator in mind, working within any size clinic or institution." Alex Harris, one of the coordinators who developed Research Hive, continued: "We also listened to the physicians, adding features to help them make clinical decisions quickly."

Research Hive has drastically improved the recruitment process, with a price that makes the decision to test it out a simple one.

Visit **researchhive.com** for more details and a free trial.

RESEARCH HIVE

Innovative Oncology Research and Participant Protection

Clinical and technological advancements have made it possible to plan groundbreaking oncology study designs and innovative cancer therapies. From a human subject protection perspective, however, these incredible advances also create potential challenges for the research community.

Communicating complex scientific and medical concepts and long lists of potential risks—all while the clock is ticking for the patient—is not easy. Therefore, while effective education is always critical, it is even more so when it comes to contemporary cancer research.

For example, the National Immunotherapy Coalition (NIC), under the Cancer MoonShot 2020 initiative, is establishing the nation's most comprehensive cancer collaborative initiative to accelerate next generation immunotherapy as a viable treatment for cancer. Novel therapies and study designs like those planned for the program create unique challenges in protecting study participants.

Cancer MoonShot 2020's Quantitative Integrative Lifelong Trial (QUILT), specifically, seeks to test combinations of therapies on up to 20,000 patients, and an expected 15,000 research sites will participate in the Phase II combination immunotherapy trials across the U.S. as part of the initiative.

Due to the massive scale and complex nature of such innovative cancer research, Schulman IRB, the industry leader in technology and advanced oncology expertise, will serve as the national IRB for Cancer MoonShot 2020 and will help to ensure appropriate protections are in place for those participating in the studies. When it comes to the informed consent process, the specific areas of concern for IRBs are the same for any innovative oncology research initiative or study, even on a smaller scale:

Selection

Equitable selection of participants is addressed through careful evaluation of the study eligibility criteria, including potential drug interactions that may be associated with co-morbidities from standard treatment.

Vulnerable Populations

Particular attention should be paid to protecting those made vulnerable by socio-economic situations or by the disease itself to avoid potential manipulation or misinformation when the patient considers research participation.

Timing

Potential participants need enough time to process their diagnosis and prognosis prior to considering a research treatment option, and the patient's participation should be an ongoing conversation, especially as risks and benefits change over time.

Impact on Quality-of-Life

Quality-of-life impact, financial risks, and other inconveniences related to research participation may need to be dealt with during the study and must be a part of the consent process.

Biospecimen Permissions

Collection of biospecimens with associated genomic, epigenetic, and phenotypic data is standard in oncology research. The collection and the possibility of future research must be carefully detailed and discussed throughout the informed consent process.

> "Oncology disease diagnosis and prognosis, as well as standard and research options, are already complicated, and are becoming ever more so. Informed consent should be a process, not just a document, that requires ongoing conversation and education to ensure participants understand the risks and benefits of the study, especially as those risks and benefits change over time."

Complex Concepts, Long Forms

Oncology research consent forms are typically lengthy and complicated. Utilizing eConsent technology instead of printed text to present consent form information and educate subjects and their families may be of particular value in cancer research.

Summary

Innovative research can benefit from thoughtful, contemporary human protection processes and tools such as those designed and offered by Schulman IRB. By carefully considering the challenges inherent in oncology research and discussing them with potential study participants effectively and frequently, we can both respect the participants' valuable contribution, and conduct quality, responsible research to gain a greater understanding of this terrible disease and its treatment.

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Maximize Your EHR Systems for Clinical Trials Operations

PEER REVIEWED | David M. Vulcano, LCSW, MBA, CIP, RAC
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At the Association of Clinical Research Professionals (ACRP) 2014 Global Conference, representatives from Epic, Cerner, and Allscripts were present to address many myths about electronic health record (EHR) systems. The results from 2014 were posted on the ACRP Online Community for Epic and Cerner. As it turns out, these systems are capable of tasks that many clinical research coordinators (CRCs) and others had believed the systems could not do.

LEARNING OBJECTIVE
After reading this article, participants should be able to describe how an electronic health record (EHR) system can assist researchers with patient safety, billing compliance, patient recruitment, and clinical trial metrics.

DISCLOSURES
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Nothing to disclose

One overarching myth addressed was that the EHR companies are the ones to solve all our problems and hand the solutions to us, but it is not that easy, nor is it their place to solve problems at that level. An analogy is Microsoft Office, which comes with a powerful set of functional tools that must be customized at the institutional and personal level. Microsoft Corporation is not going to design and build an individual company's balance sheet in Excel, nor is the software manufacturer going to build an Access database and its front-end forms. Microsoft can provide the functionality and some basic training, but how that software is used is an institutional preference.

EHRs are arguably no different. Generally, the functionality desired by principal investigators (PIs) and CRCs is available, but is not used or promoted for a variety of reasons, ranging from not knowing it is there to not having developed it for use.

As a follow-up to the 2014 conference session, a 2015 session focused less on debunking the same myths and honed in on how to build the bridges in an organization and provide the business case for adding research functionality. Today, competing resources such as ICD-10 conversion and meaningful-use attestations are taking priority, but nevertheless the business cases can be built for improved research functionality.

This article focuses on three core areas that will pay dividends: 1) Building a Business Case; 2) Strategies for Implementing a (Retroactive) Business Case; and 3) Building the External Support Network.

PART 1: Building a Business Case

"Executers create energy, they do not drain it."
—paraphrased from "Execution," by Larry Bossidy and Ram Charin

First, Mitigate Subject and Business Risks

PATIENT SAFETY

For nearly all EHRs, active alerts (see Figure 1) can be built to include notification to the research staff of any of their research participants who enter the emergency room, are seen in an outpatient clinic/satellite facility, or are admitted to the hospital (provided that the EHRs for the different facilities

are linked). This notification is particularity important, given that inpatient hospitalization meets the definition of a serious adverse event (SAE) (as found in ICH E6 1.50 from the International Conference on Harmonization).

In order to fully utilize these safety features, patients must be properly designated as participants in a research study and linked to the proper study. This should be done both through the EHR and in conjunction with a clinical trial management system (CTMS).

FIGURE 1: Example for Creating "Alerts" Within an EHR

Patient Safety Alert

- This patient is on a CLINICAL RESEARCH TRIAL
- Trial: Protocol Name
- COMMENTS: Subject randomized to placebo or active factor X inhibitor
- Contraindicated Medications: antithrombotics
- National Clinical Trial #: NCTXXXXXXXX
- Primary Investigator: Name and Number
- Research Coordinator: Name and Number
- Research Department Main Phone:

Additional safety measures that should be added include hard stops and/or alerts for potential medication contraindications. All hospital medications, including those administered as part of a research study, are ordered almost exclusively through the EHR.

Inasmuch as strict adherence to the protocol is foundational to protect the safety of research participants and to ensure the integrity of scientific findings, deviations from the protocol must be fully identified, promptly reported, and documented accordingly. An EHR e-mail message can be utilized to alert the PI and study team to potential deviations to the protocol in real time, which may result in discovery prior to internal quality inspections or external monitoring.

Electronic research order sets can be specifically built to protocol specifications to prevent persons not involved in the study from inadvertently altering study orders. This not only saves valuable time, it also enhances safety by providing an electronic means of tracking protocol requirements and preventing noncompliance. Mechanisms for building order sets vary among institutions and may require programming expertise. Some institutions may incorporate electronic order sets or "builds" as the expense of doing business, while other institutions relegate the build to each research team.

Each institution must decide if the utility of order sets should be internally supported or if research teams must secure their own expertise and/or funding. Research order sets and orders associated with research also play an important part in facilitating billing compliance. The additional function is institutionally dependent, based on whether the EHR is directly linked to billing modules.

BILLING COMPLIANCE

Billing compliance, especially when it involves the billing of federal payers, is a complex matter that creates many challenges (see Figure 2). Although entire conferences are dedicated to effective billing practices, participants remain confused on many counts. Even when the regulations and coverage decisions can be navigated correctly, it is difficult to implement a compliant billing system in a fast-paced and complex healthcare organization because of the many handoffs.

Any compliance officer in a healthcare-related entity should be well versed in the Stark Laws, False Claims Act, and Anti-Kickback Statute, as well as their penalties. Integrating research into this already complex system increases the risk for double-billing. Examples include billing Medicare for something for which the sponsor is paying the hospital and/or the research site/physician, billing

FIGURE 2: Billing Compliance and Work Effort Summary

Billing Compliance	Work Effort
Delineate standard of care vs. research	Increase study subject recruitment and retention efforts
Create charges in real time by automatically adding research billing codes and modifiers.	Improve accuracy of cohort discovery
Improve reimbursment collection	Automate source data collection and verification directly within the source
Manage potential fraudulent charges and decrease false claim submissions	Decrease potential adverse events for study subject; reduce care management time and possible length of stay

for nonreimbursable investigational products or for nonroutine care items, or billing Medicare when a sponsor agrees to pay for a clinical trial–related injury (which violates the Medicare Secondary Payor provisions).

There have been many well-documented cases in which providers have had to pay millions of dollars in fines and/or settlements due to inaccuracies in research billing. EHR systems often touch all points at the beginning of the billing cycle and personnel involved in the beginning of the billing cycle (such as clinical staff, coders, and others in charge of revenue integrity); therefore, the EHR is often that single source of all billing-related truths, including items significant to research-related billing.

HEALTHCARE SYSTEM ACCREDITATION

Hospital accreditation agencies such as the Joint Commission and Det Norske Veritas (DNV) Healthcare provide specific requirements for research operations (see Table 1). For research consent documents, the Joint Commission's standard (RI.01.03.05) and DNV's standard (PR.4) address the hospital's obligations independent of what the U.S. Food and Drug Administration (FDA) or Office for Human Research Protections (OHRP), both part of the Department of Health and Human Services, may require.

Both agencies also have standards that pertain to the management of investigational drugs. The Joint Commission's standards (MM.04.01.01 and MM.06.01.05) require a hospital-specific policy for investigational drug orders and management. Similarly, DNV's standard (MM.1) indicates that overall policies must include investigational medications/drugs that are not eligible for scheduled dosing times and provide general guidelines for what medication policies must include.

Specific tabs in the EHR can be utilized to easily identify research consents and medication records. For those nonhospital entities accredited by the Accreditation Association for Ambulatory Healthcare (AAAHC), Section 19 puts forth requirements similar to those of the Joint Commission and DNV regarding documenting the informed consent process for research participants who are independent of FDA and OHRP requirements.

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) PRIVACY RULE AND NON-HIPAA PRIVACY AND SECURITY

Providers in the United States' healthcare delivery environments are no strangers to the privacy and security restrictions put forth by HIPAA. HIPAA is also intended to provide the parameters for the appropriate use and disclosure of health information for legitimate purposes, such as research. The process of releasing those data (usually pursuant to a signed authorization from the clinical trial participant) must be done in a HIPAA-compliant manner.

In a paper-based world, this introduces privacy risks for the patient and regulatory risks for the provider. Shifting the records with patient-identifiable protected health information (PHI), be they medical records or other paper source documents, into the EHR environment provides a secure storage mechanism that places the provider more in control of who is accessing that information.

The security of the subject's record may be ensured by issuing study monitors with their own user identification and password, so that their activity can be limited and tracked (even if they log in remotely) or by having them review the material over the shoulder of a staff person with access. Heads of organizations that have transitioned to EHRs would likely shudder to think that they would keep shadow paper copies of identifiable medical records of their patients. Arguably thus, the risk of a PHI breach to the research subject and the institution is no different if the PHI was on a medical record page or a research source document.

Although health information that has been de-identified according to HIPAA standards goes unregulated by HIPAA, there are still risks to be addressed. Large research datasets that otherwise could have been part of the EHR reside in the proverbial "locked filing cabinet" or in Excel spreadsheets and other database programs on laptops and USB "thumb" drives. The literature is full of incidents of lost research laptops.

Even if the data are de-identified, a business risk is still posed to the institution as well as the individual, given the ease of combining the information with other publically available datasets for what is known as "re-identification attack." Overall, having the research source data as part of the EHR protects not just the privacy of the subjects, but also the actual data, from potential breaches.

TABLE 1: Accreditation Within Institutions Supported by Clinical Research Centers/Institutes

Policy or Process	American College of Surgeons (and Similar Organizations)	The Joint Commission/ AAAHC	Det Norske Veritas
Research Policies and Procedures	Specific to Type of Accreditation (Comprehensive Cancer Centers, Breast Centers, Stroke Centers, Trauma Centers, etc.)	Yes	Yes
Formal Screening Process to Identify Potential Patients	Specific to Type of Accreditation	No	No
Policy Related to Management of Investigational Drugs	Specific to Type of Accreditation	Yes	Yes
Policy Related to Documentation of Informed Consent	Specific to Type of Accreditation	Yes	Yes

OTHER REGULATORY CONSIDERATIONS

FDA Form 1572 for investigational drug clinical trials and "The Statement of the Investigator Responsibilities" for investigational device clinical trials are, respectively, signed acknowledgements that investigators will adhere to FDA regulations regarding the conduct of investigational agents. Per 21 CFR 312 in the *Code of Federal Regulations,* investigators are required to delegate appropriate tasks to others based on their education, training, and qualifications.

The Delegation of Authority Log lists all persons to whom the PI has delegated significant trial-related duties (ICH E6 4.1.5). In some cases, discrepancies exist between the log and institutional policies for study team members. A CRC who is delegated medication dispensing responsibilities by the log may lack the credentialing necessary to enter medications in the EHR.

The log must be consistent with internal policy for the EHR to be fully effective. Depending upon the organization and the state it operates in, any activity documented by an unlicensed coordinator may need to be reviewed and signed by the appropriately credentialed and licensed staff to ensure that activity is not beyond the scope of services of the job description or licensure of the individual. Role-based security may be considered burdensome by study teams at first, but the safety, consistency, and transparency provided by EHRs ensure better alignment with institutional guidelines and protections.

Second, Capitalize on Business Opportunities

FEASIBILITY

EHR records support a vibrant environment for quick and accurate feasibility assessment for potential clinical trial offers. The skill set of information technology (IT) analysts decreases the work effort spent on behalf of the research staff by querying the existing data within an active EHR.

An accurate assessment of feasibility creates an environment of respect and trust among research centers and industry leaders. A researcher can submit the initial feasibility questionnaire to the IT analysts, or an automated process may be developed. Reports may be available in real time or by the end of the business day, depending on institutional policies and procedures.

The feasibility report provides accurate data regarding the center's potential study subject pool. If the report does nothing else, it prevents institutions from accepting studies for which they cannot adequately recruit, not only saving these institutions time and expense, but also preventing them from gaining a reputation of being a "low enroller" or "zero enroller" in sponsor and contract research organization (CRO) databases.

Uploading EHR data to a cohort discovery tool, such as the National Institutes of Health (NIH)-funded i2b2 (Informatics for Integrating Biology and the Bedside) (see https://i2b2.org/), provides a fast and convenient way to identify a specific cohort of interest. A customized search for demographics, disease states, or lab values reveals the number of potential participants meeting the specified criteria. i2b2 searches millions of unique data elements at once without involving the use or disclosure of any PHI, and before an institutional review board (IRB) application is needed.

Based on the results, the investigator can make a more informed decision whether or not to proceed, saving countless hours, preventing studies "doomed to fail," and greatly aiding in the selection of inclusion/exclusion criteria likely to make enrollment successful. In the past, this was possible only through IRB approval and exhaustive paper chart review. Once the decision is made to proceed with the study and IRB approval is obtained, the investigator can access PHI for the identified cohort.

CLINICAL TRIALS RECRUITMENT

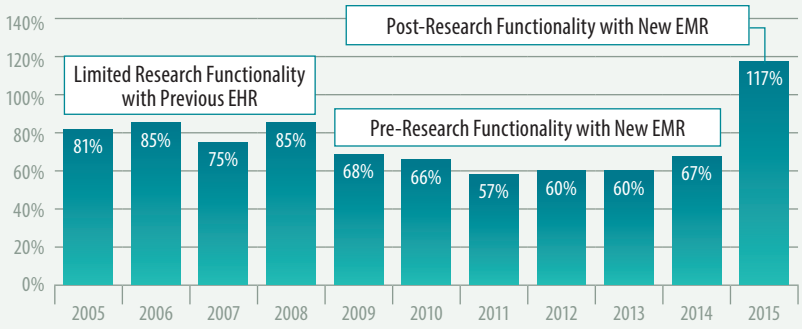
Many practitioners attempt to recruit participants through an EHR's patient portal. Participants receive a message through their portal indicating that they may be eligible for a study. Interested participants can consent online and complete the study questionnaire or other tasks related to recruitment.

The capability to engage the participant in the clinic is particularly exciting, given recent interest and funding opportunities for patient-centered outcomes research (PCOR). As IRBs are charged with the

CASE STUDY #1

Deaconess Clinic, a multispecialty group of more than 160 providers in Evansville, Ind., recently implemented surveillance and notification functionality for a long-term cardiovascular outcomes study. Using the study's screening criteria, the EHR continuously monitored patients who were scheduled for upcoming appointments. The physicians' daily appointment schedules were customized with "research-centric" views or columns to flag the appointments for selected patients who might qualify for the study. Physicians were then able to directly refer the patients to the study through the EHR; this is similar to how patients are typically referred to a specialist for an ancillary procedure. The research nurses were also alerted about the patient's appointment in case the physician wanted to have the patient consented. As a result, 513 patient appointments were identified by the EHR, and 157 patient referrals were sent by 34 referring providers, more than tripling the targeted enrollment for the study. The impact on the research revenues due to this implementation was more than $1 million over the course of the five-year study. Prior to this implementation, all studies were hitting only 57% to 67% of their enrollment targets. By building this functionality into their EHR, researchers were able to increase that percentage to 117% of their enrollment targets on a year-to-date basis (see graph below).

Average Enrollment Rate for Closed Studies 2005–2015



protection of research risks to human subjects, it will be essential to engage IRBs to assure that adequate informed consent and appropriate confidentiality measures are in place for this new era.

In the fast-paced emergency department setting, patients are not scheduled, and volume and acuity cannot be predicted as accurately as in other healthcare settings. An EHR's built-in notification system can greatly aid the ability to identify participants by alerting the study team to a patient's real-time presence via phone or e-mail after a certain diagnostic test/procedure (i.e., urinalysis) is ordered or a certain diagnosis made. Once the move to an EHR system is announced, research teams should petition leadership to have this type of functionality incorporated.

A paging communications workflow utilizing an order transmittal rule was built into the new EHR system to facilitate paging of emergency department study teams when an order for a certain test or medication is placed. A recent example utilizing an alert concerning any patient having a urine culture allowed the emergency department to enroll 90 participants in a kidney infection study much faster than anticipated. Once study enrollment was complete, the alert was simply inactivated.

A physician can also directly communicate with study teams by entering a nursing communication order. The order becomes a part of the EHR and documents that the provider has communicated with the patient and that the patient has given approval to be contacted by the study team. Because the order meets the order transmittal rule, an alert is sent to the study team.

Recruitment of study participants via EHR can also include direct notification of the physician. A significant challenge of recruitment involves simply maintaining provider awareness of active studies and their inclusion/exclusion criteria for screening. The potential exists for EHRs to maintain an active surveillance of scheduled patients and alert the provider to those who may be eligible for a study.

The applicability of this approach will vary by study. For example, an EHR may be able to discern all screening criteria for a prospective registry-based observational study, but only be able to provide high-level screening capabilities in the case of a randomized oncology treatment clinical trial (see Case Studies #1 and #2 for examples).

TRIAL METRICS

A benefit of EHR in the healthcare setting is the derivation of metrics from existing data. The monitoring of metrics is an important and useful practice in any business setting, though care must be exercised to focus on relevant metrics. Sometimes administrators simply need to ask, "How many clinical trial patients have we had?" or "How much revenue did this study bring?" or (after reading a bad press report) "Did we have anybody on that particular study in our hospital?"

Aspects such as productivity, efficiency, and even qualitative measures could also be utilized for more sophisticated inquiries and planning. Many clinical trial sites use a CTMS for such measures, but many sites do not have the benefits of such a robust system. For whatever reason, a number of sites unfortunately do not conduct metrics, and the end result is a poor awareness of their performance. This can be true for the site as a whole or for individual studies.

Reasons for not implementing metrics can vary, but a lack of time may certainly be one. The EHR can potentially automate the process, especially in the absence of a CTMS. Individual measures of study performance, such as enrollment rate, can be aggregated to provide a view of site performance. A dashboard can be developed for the site to monitor itself. In addition, data from different sites can be used to develop benchmarks for performance.

OPTIMIZATION OF WORKFLOWS FOR CRCS AND CLINICAL RESEARCH ASSOCIATES (CRAS)

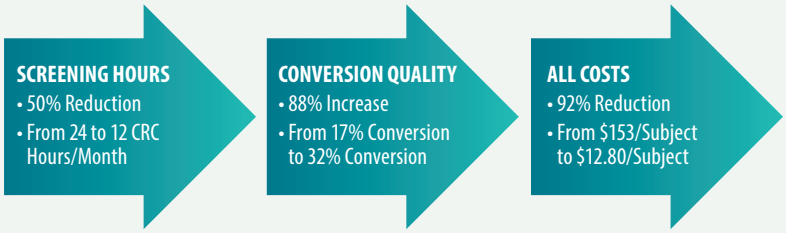
CRCs often have to abstract data from EHRs to enter into case report forms (CRFs). Conversion to EHRs makes this task easier. While this is generally a standard feature of EHR functionality that does not need extra builds above and beyond those required for normal operation, sometimes there are internal obstacles that slow down CRC access to the EHRs (see Case Study #2 for an example of the improved efficiency).

To also enhance the utility of EHR in research studies, it would be beneficial if data could be uploaded from the EHR into the electronic CRFs (eCRFs). This is technically feasible, and has been demonstrated in pilot studies by the Clinical Data Interchange Standards Consortium (CDISC); however, it has not been adopted by sponsors and sites in any meaningful manner.

The upload would have to be managed by the department in charge of health information management to ensure security and accuracy of information, as well as to ensure that only minimal necessary information is uploaded. The data upload would ensure accuracy of data, reduce time needed for data entry (especially "double entry"), and allow CRC efforts to be focused on data verification and completion of additional elements prior to submission of eCRFs.

CASE STUDY #2

An unpublished case study conducted within another large healthcare system identified the following study metrics related to screening utilizing a manual vs. an automated EHR process. A significant finding was that the screening process timeframe was cut in half and the weekly labor effort was significantly decreased after implementation of an automated screening process.



The same case study demonstrates that there is significantly improved quality and cost savings when a CRC can realize the full functionality of the EHR's search features. Note that CRCs whose duties include higher amounts of chart abstraction will realize more productivity advantages here than will their counterparts who perform more clinical procedures.

The use of tablets and other mobile devices is now possible for many EHRs. This may increase functionality in active settings, where sitting at a desktop is neither practical nor optimal.

Although tablet use may involve providing a custom build to the EHR system instead of creating separate eCRFs on the tablet, there are also technologies that can enable an eCRF to be automatically completed within the user's current application, saving the need for double entry or manual uploads from the EHR. Again piloted by CDISC and again not yet widely utilized, the "remote form for data capture" technology promises to be the one of the most influential tools for integrating the workflow processes of clinical care and clinical research.

As part of the protocol monitoring process, monitors or CRAs may be required to review records, but it is often challenging to isolate only the records of subjects in the clinical trial. Monitors have either had to look over the shoulder of a research staff member (which is not the most optimal use of the research staff's time) or been subjected to a security background check (requiring them to give their Social Security Number) in order to be granted direct electronic access.

Given the lost productivity and high costs of travel, any investment in remote monitoring sessions can be seen as a win-win scenario for sponsors/CROs and sites.

Setting up a system to support remote monitoring of EHR data is feasible (and is often done for peer or legal review), and the costs can be shared with the sponsor or CRO. Given the lost productivity and high costs of travel (typically $700 or more in direct travel costs for a two-day monitoring session), any investment in remote monitoring sessions can be seen as a win-win scenario for sponsors/CROs and sites.

CLINICAL "BLUE RIBBON" MANDATES

Achieving certain quality designations, whether mandated or voluntary, is an important focus of leadership in healthcare organizations. Programs responsible for designating Centers of Excellence or other national and international designations have become industries unto themselves.

To earn many of these "blue ribbons," be they in clinical areas (such as cancer, stroke, or trauma) or for professionals (such as the American Nurses Credentialing Center's MAGNET Recognition Program), the institution must be engaged in varying degrees of research. While some of the research requirements are very onerous, many can be accomplished with simple utilization of existing health data.

Before EHRs became available, data collection, processing, abstraction, analysis, storage, and transmission was an expensive manual process, even for retrospective research, due to the onerous task of digging through medical records. With the right capabilities, the EHR can be a powerful and inexpensive source of easily extracted and analyzed data that meet these requirements.

PART 2: Strategies for Implementing a (Retroactive) Business Case

"The best time to plant a tree was 20 years ago . . . the second best time is now."

—Chinese proverb

WORK WITHIN THE SYSTEM THAT IS GREATER THAN THE RESEARCH DEPARTMENT

Regarding the conversion to EHRs, David Blumenthal, one of the architects of the Health Information Technology for Economic and Clinical Health (HITECH) Act and the former National Coordinator for Health Information Technology, stated, "These IT implementations are rare, once-in-an-organization's-lifetime opportunities . . . [to clean up messy systems and to make fundamental decisions about workflow and governance]. I just wish more organizations would take advantage of them." Blumenthal also stated that the implementation of health IT is "not a technical project, it's a social change project," meaning that the IT department is not just downloading software and clicking "I Accept" the Terms and Conditions.

Many of the challenges faced by research staff result from their not having a voice at the table when decisions are being made about EHR systems that directly or indirectly affect the staff. Most hands-on users of the EHR system are not in senior-level decision-making positions; thus, there exists an inherent disconnect that is linked only by the voices at the table, either in person or by proxy.

Given the higher priorities and louder stakeholders at hand, it seems that research staff have to be assertive and invite themselves in order to have a place at the table. Assuredly, one of the best ways to have one's voice heard over the myriad of other demands is to personally be there to give it; therefore, research staff should find out when these meetings are to be held and/or who is in charge of the agenda.

Alternatively, a list of research needs can be inserted into status reports to make sure the research department has a voice (see other sections in this article that reference Physician Champions and discuss parallels for synergizing voices). Having a spot on the written plan, even if that spot has low priority and results in no action, is arguably better than not having a spot on the plan, as somewhere, somebody is evaluated on that plan.

Other challenges include not knowing whom to ask for answers or solutions. It is not uncommon, especially in large organizations, for several IT personnel to respond to an inquiry by saying that the EHR system "can't do that" and for the next person (IT or otherwise) to respond by showing that it could have been done all along. Persistence here often pays off, and these systems often can do what is wanted (as-is or with some tweaking).

Clinical staff who best know the functionality and/or an operator who best understands the business impact can be valuable resources

to overcoming challenges. IT personnel work hard, yet are unfamiliar with the specific needs of end-users. Effective partnerships—including detailed requests, engaged IT personnel, and strong working relationships—are key to overcoming many challenges.

FIND ONE OR MORE PHYSICIAN CHAMPION(S)

The implementation of an EHR likely represents a significant capital investment by the institution, based on input from leaders across many departments. Finding a voice and forum to convey needed changes can be difficult in even the most accommodating firms. Individuals in firms without an existing or effective change-control process may be relegated to simply discovering creative workarounds.

Enlisting a Physician Champion (especially one who is computer savvy) is often the best, and perhaps only, way to affect positive changes. A strong case with sufficient documentation and justification is still required, but a Champion will get the message to those in a position to act and follow through. An advocate who is both a respected clinical leader (knowing what is needed) and an acknowledged business leader (knowing what is possible) can present the message strongly and to the right individual(s), who are empowered to make selections of vendors and/or who have the authority to allocate resources.

FIND PARALLELS TO MAKE RESEARCH NEEDS EASIER TO ASSIMILATE

Often, the research-related requests for EHR functionality are not necessarily unique. A request may often be stigmatized because it comes from the research office when, in fact, with little to no creativity there is existing functionality that can be piggybacked. For example, a research department's request to split bills between a research sponsor and the patient's payor could be met with unnecessary obstacles, although the request could involve simply finding out how bills may be split for routine-care procedures, such as a hysterectomy (which insurance covers) and a tummy-tuck (which is cosmetic and often not covered) during the same hospital stay.

Once a research staffer has found a parallel, it is much easier to add research to existing policies and practices than to try to define a whole new process for research. Simple things such as notifying research staff of subsequent care a patient/subject receives and ensuring the availability of custom order set functionality, processes for remote viewing of medical records, functionality of pop-up warnings, etc., are all items utilized in routine care from which the research staff can benefit.

Shifting the request from something like "for research, because we're different, we need to add…" to something like "you know how we accommodate for [nonresearch activity that the EHR already supports], well this is essentially the same thing" could make all the difference.

IDENTIFY RESEARCH FUNCTIONALITY GURUS/SUPER-USERS

For the successful implementation of EHRs, end-users need to be appropriately trained on the basic functionality of the EHR system being utilized (identifying patients, obtaining results, accessing information, etc.). Additional job-specific training is needed (e.g., how to enter billing codes/insurance information for personnel in the billing department and how to dictate notes/write orders/transfer charts for personnel in the clinical area).

However, if individual personnel are familiar with only their "piece" of the system, no one will have the overview necessary to know how tasks within the EHR are inter-related, find more efficient ways to perform tasks, or identify potential "gaps" in the system. The super-user or EHR guru needs to have a high level of computer literacy, be able to communicate information in an understandable way to end-users to facilitate their learning, be able to understand difficulties and identify solutions, and be a leader and champion for the implementation of the EHR.

If the user groups have someone who can be a super-user, the system will be easier for those with limited computer literacy to implement. The super-user also needs to be comfortable and confident enough about his or her abilities to search out answers or solutions from blogs, other super-users, or EHR representatives. If an institution does not have an identified super-user, it would be best to identify one right away, even if that person temporarily has to be you, the reader.

If individual personnel are familiar with only their "piece" of the system, no one will have the overview necessary to know how tasks within the EHR are interrelated, find more efficient ways to perform tasks, or identify potential "gaps" in the system.

PRESENT YOUR NEEDS AS A SOLID BUSINESS CASE

Business can improve only to the extent that performance improves. Two factors come into play in this regard. The first is knowledge of the quality of existing performance, and the second is the ability to act on that knowledge. The use of EHRs in clinical research can fulfill both of these factors.

In the first case, the ability to collect and aggregate data into meaningful metrics provides the ability to develop an awareness of one's performance level. In the second case, EHR capabilities can be utilized to act on and improve such measures, both quantitatively and qualitatively. Individual study performance, enrollments, staff performance, and participant compliance are examples of measures that can add value to a busy clinical research site.

The business case (see Table 2) for the use of EHR for research enhancement, site performance, and metrics development also incorporates an indirect aspect. This is the relationship of a research department within the overall healthcare organization. Simply put, hospitals and healthcare systems have expectations of their departments in terms of efficiency, cost reduction, and improved performance. By extension, decisions about reductions in departments may be based on these aspects, especially for healthcare systems operating on thin margins.

That said, an additional challenge faced by research sites is the need to educate leadership about the business of research, which is an area with which many healthcare leaders may not be familiar. The use of EHRs in research is a means to address these concerns of healthcare leadership relevant to research. Again, the usefulness of EHR in this regard involves the development, implementation, and utilization of practical metrics.

TABLE 2: Resources to Support the Business Case of EHR Support in Clinical Research

Benefit of IT Solution	What/How to Measure
1. Transparency Related to Clinical Documentation	• Decrease deviations related to clinical standard of care. • Promote provider awareness within health system. • Comply with responsibilities related to accreditation/licensure requirements.
2. Awareness of Investigational Drugs/Devices	• Prevent medication/device-related errors. • Comply with requirements related to protocol adherence.
3. Emergency Use of Unapproved Drugs/Devices	• Monitor drugs given/devices used and study subjects receiving drugs/implants prospectively; currently, tracking can be done only retrospectively, thus increasing potential harm to patients.
4. Humanitarian Use Devices	• Monitor devices used, number of devices implanted, billing and revenue reimbursement related to Humanitarian Use Devices, and benefit to health system as a whole for access to advanced device practices for underserved patient populations.
5. Identification of Study-Related Procedures That are Not Standard of Care (SOC) Per the Protocol	• Identify research-related costs and differentiate between SOC and research billing to ensure investigational billing compliance. • Monitor patients effectively who are on clinical trial protocols; decrease administration of contraindicated medications and/or procedures related to clinical care outside a clinical trial protocol. • Justify SOC/non-SOC decision to sponsors/auditors using historic data for justification.
6. Billing for Hospital Services Pursuant to the Clinical Research Protocol	• Monitor orders for procedures and treatment plans as indicated within the protocol for research SOC treatment vs. investigational care treatment. • Comply with billing and reimbursement requirements.
7. Centers for Medicare and Medicaid Services Coverage of Routine Costs in Qualifying Clinical Trials	• Monitor (decreased) coding/billing errors, improve the turnaround time, and decrease the work involved in retrospectively monitoring claims related to clinical trial patients. • Decrease potential fraudulent billing related to research subjects.
8. Prediction of Enrollment for Clinical Trials	• Decrease inappropriate acceptance of clinical trials when the facility does not have the required study patient population. • Decrease cost burden associated with acceptance of protocols for which providers cannot enroll patients. • Decrease regulatory burden and work effort for unproductive clinical trials.
9. Increase in Clinical Trial Compliance	• Decrease deviations related to study-subject safety and protocol compliance. • Comply with protocol procedures and orders.
10. Documentation of Clinical Research Source	• Assure compliance with ICH E6 (Good Clinical Practice) related to essential documentation in clinical research trials. • Increase documentation efficiencies (i.e., ability to sign research related records electronically, decreasing clinical research coordinator work effort and improving investigator oversight, etc.). • Assure HIPAA compliance related to PHI. • Assure human subject protection and safety.
11. Identification of Human Subjects Research	• Increase quality of recruitment pool based on improved inclusion/exclusion screening. • Decrease pre-screen failures and screen failures.
12. Response to Allegations of Research Misconduct	• Provide transparent auditing system to track clinicians and providers who are investigators or who provide patient care for clinical trial protocols. • Monitor ongoing SOC with respect to transparency for clinicians and providers who are not part of the clinical research team.

PART 3: Building the External Support Network

"Be the change you want to see in the world."
—Gandhi

ENSURE THAT IMPLEMENTATION IS IN THE HANDS OF IMPLEMENTATION EXPERTS

People generally agree that if you do something right the first time, you save time and money that would otherwise be spent in redoing the work. While CRCs are generally seen as jacks of all trades, even computer-savvy CRCs rarely have experience in EHR implementation and functionality. As stated above, there should be an identified super-user, who will likely be a CRC, but the super-user role should not be confused with the implementer role.

There are generally expert implementers (or at least identified/trained implementers) within the IT staff, project management personnel, and/or nursing informatics specialists charged with the migration of functionality. Assuming that research is on their punch-list, let them do the job that they do best instead of trying to change a CRC or PI into an EHR implementer. Taking a CRC out of a revenue-generating role to learn how to be an EHR implementation expert is unlikely to be time well spent.

FIND ONE OR MORE HELPLINE(S)

All EHR vendors have technical support (online or in-house) and even some research functionality support available for implementation, trouble-shooting, and maintenance of the system. In addition, a number of online communities (blogs, forums) are available through the different EHR vendors (as well as independent organizations). Many vendors have live meetings that have research-specific breakout sessions. Even if a user cannot go to the meeting, he or she can ask an attendee to pick up the materials or ask the vendor to send them.

SHARE TRAINING/TIPS WITH OTHERS

Sometimes EHR support forums may be nonexistent or inaccessible to the research staff, either by omission or by institutional design. Instead of (or as a supplement to) vendor-supplied assistance, most professional societies (such as the ACRP) have discussion forums that can provide help from peers in similar positions.

Further, institutions are partnering to share best practices. Effective change realized in one place is often easily duplicated elsewhere. Research professionals with an interest in and a working knowledge of EHRs must continue to build bridges among peer institutions and alongside other forums. These mavens can advance the cause in many ways, such as by volunteering to be leaders, conducting solution-finding sessions at local professional chapter meetings and conferences, or writing grants for implementation through the NIH or the Clinical and Translational Science Awards (CTSA) program, among other examples.

Conclusion

In the book "Management: Ready Aim Fire," Anthony La Russo states, ". . . managers can find that they have set a long term path for their organization by making a series of decisions focusing on numerous separate short term problems." He goes on to state, like so many others, that you have to initiate the change you need rather than wait for your organization to evolve (look what waiting for evolution did to the dinosaurs). Thus, although people often state that "someone needs to fix this" and "someone needs to lead this effort," they frequently forget that they are "someone" as well.

It is up to clinical research operators to make their needs known, struggle to the top of the list, and lead the change in their organization. By presenting a solid business case, you can differentiate your needs from those of others who cannot articulate the value of the investment to the organization.

Research professionals must work within their own institutions to build and maximize EHR benefit(s) and spread their success stories across the broad research landscape. This must be done to enhance the benefit and safety of all research participants, to meet the scientific and ethical responsibilities of research professionals, and to derive maximum benefit and efficiency among research teams.

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eSource and Risk-Based Monitoring: *A Favorable Union for Future Clinical Trials*

PEER REVIEWED | Neha Sharma, MSc, MA

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The growing cost of drug development is paving the way for newer technologies in clinical research. Taking its cue from success stories of automation across other industries, the pharmaceuticals sector's acceptance of the Cloud, "big data," and analytics stands as a testimony to changing times.

The focus now is on risk-based monitoring (RBM) for enabling early risk identification and mitigation while aiding targeted actions for sites requiring attention. RBM looks at issues at the root level, and uses technology for challenging the status quo. The need for 100% source data verification (SDV) is being challenged, and innovative ideas to reduce SDV are being explored.

The use of electronic source (eSource) technology can potentially catalyze clinical trials transformation via RBM.

This paper will explore how eSource provides a solution to labor-intensive SDV practices and accelerates data review, and offers some factors to consider for eSource deployment. It highlights how eSource maximizes the utilization of monitors' capabilities to channelize source data review (SDR) for RBM. Lastly, it covers some of the players offering eSource technology and services.

Background

As per Medidata's infographic on RBM released in July 2014, trial monitoring represents 30% of the cost of conducting a clinical trial, with 85% of the monitoring time being spent on SDV. However, these extensive efforts and costs linked to SDV result in less than 3% of data being updated to any significant degree.

With these facts in place, industry was still expected to spend $7.5 billion on SDV in 2014.[1] With the goal of encouraging the industry toward effective transformation, the U.S. Food and Drug Administration (FDA) published three back-to-back guidance documents for pushing technology adoption in clinical trials. This included guidance for RBM in August 2013,[2] guidance for use of eSource in September 2013,[3] and guidance for regulatory submission using standardized study data in February 2014.[4]

With this support and push for disruptive innovation, technologies like Cloud-based data storage and its solutions (e.g., eSource) are being extensively explored in the life sciences sector. With the Cloud, since software resides on a web-based server shared with virtual resources vis a vis desktop, the efficiency gains are higher. Costs related to information technology expenditure and inefficiencies of manual paper processes are eliminated, though security is enhanced.

Since paper-based data collection fails to provide similar control, Cloud-enabling eSource solutions can be a boon for a regulated industry like clinical research. Companies like Eli Lily and Johnson & Johnson are already adopting the Cloud to empower their scientists across the globe, while building capabilities for data-crunching functions.[5]

In addition to paper case report forms (CRFs), use of computerized systems for capturing data and recording some source data electronically during clinical investigation has been common. As per the FDA, source data include all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing

LEARNING OBJECTIVE
After reading this article, participants should be able to discuss how eSource can enable effective risk-based monitoring for clinical trials.

DISCLOSURES
Neha Sharma, MSc, MA:
Nothing to disclose

and evaluating the investigation (electronic source data are data initially recorded in electronic format). Examples include, but are not limited to, clinical data initially recorded in electronic health records (EHRs) maintained by healthcare providers and institutions, electronic laboratory reports, digital medical images from devices, and electronic diaries completed by study subjects.[3]

The traditional data entry mechanism by which site coordinators transcribed data from source documents to a database drove the need for SDV and posed challenges to real-time data review. The following sections of this article will briefly review the factors that led to the modern focus on eSource.

Issues of Delayed Data Review and Data Cleaning—eSource Offers Solutions

Following a patient's visit, conventional data review and cleaning methodologies are data entry–dependent. Sites typically take three to five days for data transcription from source document to CRF. This creates a first level of dependency and delay in data review in terms of data availability. With onsite monitor visiting site every four to six weeks, a second level of data cleaning delay occurs for already-available data in the database. Since the data are reviewed weeks after a patient visited the site, follow up for data issues becomes a big challenge that delays the overall data-cleaning process.[6]

For eSource solutions with real-time data entering a database, the eCRF itself becomes the source. Since patient data are directly fed into an eCRF, any discrepancies or missing data can be corrected in the patient's presence. This implies that the need for performing transcription checks via SDV can be eliminated for studies in which eSource is used. High-quality data and cost efficiencies related to query management can also be achieved through the decreased effort devoted to data cleaning by data managers and monitors.

Impact of eSource on Changing Role of Onsite Monitors

Based on guidance provided by FDA on RBM and eSource, pharmaceutical companies are taking measured steps. The vision of conducting trials that are focused on maximizing the right usage of resources and technology is coming to fruition. Onsite monitors are being retrained to think differently and drop age-old habits.

The need for transitioning monitoring activities from being seemingly futile clerical efforts to being value-added uses of skills is being mandated. With less effort spent on data transcription, the focus of monitoring can be easily shifted to SDR. Onsite monitors can now review data patterns aimed at identifying risks early; their reviews and analyses of trends, key risk indicators, and signals can help investigators better conduct their trials. All of this helps channelize site monitoring efforts based purely on the site's risk profile, which is a successful realization of one of the core RBM goals.

Management of discrepant data as a result of incorrect transcription, noncompliance to data entry guidelines, and other factors is traditionally under the purview of data managers; with eSource, the scope of data manager review would also change. The dynamics of these changes are also of substantial interest in the overall scheme of RBM, and should be considered for future discussions.

Convergence of eSource and RBM

It can be seen by previous discussions that the needs of RBM can be fulfilled by eSource in many ways, and that for problems related to delayed data review, 100% SDV, and more, eSource with its multiple benefits offers the key. Some key features of eSource that make it an extremely powerful tool involve how it:

- enhances significance of onsite visits by collecting patient data while the patient is onsite;
- aids flagging and cleaning of data issues while data are being entered;
- significantly decreases the human error element by removal of the data transcription step;
- provides a solution to sites for adopting RBM by not only reducing, but by eliminating the need for SDV;
- enables real-time analytics and trend review to help trial leaders make informed decisions;
- provides a common area for data review to multiple stakeholders in a study;
- allows integration of lab results and medical records for quick decisions;
- can be easily customized to be accessible via web; and
- complements RBM execution and cost savings for sponsors.

Taking its cue from success stories of automation across other industries, the pharmaceuticals sector's acceptance of the Cloud, "big data," and analytics stands as a testimony to changing times.

The traditional data entry mechanism by which site coordinators transcribed data from source documents to a database drove the need for SDV and posed challenges to real-time data review.

eSource thus provides the pharmaceuticals industry with an answer to one of its biggest pain points related to cost implications of frequent monitoring visits for 100% SDV, thereby improving trial budgets. It can enable availability of real-time data for central monitor review and be a boon for data analytics. eSource enables a holistic review of data coming from multiple sources, thereby helping clinical project managers assess and mitigate risks from several functional areas at one go.

Growing Acceptance of eSource Among Stakeholders

Lack of effective change management has been an impeding factor for the pharmaceutical sector in its RBM implementation. In an environment where the roles of clinical trial stakeholders are changing and performance is the driver, eSource is seen as one of the best options for making life easier. Site coordinators and monitors are able to effectively manage queries in a patient's presence at sites, thereby reducing follow ups, and eSource further minimizes the probability of errors through pop-up alerts that call the user's attention to potentially bad entries to the database.

The use of eSource is particularly helpful for investigators who have to remember the trial designs of various projects they are working on. Meanwhile, onsite monitors can focus more on building site relationships and SDR. With site performance being linked to a monitor's performance index, eSource offers great relief to monitors who are already dealing with the increased expectations of RBM.

To assess whether eSource is beneficial in a real-world setting, a study was conducted using RBM and direct data entry (DDE) methodologies. It was reported that usage of eSource at a particular site resulted in a huge saving of effort in onsite monitoring, as compared to studies that were using paper CRFs. Protocol compliance and issue tracking was also improved, as issues identification and correction was faster.[7] An overall saving of 70 labor hours was reported by the clinical sites when they replaced paper CRFs and EDC with DDE.[8]

Considerations for Effective eSource Implementation

Having discussed how eSource enables RBM and its growing acceptance as a research tool, it is still essential to weigh out the benefits offered by eSource versus its ability to enhance patient safety and data integrity.

For trials using eSource, FDA guidance stresses the need for clearly defining the data originators, the modalities of source data capture, and what the data element identifiers are for each data element in a trial's data management plan, so that all of these elements may be referenced during audits and inspections. Integration of crucial parameters like instruments, data standards, control files, and validated data integration methodologies that are all compliant with 21 CFR Part II of the *Code of Federal Regulations* enables smooth set up of eSource; however, constraints for successful implementation must also be examined in advance.

A few considerations for successful deployment of eSource would include:

- Correct selection of eSource from a gamut of solutions based on a trial's needs and this solution's capability to export data in a format that easily integrates into EDC
- Validation of data sources (instruments, medical devices, databases) used at sites for regulatory compliance
- Incorporating electronic prompts, flags, and data quality checks for data accuracy and effective data collection (for data capture systems not having inherent checks, mapping of data element identifiers between the system and the eCRF and design of edit checks are needed to minimize data loss during data entry)
- Effective controls for role-based user access to systems and overall trial to ensure all user activities are date and time stamped

Meanwhile, agreements that describe how study information will be shared among investigative sites and third parties will need to be defined in the planning stage. During the conduct of the study, configuring the trial database to report only the data specified in the protocol will help with the data review process.[9]

With regulations favoring eSource and the array of benefits that eSource offers (including its value in facilitating RBM), various players are trying to seize opportunities existing in market. Discussed next are some of the ideal features of eSource and current players in the market offering these services.

Ideal Features of eSource and Current Players

The FDA and other regulatory agencies consider it of utmost importance that eSource technology provides substantial data element identifiers for use in any examination by audit trail of eCRF

data, and that it provides information allowing for the reconstruction and evaluation of the clinical investigation for which it was used. Companies building eSource solutions are wise to align their business plans to the specifications cited in the aforementioned FDA guidance documents.

Some of the ideal features that companies developing eSource solutions should keep in mind include the functionality needed to capture data during patient visits and to facilitate remote monitoring and real-time data review access. Data integration capabilities for data coming from multiple sources could be of immense value for overall data analysis.

eSource solutions providing final analysis datasets as per standard formats (e.g., in a study data tabulation model) would help save time and efforts during end game activities. Today, with data presentation being about pie charts and histograms, solutions offering graphical reports for data visualization and analytics in mobile/tablet handsets could be considered icing on the cake.

Currently, Clinical Ink[10] and assisTek[11] are among the companies that offer eSource solutions in the market. With increasing awareness of the potential demand for the tool, the number of players who will be developing and marketing eSource services is expected to rise. As the industry continues to gain clarity on the practical usage of eSource, there also comes the need to constantly monitor upcoming solutions for better and enhanced features.

Conclusion

For successful completion of clinical trials, among the most important parameters are timely entry and review of data; if these can happen at the time of a patient's visit, the workload of monitoring visits and data cleaning efforts can be reduced. With eSource enabling DDE, the need for paper records and SDV can also be reduced drastically.

This paper discussed how efficiencies gained through the use of eSource can enable effective implementation of RBM by way of reduced SDV and targeted monitoring of variables that "actually" matter. With data transcription being almost eliminated, real-time monitoring of data can be achieved with ease.

Furthermore, the transition from manual and effort-intensive activities to more streamlined processes paves the way for role repurposing on the clinical trials team. This paper also discussed how the role of monitors is about to undergo a paradigm shift from its nature as experienced when following traditional data review methods. The shifting of the focus of reviews from SDV to SDR for monitors, and a focus on overall risks and trend analysis for data managers, will be crucial for successful RBM.

While realizing the potential of eSource and its benefits, this paper also highlighted important factors that need to be considered while implementing eSource. Lastly, some ideal features of eSource and players currently offering eSource products in the market for cost-effective, data-driven, and effectively operated clinical trials were discussed.

For eSource solutions with real-time data entering a database, the eCRF itself becomes the source. Since patient data are directly fed into an eCRF, any discrepancies or missing data can be corrected in the patient's presence.

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The Rise of Electronic Data Capture and its Greatest Obstacle

PEER REVIEWED | Colton Castle, MS | April Bell, MS, CCRC | Patricia Gwirtz, PhD

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Advancement in healthcare-related technologies has resulted in a groundswell of information contained in patient health records. Electronic data abstraction systems have allowed medical professionals to analyze and apply vast bodies of information comprehensively. In the field of clinical trial management, electronic data capture (EDC) has become vital to this process.

LEARNING OBJECTIVE
After reading this article, participants should be able to explain the driving forces behind the increasing prevalence of electronic data capture in clinical trial management, and to examine reasons why many investigational sites still depend on paper-based data capture.

DISCLOSURES
Colton Castle, MS;
April Bell, MS, CCRC;
Patricia Gwirtz, PhD:
Nothing to disclose

Over time, EDC yields benefits in cost, trial duration, and the capacity to utilize remote monitoring. As a result, EDC usage in clinical trials has increased dramatically in the last decade. However, EDC implementation can prove costly, and often causes temporary disruptions to workflow and productivity.

EDC implementation must evolve to become less costly and more user-friendly before EDC usage reaches ubiquity in clinical trial management.

The Problem Created by Technology

Clearly, EDC has become the industry standard for information analytics in clinical trial management. Virtually all clinical trials begun in the last decade employ EDC in some capacity. However, EDC continues to struggle against a familiar (but significant) obstacle in terms of implementation and, as a result, most investigational sites still utilize paper-based data capture systems. What difficulties continue to plague investigational sites and sponsors, preventing the paradigmatic implementation of EDC?

To begin to consider the answer to this question, one must recognize that the healthcare industry is experiencing a "big data" revolution. In the minds of healthcare professionals, this means that the exorbitant amount of data management necessary for comprehensive patient care has outstripped current methods of analyzing and adapting that information in useful ways.[1]

Traditionally, a patient's health record has included a detailed medical history, a list of concomitant medications and dosing, family history, laboratory test results, etc. This body of information swelled significantly with technological advancement in medical imaging, and promises to continue increasing exponentially as genomic sequencing becomes common practice in western medicine[1,2] As an example, including clinical text and imaging data, Beth Israel Deaconess Medical Center in Boston, Mass. currently generates 20 terabytes of new health record data per year for an active patient population of 250,000.[3] Following the current trend, the volume of data storage necessary for hospitals and clinics to maintain will continue to escalate considerably with the advent of new technologies.

Quality patient care now requires a complex and costly system of analytics to comprehensively process and interpret this vast body of information in meaningful ways. Information analytics on this scale has only been made possible through the rise of electronic systems, particularly the electronic health record (EHR).[1]

In 2009, the Health Information Technology for Economic and Clinical Health (HITECH) Act authorized incentives to physicians willing to adopt EHR methods.[4] According to a 2014 data brief from the Centers for Disease Control and Prevention, the percentage of office-based physicians who employed any kind of EHR methodology in their practice increased from 18.2% in 2001 to 48.3% in 2009, and 78.4% in 2013.[4] From another viewpoint, office-based physicians' use of a holistic EHR system in their practices rose dramatically from 10.5% in 2006 to 48.1% in 2013[4] (see Figure 1).

The growing need for complex information analytics will soon necessitate systemic EHR use in every field of the healthcare industry.

The Rise of Electronic Data Capture

The field of clinical trial management has experienced a similar groundswell in electronic system implementation in the past decade. In the same manner that EHR represents the most vital component of electronic system utilization in primary care settings, EDC epitomizes this progress in clinical trial management.

In 2005, only 24% of trials incorporated EDC in their trial management system. The prevalence of EDC system use rose dramatically in the following years.[5] In 2012, 75% of clinical trials were likely to use EDC. This represents a yearly increase of 15% of clinical trials converting from traditional paper-based data capture to EDC.[5]

Why has clinical trial management evolved to incorporate the same kinds of electronic systems utilized in other healthcare fields?

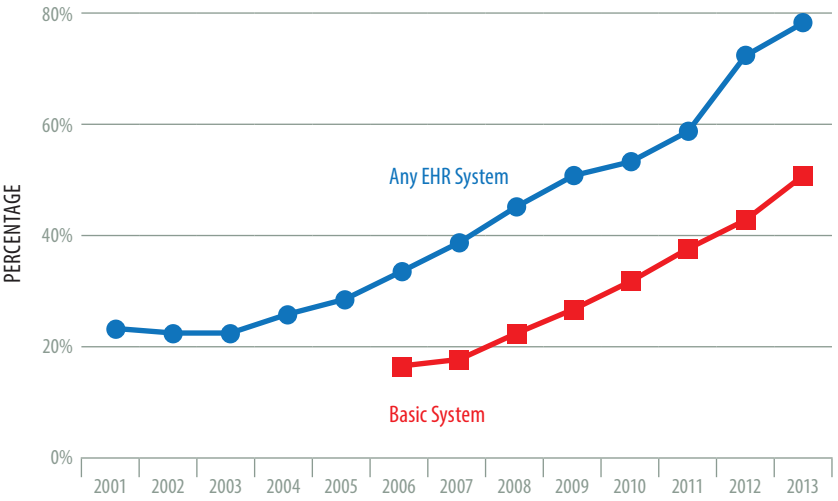
One consideration is that clinical trial cost represents a significant deterrent to medical innovation. Achieving investigational product approval is both a costly and time-consuming process and, as a result, reducing the monetary burden of clinical trials is vitally important to improving the efficiency of global healthcare innovation.

Research and development (R&D) for a new chemical or biological entity can exceed $1 billion and require 10 to 15 years from R&D to U.S. Food and Drug Administration (FDA) approval.[6] Only 333 new drugs and biologics achieved FDA approval in the United States from 2000 to 2010 and, of those, just two out of 10 produced enough revenue in marketing to compensate for R&D costs.[6]

Electronic-based systems in clinical trials have the potential to alleviate some of this burden and, in doing so, benefit both the sponsor and the consumer. Shorter, less costly trials have motivated sponsors to incorporate EDC into their studies at a dramatically increasing rate. EDC reduces clinical trial costs by decreasing the number of mistakes in data collection and management, shortening the average study duration, reducing the financial burden of trial queries, reducing data collection and monitoring costs, and streamlining database processing.[7]

Green (2015) analyzed data from four different clinical trials—one each in Phase I, Phase II, Phase IIIa, and Phase IIIb—to perform a detailed cost comparison of EDC vs. traditional paper-based data capture (Phase IIIa trials are conducted before a New Drug Application is submitted to the FDA, and IIIb trials are conducted after, but prior to marketing approval). The research included 228 investigational sites and 8,264 subjects over the course of 54 months.[8] Green compared cost metrics in three areas: approved EDC budgets

FIGURE 1: Percentage of Office-Based Physicians with EHR Systems



Source: Compiled from Chun-Ju, et al. (2001–13)

in each clinical trial, estimated costs for a paper model, and implementation and EDC costs applied under a level 2 technology transfer and enterprise relationship pricing model (this model projects cost savings associated with research sites internalizing EDC software use and performing their own electronic case report form [eCRF] design and data management, rather than outsourcing these responsibilities to the software vendor).

Green's calculations project a significant and definitive cost reduction in each clinical trial phase associated with EDC implementation (see Figure 2).[8]

In a separate study, Jeannic, et al. (2014) retrospectively analyzed the study-related costs of 27 trials from 2001 to 2011, in which 16 utilized paper-based data capture and 11 employed EDC.[7] Calculating total study expenditure as an estimate of labor-related and logistical costs, the researchers showed that the mean expense per patient was significantly less in the EDC trials ($497 compared to $1,509 for paper-based trials, for a 67% reduction in cost per patient).

Moreover, the authors demonstrated that trials employing EDC resulted in a significantly shorter study duration when compared to their traditional counterparts. EDC trials required an average of 31.7 months from the opening of the first center to database lock compared to 39.8 months for paper-based trials, despite a longer median projected duration (27 months for EDC-based and 24 months for paper-based trials)[7] (see Figure 3).

EDC implementation must evolve to become less costly and more user-friendly before EDC usage reaches ubiquity in clinical trial management.

Benefits to Monitoring

EDC yields these tremendous benefits in clinical trial efficiency, in part by decreasing the time and cost necessary for monitoring. In the course of clinical trials, sponsors usually contract clinical research associates (CRAs), more commonly known as monitors, to perform source data

In the same manner that EHR represents the most vital component of electronic system utilization in primary care settings, EDC epitomizes this progress in clinical trial management.

verification (SDV) and other examinations of investigational sites. The traditional paradigm requires CRAs to travel to sites and monitor each individual site in person.[9,10] This process is both costly and time consuming.

In order to decrease the time and cost burden, risk-based monitoring (RBM) is now the standard of practice. RBM is a method of SDV that allows monitors to focus their energies on data points that represent the most important risks to data quality, subject safety, and sponsor investment (such as trial endpoints, institutional review board approvals, investigational product accountability, etc.).[9,10] However, this method prevents a CRA from performing 100% SDV.

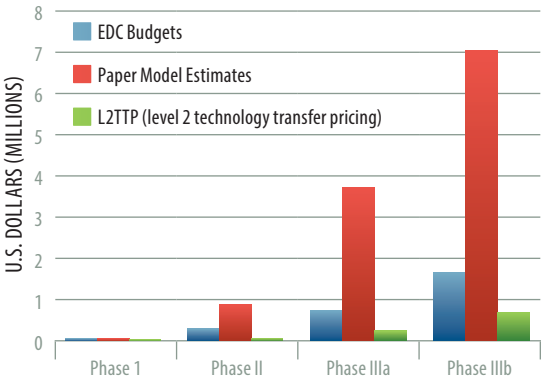
EDC presents the opportunity for remote monitoring. This process saves time and reduces cost for clinical trial sponsors by eliminating the need for onsite monitoring, and it increases overall data quality by allowing for timely, more complete SDV.[10] Mealer, et al. (2013) compared analytics between remote monitoring and traditional onsite monitoring in two national clinical trial networks. Their analysis included five hospitals and 32 subjects (16 per arm of the study). In comparison of time consumed per data value monitored, the researchers calculated a mean duration of 0.39 minutes for remotely monitored data points versus 0.5 minutes for conventional. In analyzing time consumed per CRF verified, the authors observed an average of 3.6 minutes compared to 4.6 minutes for data points monitored onsite (see Figure 4). The researchers also cited 99% SDV for remotely monitored trials.[10]

Plagued by Paper: Overcoming a Classic Obstacle

EDC offers the exciting possibility of streamlining clinical trial management, resulting in shorter, less costly studies. However, in spite of the numerous potential benefits of utilizing EDC, clinical research has failed to keep pace with the technological advance of other healthcare fields. Clinical research did not even begin to incorporate electronic systems for record storage and data capture until the 1990s.[11] Currently, most investigational sites still incorporate some kind of paper-based data capture.

What obstacle has caused clinical research to lag behind the technological curve set by the rest of the healthcare industry, and why do most clinical trials still employ paper-based data capture?

FIGURE 2: Cost Comparison of EDC vs. Traditional Trials



Source: Data compiled from Green (2001)

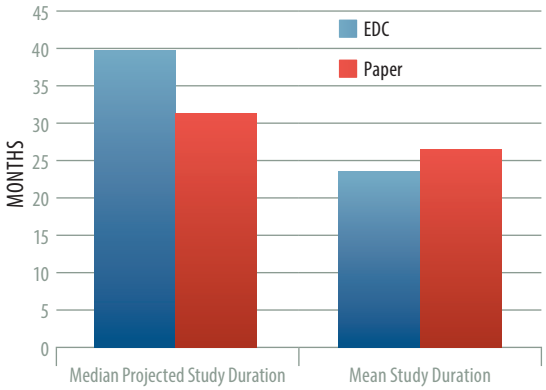
Perhaps clinical research professionals can learn from the obstacles that other healthcare professionals have overcome in their utilization of electronic systems. Historically, implementation has represented the greatest obstacle to ubiquitous use of electronic systems in healthcare, particularly in primary care settings. This challenge seems to inhibit clinical research management in the same way, in terms of its efforts to incorporate EDC and electronic systems.

Though EHR and EDC represent two markedly different tools to solve specific problems related to their own unique and respective fields, both systems must overcome this analogous obstacle. Similar to EHR, the difficulties of transitioning to EDC in clinical trial management are front-loaded, and the benefits only offset these deterrents over time. For EHR, the most notable of these challenges include high acquisition costs and temporary loss of productivity due to personnel training.[12] In the realm of clinical research, these two obstacles bifurcate; acquisition cost exclusively concerns the sponsor, whereas loss of productivity primarily relates to the investigational site and only secondarily to the sponsor.

The financial burden represents a prominent challenge faced by the healthcare field's implementation of EHR.[13] Adoption of EHR software and hardware is the biggest concern. A 2002 study of a 280-bed acute care hospital estimated the seven-year cost of implementing EHR to be about $19 million USD.[14]

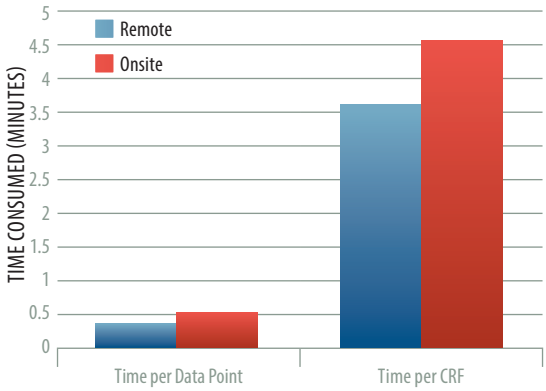
Research into the financial implications of EHR use in the outpatient setting shows similar results. Researchers estimate a cost of $50,000 to $70,000 to implement EHR in a three-physician clinical office.[15] However, as EHR technology has improved and its use become more conventional, implementation costs have declined dramatically. A 2010 study of EHR expense in the clinical setting estimated implementation costs of $14,000 for a six-physician outpatient office and about $19,000 for offices of three physicians or fewer.[16]

FIGURE 3: Study Duration in EDC vs. Traditional Trials



Source: Data compiled from Jeannic, et al. (2014)

FIGURE 4: Efficiency of Remote vs. Onsite Monitoring



Source: Data compiled from Mealer, et al. (2013)

Even after adoption and implementation of EHR systems, maintenance of those systems can still be extremely costly. Maintenance expenses include hardware replacement and upgrade, ongoing training for end-users, and technical support.[12] A 2005 study examining 14 separate clinical practices estimated the ongoing costs of maintaining EHR systems to be about $8,412 per year.[17] The study calculated that 91% of this cost resulted from hardware replacement, vendor software maintenance and support, and personnel compensation.

EHR incorporation can also cause a loss of productivity. Productivity loss encompasses any disruption in workflow caused by EHR implementation. These disruptions may present as a temporary loss of productivity in the implementation phase, or as a continuing loss of productivity due to lack of compliance with system use. These problems can result from software and hardware installation time consumption, necessary end-user training and technical support (both initial and ongoing), and the extensive time involved in converting existing paper records into an electronic format.[12]

Wang, et al. (2003) performed a five-year cost-benefit analysis of overall productivity in clinical offices implementing EHR systems. The researchers observed a 20% loss of productivity during the first month of EHR use[18]; however, this effect leveled out over time. The study noted a 10% loss of productivity in month two, 5% in month three, and virtually no loss of productivity by month four. Moreover, a 2011 study estimated that adopting EHR in 26 primary care practices required an average of 134.2 hours for training alone.[19]

The Future of Information Analytics

As technology advances, the need for electronic systems in clinical research will continue to increase. Following the trend of history, developments in healthcare technology will result in exponentially greater volumes of medical data and the need for sophisticated ways of abstracting those data.

As it pertains to clinical research, EDC will certainly play an important role in the future of clinical trial management. Clinical trial cost represents one of the foremost concerns of the industry, and EDC offers significant potential benefits in that realm. However, the difficulty of implementing EDC systems still deters many investigational sites and sponsors from seeking these benefits.

The industry must find practical ways to alleviate the burden of implementing EDC for both site and sponsor and, in so doing, tread the path cut by the rest of the healthcare industry into a brave new era of medical innovation.

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HOME STUDY HS

The Technology Issue: New Tools to Tackle Old Problems

OPEN BOOK TEST

This test expires on June 30, 2017

(original release date: 6/1/2016)

Maximize Your EHR Systems for Clinical Trials Operations

1. Electronic health record (EHR) systems can support organizational compliance by:

- **A.** Identifying if the patient is on a research study, the study name, and contact information
- **B.** Ensuring security of patient's medical record in a non-HIPAA compliant manner
- **C.** Manually adding modifiers/codes to the patient's account for billing
- **D.** Providing unlimited access to medical records with an audit trail for monitors

2. Patient safety is enhanced with the use of EHRs through the:

- **1.** Creation of medication alerts
- **2.** Use of messages to PI/study team about protocol deviations
- **3.** Identification of the EHR super users
- **4.** Use of vouchers sent to study subjects
  - **A.** 1 and 2 only
  - **B.** 1 and 4 only
  - **C.** 2 and 3 only
  - **D.** 3 and 4 only

3. The EHR can also facilitate study participant safety by:

- **A.** Identifying potential study participants for recruitment and enrollment
- **B.** Making it easier to submit materials to the institutional review board
- **C.** Incorporating electronic research order sets to prevent individuals from altering study orders
- **D.** Ensuring clinical studies adhere to the HITECH Act

4. The EHR can aid billing compliance in clinical research through:

- **A.** Generating an accurate study budget
- **B.** Identifying procedures that are standard of care as opposed to investigational
- **C.** Identification of staff time and indirect costs
- **D.** Enabling easier charge capture

5. Regulatory compliance can be facilitated through the use of EHR in clinical research via which of the following?

- **A.** Assurance of compliance with ICH E6 and HIPAA
- **B.** Creation of more policies on regulatory compliance
- **C.** Reduction in how often the Compliance Officer audits a study
- **D.** Reports of deviation to OHRP if a section of the protocol is not followed exactly

6. What is a potential relationship between the EHR and Delegation of Authority Log that could prove inconsistent?

- **A.** The PI should not sign the Delegation of Authority Log until the study has been set up in the EHR.
- **B.** Roles delegated on the Delegation of Authority Log may differ from access levels permitted in the EHR.
- **C.** All research studies with a Delegation of Authority Log should be in the EHR.
- **D.** Only study team members with access to the EHR should be listed on the Delegation of Authority Log.

7. EHRs capitalize on business opportunities by:

- **A.** Creating easily identifiable research consents and medication records
- **B.** Supporting an environment for quick and accurate feasibility assessments
- **C.** Allowing transparency related to clinical documentation
- **D.** Reducing investigator ability to make informed decision whether or not to proceed with the trial

8. Clinical trial metrics can be obtained from an EHR on all of the following except:

- **A.** How many patients participated in research studies
- **B.** What studies were charged to research not insurance
- **C.** How many research exams were done by a particular department
- **D.** Feedback provided by patients in follow-up surveys

9. Which of the following is not true according to the article?

- **A.** Most EHR systems cannot support research functionality.
- **B.** There are often online support communities (blogs, forums) available supported by the EHR vendors as well as independent of them.
- **C.** It is technically feasible to upload data from the EHR into an eCRF.
- **D.** Research functionality competes with other functionality needs such as "Meaningful Use" and standards conversions for the necessary resources.

10. What key resource do the authors recommend identifying to affect positive change?

- **A.** Physician Champion
- **B.** Creative workarounds
- **C.** EHR vendor representative
- **D.** Senior-level information technology personnel

eSource and Risk-Based Monitoring: A Favorable Union for Future Clinical Trials

11. What percentage of a monitor's time is spent on source data verification (SDV) during an onsite visit?

- **A.** 30%
- **B.** 50%
- **C.** 75%
- **D.** 85%

12. The desire to do what drives the need to conduct SDV?

- **A.** Utilize a monitor's full potential during onsite visits
- **B.** Effectively transcribe data from source documents to database
- **C.** Build better relationships with site staff
- **D.** Follow the regulations correctly

13. What dependency is created while using conventional data-cleaning methodologies?

- **A.** Delay in conducting remote visit
- **B.** Delay in conducting onsite visit
- **C.** Delay in data availability and cleaning
- **D.** Delay in submitting reports to clinical project manager

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

14. **Which activity helps in channelizing the site monitoring activities based on a site's risk profile?**
- **A.** Thorough review of data through remote monitoring
- **B.** SDV
- **C.** Source data review (SDR)
- **D.** Review of patient profiles

15. **eSource enables effective risk-based monitoring (RBM) implementation by near elimination of which human activity for site monitors?**
- **A.** Onsite monitoring visits
- **B.** Remote review of data
- **C.** Telephonic contacts to site
- **D.** Data transcription step from source to eCRF (database)

16. **How does eSource help clinical project managers in mitigation of risks?**
- **A.** By making it easier to conduct data analytics
- **B.** By providing holistic review for data from multiple sources
- **C.** By providing ready reports for decision making
- **D.** By reducing onsite monitoring visits

17. **With eSource, monitors can now focus on which two value-added activities?**
- **A.** Building site relationships and SDR
- **B.** SDV and remote monitoring
- **C.** Patient data review and remote monitoring
- **D.** SDV and patient data review

18. **What helps in effective data collection and data accuracy while setting up eSource?**
- **A.** Effective quality control checklist being used by data entry operator
- **B.** Electronic prompts, flags, and data quality checks
- **C.** Reports and visualizations
- **D.** Help by quality assurance personnel at site

19. **What helps in ensuring activities are date and time stamped?**
- **A.** Audits
- **B.** Controls for role-based user access
- **C.** Inspections
- **D.** Data entry

20. **What characteristics will provide regulatory agencies with confidence about study quality when reviewing studies using RBM?**
- **A.** Audits and inspections
- **B.** Documentation of role access
- **C.** Subject data element identifiers and ability to re-construct clinical investigation
- **D.** Frequent meetings on overall status of trials using eSource

The Rise of Electronic Data Capture and its Greatest Obstacle

21. **What phenomenon has led to the need for electronic record keeping systems to organize and abstract patient health records in healthcare?**
- **A.** The HITECH Act
- **B.** The "Big Data" revolution
- **C.** HIPAA
- **D.** The Affordable Care Act

22. **What caused the upswing in electronic health record utilization by office-based physicians, beginning in 2009?**
- **A.** The HITECH Act
- **B.** The "Big Data" revolution
- **C.** HIPAA
- **D.** The Affordable Care Act

23. **From 2005 to 2012, the likelihood of clinical trials to utilize electronic data capture (EDC) increased by how much yearly?**
- **A.** 5%
- **B.** 8%
- **C.** 10%
- **D.** 15%

24. **Three beneficial factors that motivate sponsors to incorporate EDC into their clinical trials are:**
- **1.** Reduced cost
- **2.** Easy implementation
- **3.** Shortened trial duration
- **4.** Prospect to conduct remote monitoring
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

25. **In what three ways can EDC reduce clinical trial costs to the sponsor?**
- **1.** Increasing the likelihood of investigational product approval
- **2.** Decreasing mistakes in data collection and management
- **3.** Resolving data queries more efficiently
- **4.** Streamlining database processing
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

26. **EDC potentially offers more efficient and cost-effective prospects for clinical trial monitoring. What novel approach to monitoring does EDC make possible?**
- **A.** Risk-based monitoring
- **B.** Source data verification
- **C.** Remote monitoring
- **D.** Enhanced monitoring

27. **If EDC offers so many benefits, why do many investigational sites still depend on paper-based data capture?**
- **A.** EDC becomes less cost-effective over time
- **B.** EDC produces more data collection errors
- **C.** EDC is difficult to implement
- **D.** EDC complicates the monitoring process

28. **Which obstacle represents the primary concern of the sponsor in implementing EDC systems?**
- **A.** Loss of productivity
- **B.** Increased trial duration
- **C.** High acquisition cost
- **D.** FDA data security concerns

29. **Which obstacle represents the primary concern of investigational sites in implementing EDC systems?**
- **A.** Loss of productivity
- **B.** Increased trial duration
- **C.** High acquisition cost
- **D.** FDA data security concerns

30. **Which three factors often cause a loss of productivity in the process of implementing EDC systems at investigational sites?**
- **1.** End-user training
- **2.** Lack of user compliance
- **3.** Software/hardware installation
- **4.** Regulatory complications
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

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

[DOI: 14524/CR-16-4018]

The Elements of an Effective Research Compliance Program

In *The Catcher in the Rye,* narrator Holden Caulfield dreams about saving kids from running out of a field of rye that has been planted right up to the edge of a cliff. The tragedy is that he cannot catch every kid if there really were a big game of chase being played in such a field.

Even the best compliance program will not catch all instances of fraud or abuse, much like Holden Caulfield could never be an effective catcher in the rye. An important part of research risk management is the acceptance that not all risks can be entirely prevented. Accepting that reality means viewing an effective compliance program as one that is adequately resourced to prevent the greatest risks and mitigate the likelihood of lesser risks.

An organization engaged in federally funded research faces a variety of research-related risks. In 2005, the Office of Inspector General (OIG) with the U.S. Department of Health and Human Services published draft research compliance program guidance for recipients of federal research dollars. The OIG draft guidance incorporates the seven fundamental elements of an effective compliance and ethics program described in the Federal Sentencing Guidelines.[1]

Elements of an Effective Compliance Program

The seven elements of an effective compliance and ethics program are:

1. Implementing written policies and procedures;
2. Conducting effective training and education;
3. Designating a compliance officer and compliance committee;
4. Developing effective lines of communication;
5. Conducting internal monitoring and auditing;
6. Enforcing standards through well-publicized disciplinary guidelines; and
7. Responding promptly to detected problems and undertaking corrective action.[2]

The 2005 OIG draft guidance adds an eighth element for recipients of federal research awards:

8. Defining roles and responsibilities and assigning oversight responsibility.

The OIG draft guidance describes the basic elements of a comprehensive research compliance program in this manner:

1. The development and distribution of written standards of conduct, as well as written policies and procedures, that reflect the institution's commitment to compliance.
2. The designation of a compliance officer and a compliance committee charged with the responsibility for developing, operating, and monitoring the compliance program, and with authority to report directly to the head of the organization, such as the president and/or the board of regents in the case of a university.
3. The development and implementation of regular, effective education and training programs for all affected employees.
4. The creation and maintenance of an effective line of communication between the compliance officer and all employees, including a process (such as a hotline or other reporting system) to receive complaints or questions that are addressed in a timely and meaningful way, and the adoption of procedures to protect the anonymity of complainants and to protect whistleblowers from retaliation.

TABLE 1: Essential Research Compliance Policies and Procedures

Policy	Regulation
Conflict of Interest	42 CFR Part 50 Subpart F
Federalwide Assurance	45 CFR 46.103
Research Misconduct	42 CFR Part 93

5. The clear definition of roles and responsibilities within the institution's organization and ensuring the effective assignment of oversight responsibilities.
6. The use of audits and/or other risk evaluation techniques to monitor compliance and identify problem areas.
7. The enforcement of appropriate disciplinary action against employees or contractors who have violated institutional policies, procedures, and/or applicable federal requirements for the use of federal research dollars, and
8. The development of policies and procedures for the investigation of identified instances of noncompliance or misconduct. These should include directions regarding the prompt and proper response to detected offenses, such as the initiation of appropriate corrective action and preventive measures.

Research-Related Risks

The OIG draft guidance identifies three major areas of risk for recipients of federal research awards: time and effort reporting; proper allocation of charges to award projects; and reporting of financial support from other sources.[1] "A problem related to the failure to accurately and completely report support from other financial sources is the charging of both award funds and Medicare and other health care insurers for performing the same service. This is clearly improper and has subjected institutions to fraud investigations."[3]

Essential Policies and Procedures

There are a few policies and procedures that must be in place at each institution that receives federal money in the form of research awards (see Table 1).

Each institution that applies for or receives federal research funding must maintain an up-to-date policy on reporting financial conflicts of interest (see 42 CFR 50.604 in the *Code of Federal Regulations*). Each institution engaged in federally funded human subject research must have a policy to assure compliance with the basic Department of Health and Human Services policy for the protection of human research subjects (45 CFR 46.103). Any institution that applies for or receives federal funding for its research activities must have written policies and procedures for addressing and reporting allegations of research misconduct (42 CFR 93.300).

Research Compliance Officer

Smaller organizations may have one compliance officer responsible for the entire compliance and ethics programs. Larger organizations may have several compliance officers, including a designated research compliance officer. The OIG draft guidance suggests that the research compliance officer's primary responsibilities should include:

- Overseeing and monitoring implementation of the compliance program;
- Reporting on a regular basis to the board of regents, president, and compliance committee (if applicable) on compliance matters and assisting these individuals or groups to establish methods to reduce the institution's vulnerability to fraud and abuse;
- Periodically revising the compliance program, as appropriate, to respond to changes in the institution's needs and applicable program requirements, identified weakness in the compliance program, or identified systemic patterns of noncompliance;

An important part of research risk management is the acceptance that not all risks can be entirely prevented.

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

The OIG draft guidance identifies three major areas of risk for recipients of federal research awards: time and effort reporting; proper allocation of charges to award projects; and reporting of financial support from other sources.

- Developing, coordinating, and participating in a multifaceted educational and training program that focuses on the elements of the compliance program, and seeking to ensure that all affected employees understand and comply with pertinent federal and state standards;
- Developing policies and procedures;
- Assisting the institution's internal or independent auditors in coordinating compliance reviews and monitoring activities;
- Reviewing and, where appropriate, acting in response to reports of noncompliance received through the hotline (or other established reporting mechanism) or otherwise brought to his or her attention (e.g., as a result of an internal audit or by counsel who may have been notified of a potential instance of noncompliance);
- Independently investigating and acting on matters related to compliance. To that end, the compliance officer should have the flexibility to design and coordinate internal investigations (e.g., responding to reports of problems or suspected violations) and any resulting corrective action (e.g., making necessary improvements to policies and practices, and taking appropriate disciplinary action) with particular departments or institution activities;
- Participating with counsel in the appropriate reporting of any self-discovered violations of federal requirements; and
- Continuing the momentum and, as appropriate, revising or expanding the compliance program after the initial years of implementation.

Conclusion

The elements of an effective compliance and ethics program are described in the United States Sentencing Commission's Federal Sentencing Guidelines.[2] The OIG incorporates those seven elements and adds an eighth element to describe the essential elements of an effective research compliance and ethics program.[1] The funding, resources, and staff required to perform these essential elements would depend on the size of the organization and depth of its research portfolio. However, given the steep monetary penalties associated with fraud and abuse risks, an effective compliance and ethics program would place at least one catcher in rye—if not more.

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The Future of Drug Development is Virtualized and Personalized

Today, drug development is carried out in human subjects and animals. However, as computing power and the number of sophisticated technology platforms grow exponentially, and our knowledge of human health and disease increases, the virtualization of clinical research and development will grow steadily.

The new blockbuster will target a well-defined patient population with clear and precise dosing instructions, with full understanding of the patient or subpopulation genetic polymorphism, and with full accountability of the patient-specific epidemiologic and epigenetic factors.

Biosimulation (also called modeling and simulation), which integrates computer-aided mathematical simulation and biological sciences, will continue to tap into synergy between those two trends.

We have already seen increased use of modeling and simulation to inform drug development and drug labels, which is positively impacting payors, patients, and drug developers.

Regulatory agencies have fully embraced modeling and simulation as part of the drug development process. In fact, in the Food and Drug Administration's (FDA's) paper on "Catalyzing the Critical Path Initiative: FDA's Progress in Drug Development Activities,"[1] Janet Woodcock, MD, director of the agency's Center for Drug Evaluation and Research (CDER), identified modeling and simulation as core disciplines that are likely to modernize drug development and clinical research.

"Fifteen years ago, 20% of drug candidate attrition was due to poor absorption, distribution, metabolism, and excretion (ADME) characteristics; now, the attrition rate due to ADME problems is down to 1 to 3%," says Lawrence Lesko, PhD, FCP, former director of the Office of Clinical Pharmacology for CDER and current clinical professor and director of the Center for Pharmacometrics and Systems Pharmacology in the University of Florida College of Pharmacy. "That's due to the use of modeling and simulation, because we can simulate not only structure-activity relationships, but also simulate realistic dissolution and pharmacokinetic profiles."

Lesko adds, "Physiologically based pharmacokinetic (PK) models now allow researchers to predict clinical drug-drug interactions and drug-gene interactions in untested scenarios. Biosimulation approaches also enable those predictions to be made from a limited number of clinical trials. Such information is now almost routinely being included in the labels of FDA-approved drugs."

Biosimilar registration is a future opportunity for biosimulation, according to Lesko. Earlier this year, FDA approved the biosimilar of Remicade. Its sponsor conducted a three-way PK bridging study to justify the clinical relevance of comparative efficacy data using the European version of Remicade. That PK study could have been done by biosimulation if it was not the first biosimilar of Remicade.

Virtual Drug Development

Virtualization is going to become a dominant trend. When that occurs, pharmaceutical companies will develop parallel drug developments paths. They will create a virtual drug development path, and a real-patient, real-life drug development path—one guiding the other and establishing a mutually positive feedback loop.

The virtual drug development program will, on an ongoing basis, inform each phase of development. It will receive data from the real world and use them to refine the models for the next phase. The virtual drug development program will then provide those data for the real-world drug development to start a new phase. In a very positive cycle, the virtual world and real-life patient drug development will become intimately intertwined.

Today, the percentage of virtualization in drug development is quite small. No more than 10% of the $150 billion drug development market is thought to be virtualized. Therefore, this market has an extraordinary opportunity to grow.

Biosimulation and precision medicine will definitely move into patient care—first at the hospital level, to inform precise dosing for complicated patient populations; next for multiple in-hospital applications; then for outpatient treatment; and eventually inside patient homes (the ultimate point of care).

That trend is not unique to biology. In fact, this industry is late to that process. In 2007, the British government and the aerospace industry agreed to a three-year, £17.4 million modeling and simulation program to accelerate aircraft design.[2] The program goal was to reduce development time and create a more eco-friendly process.

The aerospace consortium (led by Airbus) developed the simulation software. The British Department of Trade and Industry predicted that by 2012, simulations would replace physical testing, cutting parts of the design process from 350 days to 36 days.[2] It decided to invest in that transformative technology.

The Next Scientific Horizon

For biosimulation to reach its full potential, there will need to be additional work done in the area of mechanistically based pharmacodynamics (PD) or response to exposure to drugs, says Malcolm Rowland, PhD, DSc, professor emeritus at the Manchester School of Pharmacy at the University of Manchester, U.K., and adjunct professor in the Department of Bioengineering and Therapeutic Sciences in the Schools of Pharmacy and Medicine at the University of California San Francisco (UCSF).

PK-related issues and epigenetic and epidemiological factors are well-represented in the current biosimulation models; however, PD-related issues are not as well understood.

Rowland adds, "Advances will need to be made in quantitative systems pharmacology (QSP) and therapeutics, so that researchers can understand the underlying pathophysiology of individual processes in the body and the network system that operates. Most drugs fail in Phase II clinical trials due to lack of efficacy. But if researchers can understand mechanistic PK/PD, and the networking structure better, they will be able to produce drugs that are efficacious and also have a better safety profile. They will be in a better position to predict more accurately which drugs are likely to produce adverse events, enabling their development to be stopped much earlier, before they are given to large groups of patients."

QSP is a relatively new discipline, but it has the potential to dramatically improve pharmaceutical research and development productivity. By furthering their understanding of QSP and systems biology, researchers will be able to create a comprehensive modeling and simulation system that will improve prediction of the safety and efficacy profile of investigational drugs in virtual patients.

Biological Personalized Avatars

Precision medicine will become dominant in drug development, and it will become a core approach in patient care. "Precision medicine" refers to developing drugs and treating patients with a precise understanding of the subgroup or individual PK, PD, and epidemiologic or epigenetic factors that will impact their drug response.

The new blockbuster will target a well-defined patient population with clear and precise dosing instructions, with full understanding of the patient or subpopulation genetic polymorphism, and with full accountability of the patient-specific epidemiologic and epigenetic factors.

In two or three decades, when modeling and simulation and the virtualization of drug development and precision medicine have undergone their next evolution, we may be living in a virtual drug development and patient care world where biological computer–based avatars will guide drug development and point-of-care solutions on an individual basis. That is to say, each individual will have his or her own avatar, just as everyone in the U.S. currently carries a driver's license or social security number that identifies them as a specific person. That avatar will be used in drug development when the individual is part of a clinical trial, when they are hospitalized, or at the point of care when they are undergoing a specific treatment.

Even better, the avatar will be used for prevention and wellness purposes. Once the specific characteristics of a patient's cell signaling pathways are understood, and how their polymorphisms can impact those pathways, physicians will be able to maximize that individual's ability to take medications safely and effectively. They will also be able to ensure that the patient has the right macro and micro nutrients to enhance their wellness and prevent disease.

From Monotherapies to Combination Therapies

The University of Florida's Lesko also predicts a move away from monotherapies toward combination therapies that better address the multifactorial nature of disease pathology. This will result in an increasing reliance on biosimulation to integrate combination therapies and environmental factors into clinical trials and optimize medical treatments.

As more drugs are added to a patient's regimen, the number of potential interactions grows rapidly. Biosimulation can help to determine the optimal drug combination, which maximizes benefits whilst minimizing toxicity; it can also identify the best dose, frequency, and timing for each drug.

Using Biosimulation to Enhance Patient Care

Biosimulation and precision medicine will definitely move into patient care—first at the hospital level, to inform precise dosing for complicated patient populations; next for multiple in-hospital applications; then for outpatient treatment; and eventually inside patient homes (the ultimate point of care).

Certara Chief Scientific Officer Amin Rostami, PharmD, PhD, is working with several research centers in the U.S. and the U.K that are already using biosimulation to inform patient care.

For example, modeling and simulation are being used to define the drug dose changes required for bariatric surgery patients. These patients are undergoing major surgery on their gastrointestinal (GI) tract, which will impact their rate and particularly extent of drug absorption after the operation. Sometimes patients' drug doses need to be increased, as the molecules are now being absorbed through an area of the GI tract that absorbs less.

Biosimulation is also being used to define the appropriate drug doses for pregnant women. Many changes to the body occur during pregnancy, and some women have conditions, such as epilepsy, for which they need to keep taking their drugs. These patients can experience epileptic fits if medications are not getting into their bodies at the intended levels. Biosimulation is used to determine whether their drug dose needs to be adjusted at different stages of their pregnancy.

Furthermore, patients with HIV or hepatitis C infection normally receive multiple drugs, and are thus at risk for drug-drug interactions (DDIs). Biosimulation is being used to preemptively identify potential DDIs. Oncology or elderly patients also often take multiple medications, and require similar assistance.

In addition to providing important drug dosage recommendations for difficult cases at research centers and in clinical practice, biosimulation offers important insights for forensic medicine and helps to test hypotheses in retrospective studies.

Wearable Devices Will Inform Drug Development

Lesko also predicts an increased use of data from wearable devices to complement drug development. These devices currently measure a person's heart rate, sleep pattern, steps taken, and calories burned. In 10 years, they will likely be able to capture almost any physiological data required. Biosimulation will play an important role in this trend because computer modeling will be required to analyze these data.

Most of the patient-related data that are currently used in biosimulation come from measurement devices of some sort, whether in the form of biomarker data, blood pressure readings, the presence or absence of polymorphisms in genes, or the drug levels in plasma. Over the next few decades, those devices will become smaller, much more precise, and portable and wearable.

UCSF's Rowland agrees that biosimulation is going to have an impact at the patient level in terms of improving the individualization of medicines and therapeutics. "People will know a lot more about themselves; they will be aware of features that are either unique to themselves or family characteristics. They will also be more cognizant of their drug responses," he adds.

The Coming Brave New World of Biosimulation

Biosimulation has been widely adopted by sponsors and regulatory agencies alike. It is already playing an integral part in the drug development process, influencing everything from first-in-human dose selection to the language used on the drug label. However, it is destined to play an even bigger role going forward, as sponsors create parallel real and virtual drug development paths to create safer and more efficacious drugs. Each individual will also have a personal avatar on which a proposed treatment will be tested before any real-world intervention is taken. Precision medicine will soon become a reality from which we can all benefit.

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Implementation of a Research Participant Satisfaction Survey at an Academic Medical Center

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This descriptive case study covers the development of a survey to assess research subject satisfaction among those participating in clinical research studies at an academic medical center (AMC). The purpose was twofold: to gauge the effectiveness of the survey, as well as to determine the level of satisfaction of the research participants.

The authors developed and implemented an electronic research participant satisfaction survey. It was created to provide research teams at the authors' AMC with a common instrument to capture research participant experiences in order to improve upon the quality of research operations. The instrument captured participant responses in a standardized format.

Ultimately, the results are to serve as a means to improve the research experience of participants for single studies, studies conducted within a division or department, or across the entire research enterprise at the institution.

For ease of use, the survey was created within an electronic data capture system known as REDCap, which is used by a consortium of more than 1,800 institutional partners as a tool from the Clinical and Translational Science Awards (CTSA) program of the National Institutes of Health (NIH).

Participants in the survey described in this article were more than 18 years of age and participating in an institutional review board (IRB)-approved study. Results showed that the vast majority of participants surveyed had a positive experience engaging in research at the authors' AMC. Further, the tool was found to be effective in making that determination.

The authors hope to expand the use of the survey as a means to increase research satisfaction and quality at their university.

Background

In a competitive market, the presentation, efficiency, and delivery of care can influence which healthcare facilities patients choose. These same characteristics are also critical to the success of clinical research operations.

Many factors contribute to research subject recruitment and retention, and it is imperative that research programs engage in behaviors that contribute to a positive experience for participants, in a manner similar to healthcare facilities. Hospitals and clinics utilize tools, such as Press Ganey surveys, that are sent to patients after use of healthcare services to gauge patient satisfaction and to identify areas for quality improvement. Currently, more than 50% of hospitals in the United States use Press Ganey surveys to enhance quality care, patient satisfaction, and institutional success.[1]

Moreover, in recent years patient satisfaction surveys have been linked to reimbursement. In the 2015 fiscal year, Medicare utilized a hospital Value-Based Purchasing Program, whereby hospital payments are adjusted based on performance across four quality domains, including clinical process of care, patient experience of care, outcome, and efficiency.[2]

Satisfaction is at the core of the patient experience, and feedback provided on healthcare services is not only valuable for quality improvement, but also critical for sustained fiscal solvency. In this same spirit, leaders of clinical research programs carefully watch the financial bottom line of their operations, making knowledge of research participant satisfaction an important contributing factor for financial success.

Patient satisfaction is arguably more applicable to clinical research, because patients and healthy subjects are not required to participate in medical studies. They are also not required to continue participation once started, because volunteerism is key to human subject protections.

Knowledge of the participant experience is critical for those entities invested in the clinical research enterprise. Importantly, satisfaction of research participants may serve as a proxy for study integrity. It may be conjectured that if a participant is having a positive experience, that person is more likely to complete a study than one who has not. Moreover, an experience that is not positive may dissuade one, and in turn others, from participating in future studies.

An electronic format would allow for groups to easily access the survey and analyze the results collectively, according to who a study's principal investigator (PI) was or across the enterprise.

Clinical researchers need participants to complete studies to ensure that trial milestones are captured. Not only does this ensure study completeness, it is also imperative for the population at the heart of the investigational product. Study participants create new understandings by bringing new drugs and devices to market. For these reasons, teams invested in clinical research should consider this assessment strategy and platform during the conduct of clinical research studies.

Literature Review

The available literature on clinical research participant satisfaction assessment supports the use of this measure in research programs, and has yielded a broad array of findings.

Verheggen and colleagues[3] used personal interviews and a telephone questionnaire on patients participating in clinical trials at the time of consent and one month into the study. They found that although overall patient satisfaction was high, areas of dissatisfaction were revealed after consent. They concluded that patient expectations prior to study entry ultimately impact the reality of subsequent clinical research participation. This study provides support for the notion that simply surveying participants at one point in time is not enough to gauge their feelings on participation.

A study by Reider and colleagues[4] found that, of 155 participants in a General Clinical Research Center, 90.9% of respondents said that the purpose of study had been explained to them and 94.9% said that the risks of the study had been explained. These critical informed consent elements are crucial to participant satisfaction as a foundation for their experience. The interpersonal relationship between participant and research staff is also key to the participant experience, and the authors found that 99.4% of respondents were pleased with the care from research nurses. The authors believed that participant feedback provides valuable input for the implementation and delivery of research.

In 2015, the Center for Information and Study on Clinical Research Participation published its latest report on patient experiences in research studies.[5] From this report, one can say that the most common reasons people participate in studies were to help advance science and the treatment of a particular condition/disease, and to help others. The report's organizers found that 95% of those surveyed would recommend clinical research participation to their friends and family. Approximately one-third of the respondents indicated that there was nothing they disliked about their clinical trial experience. Among those respondents who disliked something, the possibility of receiving a placebo and the physical location of the study center were the top two dislikes. Almost half of the participants (46%) reported that their research participation experience exceeded their expectations.

Methods

PATIENT RESEARCH SATISFACTION SURVEY DEVELOPMENT

In 2011, a task force was formed consisting of researchers from select clinical departments (e.g., family medicine, dermatology, gynecology, gynecology-oncology, neurology, and the inpatient Clinical Research Center) across the authors' medical center. Prior to this time, a few departments had their own satisfaction tools in a paper format, but the task force collectively sought to standardize this process and to do so in an electronic format. An electronic format would allow for groups to easily access the survey and analyze the results collectively, according to who a study's principal investigator (PI) was or across the enterprise.

The task force met on a routine basis to discuss and develop items that would encompass a variety of participants enrolling in any of the many types of research studies at the institution (e.g., observational studies, clinical trials).

To effectively execute this initiative, the support of the institution's Center for Clinical and Translational Science (CCTS) was solicited. The CCTS was funded by a multiyear CTSA grant from the NIH, as a collaborative effort of The Ohio State University, the university's Wexner Medical Center, and Nationwide Children's Hospital.

The tool described earlier as being available through the CTSA program, REDCap (Research Electronic Data Capture), was determined by the authors to be the best platform for implementing the process capturing the details of research participants' experience across the university, inclusive of its medical center. REDCap provides a secure, web-based application that is flexible enough to be used for a variety of types of research. It offers easy data analysis with audit trails, along with the ability to export into common statistical

TABLE 1: Ways participants learned of a study

I saw a flyer about it.	21.3%
I was approached about it during a healthcare appointment.	18%
I was contacted by a study coordinator or physician.	14.8%
I saw it on Study Search.	9.8%
I saw it on a social networking site.	10.3%
Contacted via ResearchMatch.org.	17.5%
I called the Hero line.	0.6%
I saw/heard an advertisement.	15.1%
A friend or family member told me.	20.7%
I don't remember.	1.5%

TABLE 2: Motivating reasons for participation

To help others.	70.5%
Because my caregiver encouraged me to do so.	5.6%
Because of a positive experience in another study.	17.4%
To find out more about my condition.	13.3%
To gain access to new treatment/therapy.	19.5%
Because of the good reputation of this AMC.	35.1%
To earn study payment.	49.6%
Because there were no other options available to treat my condition.	6.2%

packages, and is compliant with 21 CFR Part 11 of the *Code of Federal Regulations*.[3]

A protocol for implementation was developed and then approved by the university's IRB before the survey was implemented. Once approved, task force researchers with IRB-approved studies conducted a pilot of the Research Study Participant Survey in their respective research programs.

PATIENT RESEARCH SATISFACTION: DATA COLLECTION

Pilot

The survey was launched in late October 2013, and data were collected through April 2014. The research sites of the task force members were the locations of the pilot, lasting for the first six months of implementation.

The survey was administered to research participants ages 18 years and older who were participating in an IRB-approved clinical research study at the university. After six months, the survey was analyzed and determined to be working appropriately by task force members. This was evidenced by evaluating the request system, the URLs provided, pulled data by site, and data in aggregate; all without issue.

Enterprise Launch

After the pilot was deemed successful, the survey was made available to all researchers at the university in May 2014. Interested researchers were able to access the survey via a request for use through the CCTS. Researchers were then provided with a URL to the survey that was customized to each relevant PI, whose study teams then invited their participants to take the survey.

This allows PIs to extract participant information from REDCap on their own studies. Results may be requested by the CCTS at any time and presented to the respective department or other stakeholders.

The survey was designed to be utilized at any point in a participant's research experience—from the first visit, annually for multiyear studies, or at the final visit regardless of length of participation. The participant is offered a link that could be accessed onsite or at home to complete the survey (the survey contains QR coding to make it available for use from smartphones).

Personal identifying information is not collected, so that responses are not traceable back to the respondents. The survey consists of 25 multiple choice questions. Branching logic exists in certain areas, based on the participant response, with an open-ended text field at the end to capture free-form response data.

The survey takes approximately 10 minutes to complete. When participants complete the survey, the anonymous data are entered directly into REDCap. The overall methods intend to allow research teams a viable mechanism by which to improve processes to provide a more effective clinical research experience for their participants.

Results

A total of 341 completed surveys from multiple research departments were collected from October 2013 to April 2015. Data were analyzed using descriptive statistics within the REDCap database.

The Clinical Research Center was the location of 81.2% of those surveyed; gynecology-oncology accounted for 6.7%, dermatology for 2.6%, and several other departments collectively comprised the remainder of less than 10%.

Mirroring the research study pool, the majority of surveys (76%) were completed by females, and the age groups were 18–25 years (18.8%), 26–35 years (44%), 36–55 years (19.4%), 56–64 years (12.8%), and 65 and older (5.3%).

The predominant race was white/Caucasian (77.1%), followed by black or African American (15.5%), Asian (2.6%), multiracial (2.3%), American Indian/Alaska native (0.6%), Native Hawaiian or Pacific Islander (0.3%), and other categories not listed (1.5%).

A variety of reasons were listed for how participants learned about their clinical research study (see Table 1). Respondents were able to select all of the options that applied. A flyer and family or friends were the most common recruitment tools by which respondents became aware of a study.

Table 2 shows what motivated these respondents to choose to participate in a study. Those who completed the survey were allowed to choose up to three reasons that most influenced their decision to participate.

Several questions related to the elements of the process of informed consent were asked in a Likert scale format (see Table 3). Other questions were related to the dynamic between research staff and the participant. Data were collected to determine the respondents' potential future research participation and their likelihood of promoting research participation at the same sites as where their studies were based (see Table 4).

The final series of questions related to the time frame of participation, with 47.8% of respondents being part of an active study, 51.3% having completed all visits related to the protocol, and 0.9% having withdrawn early from a study. The length of study enrollment varied for participants—2.9% of respondents had only a one-time visit, while 66.9% were involved for up to six months, 11.1% from more than six and up to 12 months, 6.2% from more than one year and up to three years, and 12.9% for more than three years.

The respondents were at various time points over the course of enrollment when they completed the survey. The majority of those surveyed (72%), had only been in the study for up to three months; others had been in the study more than three and up to six months (11.3%), or more than six and up to 12 months (5.1%), or more than a year (11.6%).

Respondents could give up to three reasons that influenced their decision to discontinue participation early. For those who had discontinued, the most common reason was due to family/work issues unrelated to the study, followed by too much pain and discomfort related to study procedures, and by unexpected test results/procedures/side effects.

Discussion

The data demonstrate that the participant experience at the authors' institution was largely satisfactory when analyzed collectively for all groups. Project leaders were able to pull the responses by department to provide to the respective department and by PI. They found the instrument to be effective to elicit the information being sought from those who completed it.

The structural organization of the survey allows results to be parsed by study, by division, by department, and collectively across all studies and groups at the university. The authors' line of questioning and methodology were similar to those used by others in the field,[3–5] and yielded similar responses from research participants.

Despite the overall satisfaction the study participants had reported, a small minority of them were unhappy with their trial experience. An honest range of feedback can help research teams identify and improve appropriate areas of their research program. Of note is the fact that issues that may have impacted the participants' experiences, but were beyond the control of the team(s), such as institutional parking issues, were not included in the survey. The goal of the survey was to ask questions that could be identified and improved upon within any respective research team's scope of influence.

There are some significant limitations to be aware of in terms of the results. For example, the authors found that adult females were more likely than males to provide open-ended feedback in the survey. It was also noteworthy that the data were largely from the university's Clinical Research Center, which is explained because the center sees more patients than any one of the other areas. Further, because the design of the survey allows for participants to complete the survey at multiple time points, some surveys may have been completed by the same person longitudinally over the course of the study.

It is the intention of the CCTS and the authors for this survey tool and its underlying process to continue to be marketed to and used as a CCTS service by the previous and additional research teams across the university. It is desired that researchers utilize the survey to assess quality of clinical trial execution from the participant's experience. This feedback can help grow programs in a positive direction.

Indeed, the hope is that incorporating patient feedback into clinical research operations can positively contribute to research recruitment and retention of participants. The authors anticipate that the end result will be high-quality data from participants who are happily engaging in studies that successfully brings new drugs and devices to market.

TABLE 3: Research study site experiences

Statement	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I understood the study procedures before providing my informed consent to participate.	0.9%	0	0.6%	18.8%	79.8%
The research staff took the necessary amount of time to answer all of my questions.	0.6%	0%	0%	9.7%	89.7%
I understood that participation was voluntary.	0.6%	0%	0%	7.9%	91.5%
I understood that I could withdraw from the study anytime.	0.9%	0%	0.3%	8.2%	90.6%
I understood the risk(s) involved with participating in the study.	0.6%	0%	1.4%	15.2%	83%
I understood the possible benefit(s) involved with participating in the study.	0.6%	0%	2.6%	16.4%	80.4%
I felt the research staff were approachable when I had questions or concerns.	0.9%	0%	0%	10.9%	88.3%
I felt the research staff were easy to contact.	0.9%	0.6%	1.5%	13.5%	83.6%
I felt the research staff were professional.	0.9%	0%	0%	9.4%	89.7%
I felt the research staff were knowledgeable.	0.9%	0%	0.6%	11.7%	86.8%
I felt the research staff were courteous.	0.9%	0%	0%	8.5%	90.6%
I felt the research staff were sensitive to my needs.	1.2%	0.3%	0.3%	8.5%	89.7%
My research visits went smoothly.	0.6%	0%	0%	16.4%	83%
I was able to schedule my appointments at a time that worked for me.	0.6%	0.3%	2.3%	12.9%	83.9%
My overall experience was positive.	0.6%	0%	0%	11.5%	87.9%

TABLE 4: Future participation and study promotion

Statement	Very Likely	Likely	Unlikely	Very Unlikely
I would be _____ to recommend to others that they consider participation in a research study at Ohio State.	88.3%	10.9%	0%	0.9%
If I was aware of another research study at Ohio State for which I was eligible and I had time to volunteer, I would be_____ to participate.	77.7%	20.5%	0.9%	0.9%

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Facilitating the Transition from Operations to Project Management: *How to Mentor a New Project Manager*

A common career change for many people working in clinical research is to move from "operations" into "project management." For some, this transition may be reasonably gradual; a person may over time take on responsibilities such as managing a work area or part of a budget. For others, the move into project management may be more sudden—brought about by a promotion or when moving to another organization.

Project managers lead multidisciplinary project teams, and many projects are international (sometimes global) in scope, so they will need to consider cultural and logistical issues.

Making this transition can sometimes seem overwhelming, as it is often a stressful experience; however, one of the key roles of a manager is to help his or her staff make the transition smoothly from an operations role to project management.

It's a New Job!

Being a project manager is not like being a "super" clinical research associate (CRA) or an "uber" data manager, where someone is doing operational tasks to a more advanced level. It is a different job. True, there are some transferable skills, but also plenty of new ones to learn.

A good source of the requirements of the role should be found in the job description of a project manager. A more useful document still is a project management competency framework. Competency frameworks are documents that map competencies to roles or job descriptions. They are part of a range of standards that can be used to help organizations and individuals to assess and manage individual and collective work performance.[1,2]

Compare the skills required in the operations role with those required for project management. Make a list of the gaps, and then work with the individual to create an action plan to fill the gaps by acquiring the relevant competencies.

Encourage Thinking Big

As well as acquiring new skills, another key change that your new project manager will need to make is in his or her mind-set. Project management requires a much more strategic approach than operations, and is conducted on a much grander scale; large multinational projects may be complex and can last several years.

Help your new project managers by addressing the "fit" of their projects into the wider business context, such as the overall strategy for the development of new medical treatments, and the contributions of successfully completed projects to the (business) strategy of the organization. Also discuss what other projects are being conducted, and where the project managers' projects fit in with organizational priorities.

A new project manager's overall responsibility for a budget will probably be on a much grander scale than he or she will have been used to previously. The stakeholders—the people with a vested interest in the project—will probably be a diverse group. Some of them may hold positions of relatively high seniority. Project managers lead multidisciplinary project teams, and many projects are international (sometimes global) in scope, so they will need to consider cultural and logistical issues.

Moving Out of the Comfort Zone

Because your new project manager is taking on a new role, having to use new skills and thinking a lot more strategically, he or she will be moving into unfamiliar territory. This transition will have to occur quickly, as there is the inevitable pressure to get projects completed on schedule.

At the start of their careers, project managers may frequently feel very uncomfortable. You can help them by acting as a guide and mentor. Help them move out of their comfort zone by explaining that project managers often have to deal with uncertainty and ambiguity—it's part of the role. It may feel very awkward, but they will be undoubtedly gaining new skills and knowledge. Explain that, with time, they will gain in confidence and the feelings of discomfort will diminish (but never vanish!).

There are plenty of sayings about project management you can share. One of them is, "The most successful project managers have perfected the skill of getting comfortable being uncomfortable."

Don't Let the Perfect be the Enemy of the Good

The French historian and philosopher Voltaire is credited with the quotation "Don't let the perfect be the enemy of the good." In operations—whether in data management, regulatory affairs, or working as a CRA or other related job roles—there is a culture of doing everything to perfection. There is a good reason for this; clinical research is a highly regulated environment, and the rights, safety, and welfare of patients are paramount. Project management is a more imprecise environment.

Naturally, a project manager will attempt to make his or her estimates of timelines, budgets, and resources as accurate as possible. However, there are usually several areas of uncertainty. After all, we are conducting research which, by its nature, is designed to answer a question for which we don't yet have the answer. There is bound to be an element of guesswork supported by forecasts based on any intelligence that we may have gathered.

Help your new project managers to decide when precision is required and when it is not. Help them see that it is better to create a plan based on some guesswork than to get delayed striving for perfection in endless reiterations of something that will probably not turn out to be realistic anyway.

Helping others develop is an essential part of being a manager. One of the most challenging transitions is moving into project management, and you can add great value as a manager by helping people who report to you to make this change.

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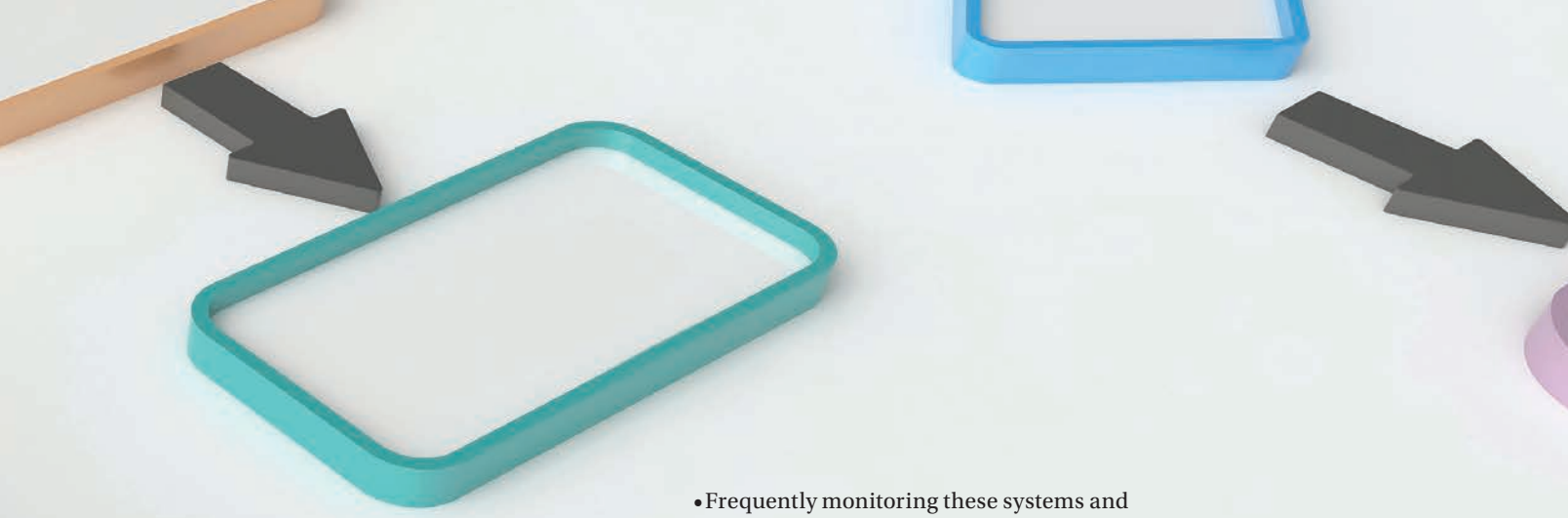
Site Monitoring an Expensive Affair? *Not Any More...*

PEER REVIEWED | Priya Temkar, MSc

As emphasized by the U.S. Food and Drug Administration (FDA),[1] European Medicines Agency (EMA),[2] and nonprofit organizations like TransCelerate,[3] the pharmaceutical industry is well on its way to embracing the shift from classical monitoring practices toward advanced and improved new monitoring practices. Risk-based monitoring (RBM), remote central monitoring, and use of eSource are already popular tactics that many stakeholders consider to be effective solutions for improved quality, as well as time and cost savings in recent trials.

This paper provides an insight on another aspect of clinical research associate (CRA) responsibilities—one that utilizes a large chunk of his/her efforts and needs attention—namely, the amount of work performed offsite in support of trial management and monitoring. This support work can be delegated/outsourced to other groups to save further on monitoring costs.

Also demonstrated in this paper is how this approach to implementing a monitoring support team can benefit a trial to strengthen its site management, ensure all-time audit readiness of clinical trial systems, and address site issues with greater speed to minimize audit findings.



The Endless List of Monitoring Activities

What many CRAs may consider to be trivial monitoring practices—those which have proven to be largely time consuming, expensive, laborious, and most importantly not very productive—often seem that way mainly in the context of the sheer volume of items to be attended to on the "to-do" list during the due course of a study. A closer examination of CRA activities (which tend to be spread across four areas: pre-study, initiation, monitoring, and close-out) reveals that more than 40% of them amount to support work.

To validate the above statistics, one can consider the fact that, on average in the industry, a CRA travels three days per week, and for two days he/she is in-house mostly performing support/follow-up work. Indeed, an impact report published by the Tufts Center for the Study of Drug Development (CSDD) mentions that "Over the past 15 years, demands on study monitors have intensified as clinical trial volume and complexity have increased. Yet, drug development managers haven't had benchmarked global metrics to assess their CRA field force capacity and utilization." The report further states that CRAs worldwide spent approximately 20% of their time traveling and devote 41% of their time at clinical trial sites.[4]

Thus, delegating/outsourcing this support work to a group of associates (with a lower billable rate than CRAs) will enable a monitor to focus on core monitoring and site management and bring down overall cost.

Need for a Monitoring Support Team

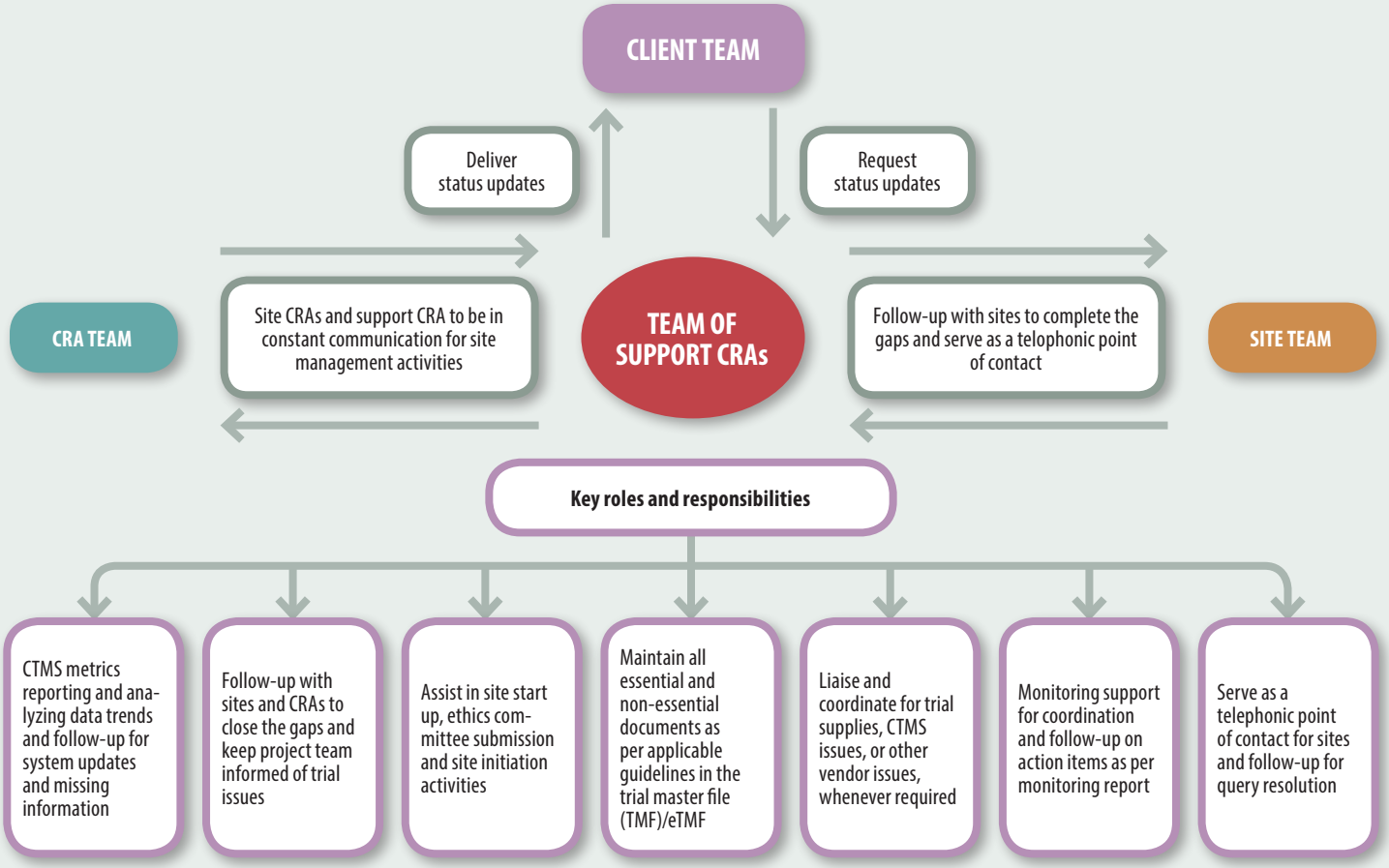
The need for a monitoring support team arises from the current key challenges faced in monitoring, especially including the difficulties of mastering the wide variety of different clinical trial management systems (CTMSs) used at study sites. Tied to developing such mastery are such factors as:

- The increasing use of electronic systems in clinical trials and the need to ensure their audit readiness at all times
- Completing trainings on these systems and developing proficiency, in order to use them effectively and achieve data accuracy
- Frequently monitoring these systems and making constant updates for real-time status availability
- Lack of system updates leading to lack of availability of real-time data and trial status updates, resulting in missed trial milestones, protocol deviations, serious adverse events, etc., and adding to audit findings
- Time lost dealing with fallout from previously unattended site issues and a lack of attention to CTMSs during site handovers, potentially leading to back-to-back monitoring visits, extensive CRA travel, and audits
- Ongoing telephonic support to attend to and address repetitive site issues related to trial logistics and different CTMSs

The above challenges can be efficiently tackled by implementing a team of support CRAs (who have prior onsite experience) whose members can help to achieve the following mitigations:

1. **Audit readiness—**The support team's key responsibility will be to regularly monitor and update the different CTMSs to ensure all-time audit readiness.
2. **Administrative support—**The support team can undertake site follow-up and other administrative activities in terms of missing documents, site start-up and initiation visit preparations, trial logistic coordination, etc., in order to reduce the load of administrative work on CRAs.
3. **Rollover of monitoring visit action items—**The support team can ensure follow-up and close-out of the monitoring visit action items in a timely manner. It can coordinate and communicate with sites after the visits, thus enabling CRAs to visit more sites and focus on exclusive field monitoring, capture findings, and document action items, while further follow-up and closure can be left to the support team.
4. **Helpdesk support—**The support team can provide ongoing telephonic support to the sites whenever site staff face difficulty in reaching CRAs who are traveling and/or busy with site audits and audit preparations, in the midst of job transitions and site handovers, on vacation, etc.

FIGURE 1: Roles and Responsibilities of a Monitoring Support Team



U.S.-based study monitors spend more time traveling and onsite than their counterparts elsewhere.

5. **Periodic site updates—**The support team can ensure that the sponsor receives periodic site updates, and can represent the CRA on meetings or calls that would otherwise be missed due to his/her travel. The team can also be a back-up available for client teleconferences to gather updates during any unexpected absence by the CRA.
6. **Optimize CRA efforts—**The support team can assist on site start-up activities, and allocation of CRAs can be done once a site list is ready for conducting selection visits. Thus, a CRA's efforts need not be billed for any site start-up activities.

Tufts CSDD gathered and analyzed data from 3,970 global CRAs and found that workload is high and varies widely by geographic region.[5] The findings also highlight the fact that U.S.-based study monitors spend more time traveling and onsite than their counterparts elsewhere, and that European study monitors spend relatively more time performing offsite monitoring and administrative tasks.[4] Thus, requirements for monitoring support teams can be estimated to be higher for European sites as compared to the rest of the world.

The CRA workload can be analyzed in terms of number of studies and sites he/she handles, along with the complexity of the protocol, the different types of visits conducted, and the trial logistics involved (e.g., how many site initiation visit preparations in a short span, how many complex protocols involving dose modifications or enrollment stratifications, how many trials involving multiple CTMSs, etc.)

Every CRA's capacity to manage workload will be different, and will mainly depend on his/her experience on the above parameters and the level of new types of studies/visits added; hence, project managers need to gauge how efficiently individual CRAs can handle different study scenarios. However, the quality and timely submission of monitoring visit reports, the quality of data generated, and

the pending issues at sites can be the factors to help in determining when the break-even point occurs beyond which implementing a support team would be wise.

How Does it Work?

Figure 1 provides a brief overview of the roles and responsibilities of the monitoring support team, and of the type of communication with the different stakeholders (i.e., CRAs, sites, sponsor team).

It is essential that, at the beginning of the trial, the study planning team performs a thorough analysis of the types of support work, complexity of trial logistics, and level of coordination/skill sets expected to be required of the sites and study team. Clear expectations need to be set about the list of support activities that the monitoring support team will perform, and these need to be documented on a checklist. The checklist would include all of the monitoring activities—further segregated into support activities and core monitoring activities—assigned appropriately between the lead CRA and the CRA support team. In addition, a clear communication flow needs to be chalked out by the project planning team with specific responsibilities assigned to all participants.

During the site initiation visit, the site team needs to be informed about the availability of the extra CRA from the monitoring support team serving as an additional point of contact for any issues, and told that they can expect follow-up/coordination calls for completion of trial activities and pending action items from this CRA. This model should be used as a customizable approach from study to study, depending on such factors as protocol complexity, therapeutic area, indication, trial logistics, etc.

Although having a monitoring support team thoroughly trained on all sponsor systems to work remotely is beneficial, and the work load (in terms of number of studies, type of studies) can be regulated as per the sponsor requirements, organizations new to this model should try it out on several pilot studies first to gain familiarity with its processes. Users of the model should also monitor communication and workflow carefully during its use to avoid any disadvantages that poor functioning in these areas may cause.

Benefits of Implementing a Monitoring Support Team

Apart from reducing the load of support work on CRAs and saving time and cost on CRA efforts, a monitoring support team can ensure all-time audit readiness of sites and systems and minimize audit findings, due to the additional attention being paid to timely resolution of critical site issues. Monitoring and CTMS support services are already increasingly common in the market, and can be viewed as additional levels of site overview that increase sponsors' ability to access real-time site updates.

Historically, it has been clinical trial associates (CTAs) who are responsible for assisting monitors to some extent; however, it is essential to note that a CTA has limitations in terms of functioning as a support CRA due to lack of monitoring/onsite experience. Further, it seems likely that most companies hire employees who are either brand new or relatively new to clinical research to serve as CTAs.

A support CRA, on the other hand, would ideally have at least some field experience as a CRA, but be someone who then has chosen to work in-house for the sponsor due to personal preferences or constraints on ability to travel. A support CRA can thus put his or her past monitoring experience to good use while monitoring CTMSs remotely, and while following up with sites on action items or coordinating with vendors for trial logistics, and this skill set should prove to hold an edge over using CTAs.

The maximum benefits and cost advantage of implementing a monitoring support team can be achieved mainly on "megatrials" running across 10 to 20 countries and involving more than 100 sites. On average, a support CRA can handle contacts with 15 to 20 trial sites (in different stages), thus remotely providing back-up for at least two site monitors. That is to say, by maintaining a ratio of 1:2 of support CRAs versus onsite CRAs, about a 40% reduction in cost can be achieved, due to having so much of the team working at a much lower billable rate.

In this scenario, project managers have the advantage of:

- greater control of sites through a monitoring support team whose members are always reachable for facilitating communications with sites for faster resolution of action items;
- greater control over monitoring-related expenses of a study; and
- real-time status updates of the sites and different CTMSs through the monitoring support team (even during the absence of a field CRA); further, the field CRAs can stop handling support/follow-up and coordination activities and focus on building site relationship and smooth trial conduct at the site.

A support CRA would ideally have at least some field experience as a CRA, but be someone who then has chosen to work in-house for the sponsor due to personal preferences or constraints on ability to travel.

Less overall investment in training efforts needs to be devoted to monitoring support teams, due to lower attrition rates estimated for support CRAs (as onsite travel will not be a parameter). On the other hand, training efforts for field CRAs are higher, because their attrition rates are usually higher in the industry due to extensive travel (29% attrition in 2012).[6]

The Tufts CSDD study report of 2012 highlights that CRAs overall have an average of 6.3 years on the job and expect to remain in their position for another three years, with both metrics varying widely by region. The report also confirms that there are 20,000 to 23,000 CRAs supporting clinical research studies worldwide.[4] Retention of field CRAs is therefore a major challenge, and having a monitoring support team is an effective mitigation strategy, as it can serve as a back-up for sites during CRA transitions/handovers.

On average, it is estimated that out of the overall clinical operations spending, monitoring accounts for about 30%,[7] and that about 40% out of the total monitoring effort is spent on support work. Hence, appropriately channelling a CRA's efforts is something the industry needs in order to save on monitoring costs.

RBM as an Added Advantage to Reduce Site Monitoring Costs

As said by industry experts, RBM is an intelligent way to monitor clinical trials with a more holistic approach of focusing on site risk factors, and its use predicts a 15% to 20% reduction in monitoring costs.[6] It is basically a methodology to assess site risks well in advance during the conduct of a trial, with the help of comparative and predictive analytic tools. Although it does not totally eliminate the need for site visits, it shifts the focus from distributing site visits equally to targeting visits to those sites identified as being at greater risk of noncompliance.

The role of the field CRA is therefore evolving from that of a traveling site monitor to more of a site/trial performance evaluator, because his/her judgement is based both on the comparative analysis of the predictive tools, as well as on the onsite visit experiences on that trial. A CRA will therefore be more of an overseer of the trial, with a reduced load of monitoring support work and a main focus on analyzing and evaluating data trends at a patient level, site level, and across sites and patients, with the help of RBM.

The monitoring support team and the field CRA team will thus function as one task force, with members working in tandem with each other to manage efficient trial conduct onsite by exchanging information, issues, findings, pending action items, etc., and resolving them collaboratively. Such resolution will be based on each member's predefined role and responsibilities, to achieve faster turnaround time for issue resolution and manage up-to-date records and smooth trial conduct.

Going forward, the role of the CRA will focus more on site performance and patient outcomes on a particular trial, and less on 100% source data verification (as opposed to more general levels of source data review). There will be a shift from routine, ongoing monitoring visits to trigger-based monitoring visits, with an emphasis on proactive planning of the action items before visits (based on the risks indicated by the RBM platform tool). Hence, site visits will be mainly for resolving issues, rather than for documenting findings to be followed up as action items after the visit.

Conclusion

By adopting RBM (or the most suitable technology options) to reduce monitoring visits and channelizing a CRA's efforts with the leveraged efforts of a monitoring support team, the pharmaceutical industry can convert clinical research monitoring into an inexpensive affair, while also achieving adequate levels of site oversight and audit compliance.

Acknowledgment

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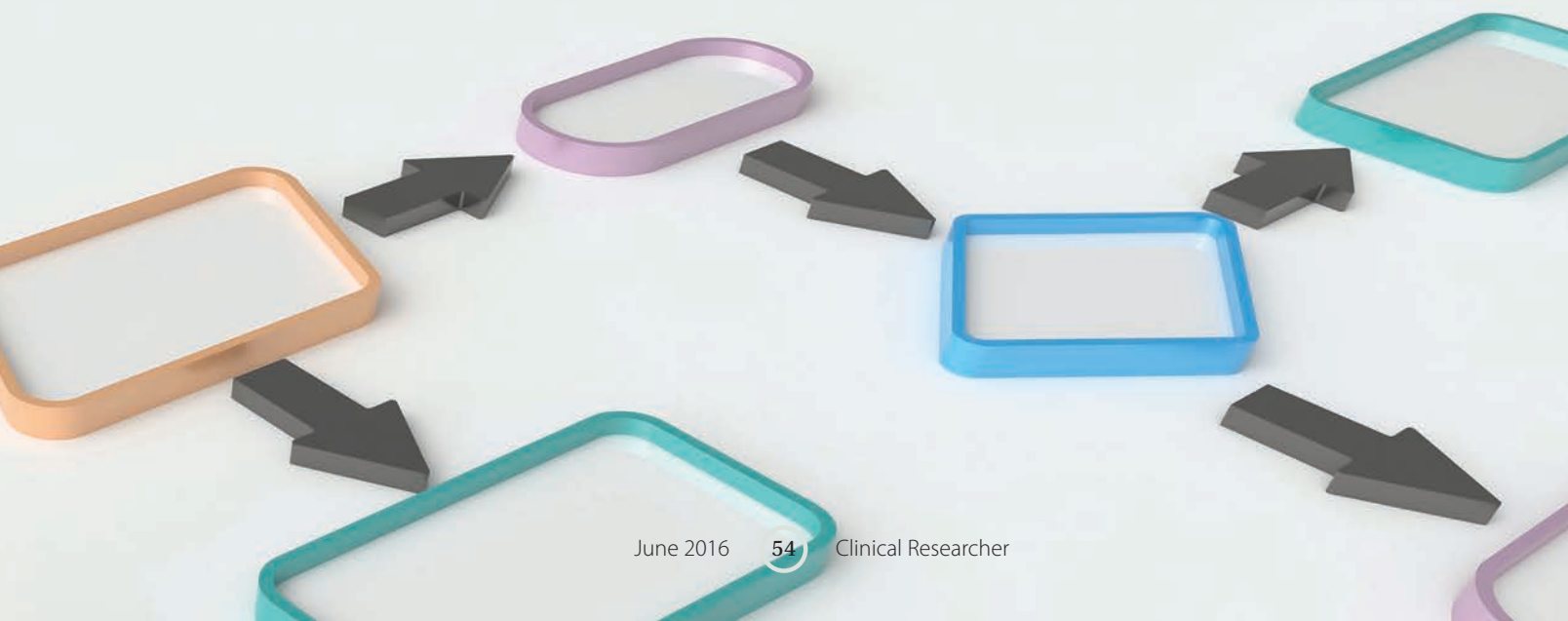

Kris Walters-Herring, PhD

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QUALITY PROGRAMS: Distinguishing Between Quality, Quality System, and Compliance

Individuals perceive topics related to quality and how to establish quality within an organization in various ways. Several misconceptions prevail regarding what constitutes "quality" and a "quality program." When designing a quality program, one must distinguish between quality, quality system, and compliance. These terms are used pervasively throughout the clinical research arena, and they are often erroneously used interchangeably.

Editor's Note: For this issue, the usual author of this column, Michael R. Hamrell, PhD, RAC, RQAP-GCP, CCRA, is pleased to present Dr. Walters-Herring, a professor and expert compliance consultant in clinical research, as an invited contributor to address the role and importance of quality programs in clinical research.

Quality, quality system, and compliance are considerably different from each other, and possess distinct and significant roles within a true quality program. Among the many misconceptions auditors face is the belief that written procedures are synonymous with possessing a quality program; such a belief could not be further from the truth. An organization might establish excellent written policies, but without a system to assure review, revision, and training pertaining to those procedures, the written standards provide no assurance of quality outcomes.

Digging Deeper into the Terminology

It bears repeating that many organizations operate under the belief that the establishment of written standard operating procedures (SOPs) is the equivalent of quality; however, without a complete quality system, an organization cannot assure that its products are of a particular quality standard. Hence, a key component of an effective quality program is an established quality system.

Many organizations establish impressive training programs pertaining to SOPs, but the training does not contain a means for assessment. Without an assessment mechanism, one cannot ensure employees comprehend a policy or procedure resultant from training. In addition, the establishment of auditing programs within an organization might assist with determining compliance to regulations and internal policies, but without trending, the stronger significance of the audit findings is frequently unexposed.

To truly establish an effective and efficient quality program, an organization must internally address the differences between quality, quality system, and compliance through defined functions and tasks.

A quality system incorporates not only written procedures, but also formalized training and assessment mechanisms to determine employees' understanding of policies and how to properly execute procedures. Detailed SOP employee training records are also maintained as a function of a quality system, and SOPs are readily accessible to employees.

An effective quality system also contains an SOP review process to assure the maintenance of policies and procedures. Details of SOP revisions, the applicable employee training, and the effective dates pertaining to SOP revisions are also clearly communicated in a well-organized quality system.

But Wait, There's More…

SOPs and training are only the tip of what is needed to establish a true quality program. In addition to policies, procedures, and training, an organization must demonstrate that its employees are compliant to its established procedures.

Compliance is the conformity to a procedure on a consistent basis. Simply put, compliance is the regular adherence to written procedures, which is often determined through incorporating a robust auditing function into a quality program. This function must remain independent from an organization's operating group to avoid undue influence when assessing compliance to policies and procedures.

The auditing function regularly observes the execution of certain tasks and compares the execution to applicable SOPs (and regulations, when applicable), taking note of deviations. The deviations might be in the form of, but not limited to, erroneously recorded datum, missing documentation, unreported information, lack of communication, and/or nonadherence to a protocol or standard. These deviations indicate noncompliance, and can potentially alter the quality of a product or service.

Another common misconception is that if an audit results in no findings, then the operation observed during the audit is completely in compliance. This misunderstanding is often associated with results pertaining to inspections performed by regulatory agencies.

The essence of an audit is to sample different aspects of an operation; hence, an audit is a "snapshot" in time. The result of one audit is not indicative of the overall compliance of an organization or function, which is to say that audit findings only reflect the information that was observed during the audit. It is not uncommon for auditors to review particular documents and procedures and produce no audit findings, but an alternative set of documents and procedures within the same function not reviewed by the auditors at the time might later generate several audit observations.

If the purpose of an audit were to assure complete compliance of a function or organization, then every document, procedure, piece of datum, etc. would require review, which would be an arduous, virtually impossible, and most likely expensive task. Hence, to truly receive the greatest advantage from an audit, a quality program must also incorporate the trending of audit findings into its regular routine.

Trending is an examination of audit findings that might reveal a common issue or common noncompliance. Trending audit deviations helps to determine if there is an underlying root cause to an issue. Once a root cause is identified, an organization can determine how to remedy the problem and better assure quality is infused into its services and products.

Lastly, identifying issues and root causes through auditing is only effective if the information is properly communicated. A quality program should include a formal means for communicating quality observations, both good and bad, to individuals most affected by the findings. Most often, organizations request audit reports to document audit observations, but a system for receiving responses to audit findings should also be established. All documentation regarding the audits and audit responses also requires a formal means for retention.

Conclusion

Quality is not an easy attribute to establish. In the clinical research arena, just having auditors inspect principal investigator sites periodically across one study and produce audit reports is not a quality program in its entirety.

A quality program is also not truly effective unless audit reports across multiple functions, studies, and sites are trended and those trending data are used to improve quality standards. Likewise, a training program regarding written procedures and regulations can only be rendered effective if an assessment mechanism exists to gauge individuals' true understanding of the material taught.

Hence, a highly effective quality program distinguishes between quality, quality system, and compliance by establishing quality through quality systems that include SOPs, a training program with an assessment mechanism, an auditing and trending function, and a means for effectively communicating quality issues and information.

> Quality, quality system, and compliance are considerably different from each other, and possess distinct and significant roles within a true quality program.

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Challenges to the Implementation of Risk-Based Monitoring

Much recent focus has been devoted to the development of a risk-based approach to clinical study monitoring. The mantra of risk-based monitoring (RBM) is simple: Optimize the limited monitoring resources available from a sponsor across the portfolio of studies that the sponsor conducts. This optimization is based on the risk factors associated with each study and, more specifically, with sites in a particular study, and seeks to maintain the expected standards for patient safety and data integrity.

PEER REVIEWED
Shilpa Patkar, MSc
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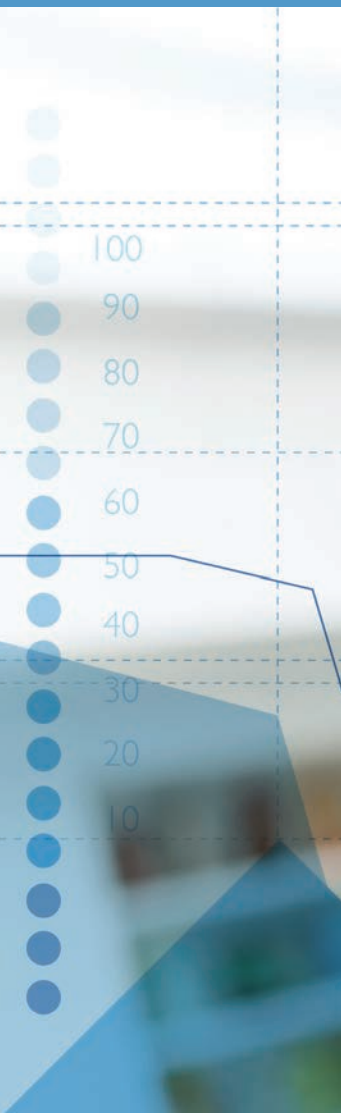
Background

Currently, more than 30% of a clinical trial budget is allocated to site monitoring costs,[1] and more than 50% of that is spent on source data verification (SDV). RBM is likely to relieve some of the escalating financial pressures on the clinical research industry.[2]

RBM is a hybrid monitoring model that includes permutations to, and combinations of, various monitoring approaches into a single, foolproof strategy based on the risk algorithms. The algorithmic assessment of risks is carried out via a risk assessment and categorization tool (RACT) based on several preset and variable risk factors.[3]

Preset or fixed factors may include the phase of study, therapy area, principal investigator (PI) and site staff qualifications and expertise in the conduct of clinical trials, and a monitor's competency and experience. These risk factors are identified through a cross-functional, program-level assessment by a comparative and predictive analysis of the business performance objectives vis-à-vis the empirical data generated from previously concluded clinical trials.

Variable or dynamic factors may be more protocol-specific, and comprise screening and/or recruitment rate, number and/or nature of adverse events/serious adverse events (AEs/SAEs) in the study, protocol deviations, study



endpoints, data entry and query resolution metrics, and so on. During the initiation of the trial, the fixed factors influence the risk algorithm generating the initial RBM strategy. However, as the trial progresses and recruitment milestones are attained, the variable risk factors begin to impact the algorithm, which astutely assesses and revises the RBM plan.

Who's Promoting the RBM Mantra?

Regulatory agencies, multinational companies, and contract research organizations (CROs) all over the globe are strongly advocating implementation of RBM.

According to an in-depth survey of pharmaceutical companies and CROs conducted in 2013 by the Metrics Champion Consortium, more than 50% of the 45 respondents were actively employing some type of RBM strategy, either on a pilot basis or across a full program, and 10% to 30% of those not then using RBM approaches planned to do so in the coming year.[4] This is a significant rise from an earlier survey of 65 respondents conducted by the Clinical Trials Transformation Initiative in 2009, which reported that 33% or less of the respondents were using centralized data monitoring to guide, target, or replace site visits.[5]

Despite the guidance provided by regulators[6–8] and tremendous cost saving potential that RBM offers, the pharmaceutical industry has yet to employ it on a full scale. While the existing literature vividly explains the concept of RBM and the opportunities it presents, none of it addresses the other side of RBM in terms of its ensuing challenges.

Challenges

THE PARADIGM SHIFT: NEED FOR CHANGE IN MINDSETS AND ROLES

The International Conference on Harmonization's Guideline for Good Clinical Practice (ICH-GCP) does not quantify or explicitly state the number and nature of monitoring visits required to be made to a site to ensure quality.[9] The general perception among all stakeholders is that sites visited more frequently will have "cleaner" data than those visited infrequently.[10]

Conventionally, a physical monitoring visit at a site lasts for two to three days and encompasses activities like SDV, informed consent form (ICF) review, investigational product (IP) accountability, review of the trial master file, and meeting the PI and site staff. The focus of each monitoring visit may also vary, thereby diverting the monitor's attention from other possibly crucial activities such as subject safety, recruitment, and any obvious trends or outliers.

Monitors currently spend more time in identifying risks onsite rather than addressing them. Sites too are heavily reliant upon the monitors and their observations during monitoring visits as a measure of data quality.

Monitors currently spend more time in identifying risks onsite rather than addressing them. Sites too are heavily reliant upon the monitors and their observations during monitoring visits as a measure of data quality.

The shift to RBM will also entail change in certain roles, including those of the monitors and data managers. With the RBM approach, monitors will have to draw high-level inferences from a low-level view indicated in the risk algorithms. Additionally, the purpose of monitoring visit reports (MVRs) will change from simply documenting risks and actions taken to address them to being a tool that continuously defines the RBM strategy for a site (e.g., data entered onto the MVR will be analyzed to flag outliers at a particular site that are not captured in any system).[11] The RBM model will also put greater accountability on the site for the quality and integrity of data.

In the last few years, several monitoring approaches have been explored, including onsite, partial or targeted, and remote monitoring. Although RBM has evolved from these approaches, the mantle of 100% SDV may still be preferred. The Metrics Champion Consortium survey reported that 85% of the respondents continued employing traditional onsite monitoring practices involving 100% SDV activities (n = 39).[4]

While the pharmaceutical industry seems both aware and interested, RBM aims at displacing a significant percentage of the onsite visits with remote monitoring. In order to manage this paradigm shift, the RBM culture will have to be embedded in the very inherent constitution of research and development, and incorporated in the monitoring plan for every study. The mindset of every stakeholder involved will have to amend and adapt for RBM to be successfully implemented.

FINANCIAL IMPACT OF RBM

RBM is an integrated model that amalgamates targeted onsite monitoring with offsite risk identification and tracking. Contrary to the general perception, RBM cannot replace traditional onsite monitoring completely. This is because several activities involved in a study (e.g., review of site facilities, ICF review, assessing site staff's confidence and understanding of the protocol and study-related procedures, review of onsite documents, performing IP accountability, assessing PI's oversight, building long-term relationships) will mandate physical visits to the site.

RBM will only assist in targeting critical data points during SDV. This is likely to reduce the frequency of onsite visits, but cannot eliminate them completely. On the other hand, the frequency and intensity of onsite visits may increase at less productive sites. The exact impact RBM will have on research and development budgets is still to be realized.

RBM will most likely impact late-phase studies. Phase I trials are unlikely to implement RBM, as they are usually shorter in duration and need more rigorous oversight.[12] Certain pivotal complex studies, such as those involving adaptive design, may not fall within the scope of RBM. Likewise, RBM may not be a suitable approach for simpler, fast-recruiting studies and bioavailability/bioequivalence studies. This may not translate into substantial cost savings for companies with a narrow portfolio focused on studies requiring more onsite visits.

To appreciate the financial impact of RBM, a company may need to have a broader spectrum of studies requiring optimal monitoring resources.

For risk assessment of global, multicenter studies with large volumes of data, validated and well-designed automated systems that can process data on a real-time basis and generate comprehensible visualizations may be required. The financial impact of developing these systems is further discussed in this article.

LACK OF ROBUST GUIDANCE FROM REGULATORY AGENCIES

The U.S. Food and Drug Administration and European Medicines Agency have supported RBM via release of the "Guidance on Risk-Based Approach to Monitoring" and "Reflection Paper on Risk Based Quality Management in Clinical Trials," respectively.[6,7] While these guidelines have busted the myth that the regulations disallow the conduct of RBM, they have failed to establish clear procedures for its implementation.

Moreover, other regulatory authorities around the world have remained silent on the adoption of the RBM strategy. As awareness about RBM becomes widespread, it would be interesting to see the take of these other authorities—especially in emerging markets—regarding adoption of RBM. This will be true especially in countries such as India that have witnessed volatile regulatory environments and reforms in the recent past.

A few years ago, clinical trial sponsors received a major backlash from the Drugs Controller General India (DCGI) for under-reporting of SAEs in studies in the country, and for inadequate payment of compensation in cases of injury or death during trials.[13] The Indian regulations have since then also mandated audiovisual recording of the informed consent process, to establish evidence that subjects have given voluntary and informed consents prior to participation in studies. In this scenario, convincing the DCGI that risks in a trial can be monitored centrally by reviewing outliers from a system may prove to be a difficult task.

It is recommended that sponsors conducting trials in markets similar to India undertake educational outreach to create awareness about RBM among the local regulatory authorities. The initial RBM plan for a particular study can also be submitted or discussed with the regulatory agencies during the regulatory submission for that study.

INCONSISTENCY IN TRAINING, RISKS IDENTIFICATION, AND DECISION-MAKING

Since the regulatory guidance has failed to establish clear procedures on implementation of RBM, currently there is no standard approach for adopting the RBM methodology. No universal module or guidelines are available for RBM training.

Different sponsors may have different processes for risk assessment and action taken. For instance, one sponsor may rely on the monitor and data manager for decision-making, whereas another may solely depend on an automated system. In this scenario, there is a chance of differentiated understanding of the RBM process, subjective risk assessment, and decision-making. Cultural biases also may play a vital role in case of large, multicenter, global trials. While empowerment is an important factor for stakeholder decision-making, it is critical that these decisions are made within the RBM framework.

It is, therefore, crucial that all the stakeholders, including sponsors, CROs, investigators, auditors, and regulators, have a common platform for understanding of RBM. It is recommended that all the stakeholders collaborate for development of a standard process for training and implementation of RBM.

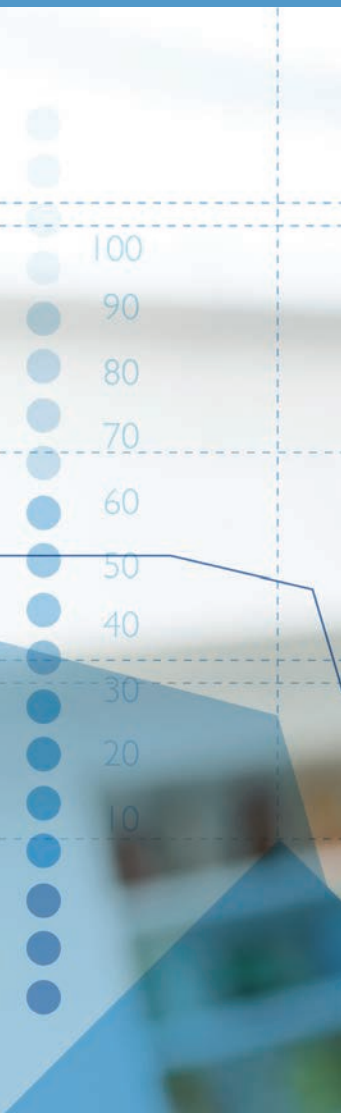
NEED FOR NOVEL TECHNOLOGY AND METRICS

The core of the RBM principle revolves around identifying, assessing, and tracking the risks associated with a study. Large-scale, multicenter studies that plan to implement RBM will depend on current and novel metric systems to perform the risk analysis.

In order to formulate an accurate risk algorithm, the existing, disconnected systems will need to be integrated centrally to generate a real-time risk register. This includes integrating systems that are responsible for flow of data from protocol development to clinical trial management system (CTMS) to electronic case report form, and to allied systems and statistical graphic applications to flag any data trends and outliers.

A central monitoring portal with integrated visualization dashboards will be used to monitor the data and provide direction on further action, based on triggers that are activated when thresholds are crossed. With a CTMS in use, it is expected that the information entered on the traditional MVRs will be collected into a database for further reporting and analysis.[11]

To facilitate the creation of such sophisticated systems, companies will have to invest heavily in existing technologies to upgrade them or build novel metric systems altogether. Either way, the initial investment for creating a robust RBM system



In order to manage this paradigm shift, the RBM culture will have to be embedded in the very inherent constitution of research and development, and incorporated in the monitoring plan for every study.

will be enormous. Companies with a small portfolio or those doing only initial-phase studies may not be able to incur such heavy spending.

It is recommended that companies that plan to engage in RBM on a long-term basis build a well-defined strategy to realize its true potential. Alternatively, RBM can be outsourced to technology vendors whose services include tools with RBM capabilities.

Conclusion

Due to increasing financial pressures and limited monitoring resources, the transition to RBM is inevitable. Its execution remains a topic that needs to be further deliberated by the pharmaceutical industry.

The shift in mindset from conducting 100% SDV to a risk-based approach involves cognizance of evolving roles, consistency in understanding of the underlying principles of RBM and its methodology, and objective decision-making. Further, more regulatory guidance is required in order to facilitate implementation of the RBM strategy confidently and consistently among all stakeholders.

In our view, sponsors will have to cease working in silos, and instead adopt a collaborative approach for a uniform understanding of RBM expectations from the regulatory perspective. One such attempt at collaboration by multinational corporations can be seen in the efforts of the nonprofit TransCelerate BioPharma Inc. TransCelerate has developed a methodology that shifts monitoring processes from excessive concentration on SDV to comprehensive, risk-driven monitoring in order to further support site processes, subject safety, and data quality.[3] This risk-based approach is a humble start to the advent of a new era in monitoring of clinical trials; one in which patient safety is well managed and data quality and integrity are not compromised.

Creation of a common platform featuring predictive analytics blended with clinical expertise and enabled by a strong technology backbone will be critical for the successful implementation of RBM.

Disclaimer

The views expressed in this article are those of the authors, and do not reflect the views of their companies.

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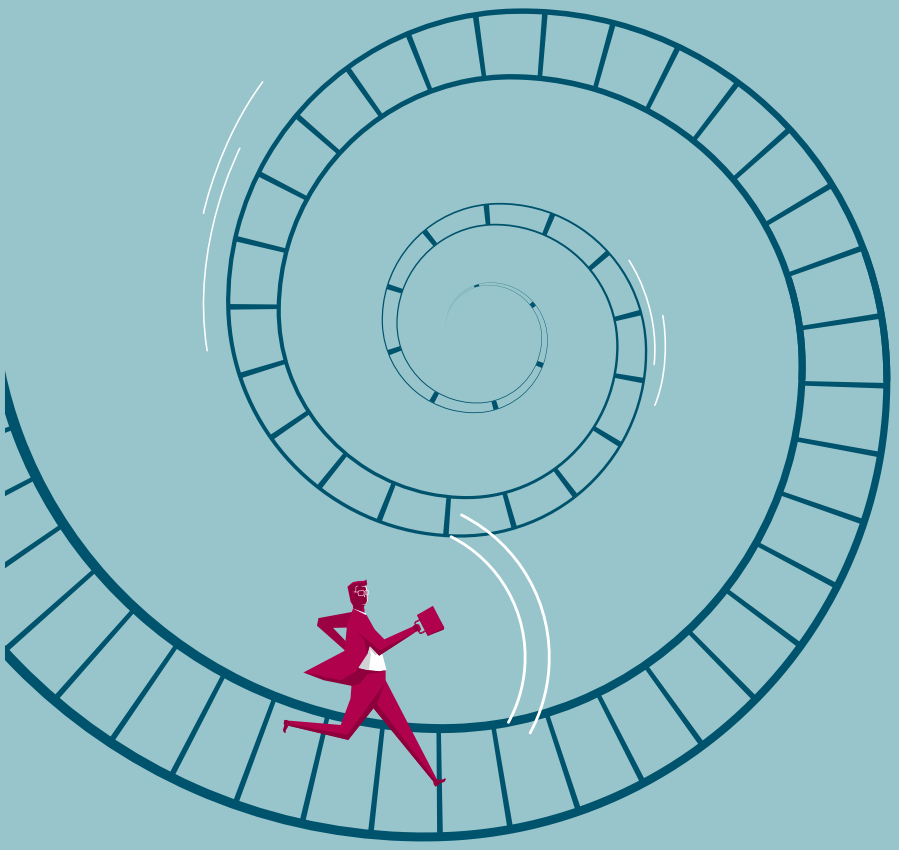

Ronald S. Waife

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Operational Mediocrity

Whatever happened to "operational excellence"? It is a beautiful phrase and a worthy goal, but as biopharmaceutical companies and contract research organizations (CROs) start to dismantle or de-fund their Operational Excellence departments, we should ask what is happening. Do we no longer desire excellence? Do we think we have achieved it?

The fundamental inefficiency of biopharma clinical development is driven by many external factors, true, but we don't do well with the hand we are dealt.

Operational excellence arrived as a melodious piece of jargon because of disillusionment with what came before it: Total quality management (TQM) first, then process improvement, then various branded methodologies (hungry-eight-Omega, you know who you are). The "excellence" efforts have suffered fates similar to those of the earlier incarnations—underfunding, insincere management commitments, skepticism, fatigue, and fundamental misunderstandings about what process improvement can and should be.

Changing the branding does not change the results because of these key flaws, and they all contribute to a negative feedback loop. Missed expectations leads to skepticism, poor techniques lead to change fatigue, underfunding prevents sustained effort, and insincere commitments make re-prioritizing all too easy.

Improvements to clinical development's methods are still very much needed. The fundamental inefficiency of biopharma clinical development is driven by many external factors, true, but we don't do well with the hand we are dealt; and we've seen that simply outsourcing the problem (by far the most common solution today) has only created variable-cost inefficiency instead of fixed costs.

Outsourcing Does Not Equal Process Improvement

The irrelevance of outsourcing to improving efficiency is another column in itself. Sponsors like CROs to use methods they recognize, no matter how suboptimal, and CROs know they will be paid regardless, so the system has no meaningful incentives to efficiency besides competing billing rate charts. For all the many failings of biopharma outsourcing procurement departments, their inability to make an impact on overall industry methods may be the most damning.

Process improvement is ripe for action in all aspects of clinical development: protocol design, subject enrollment, data management, study team conduct, trial operations oversight, safety surveillance, use of information technology, investigative site communication and performance, monitoring, and more. Your company probably has had multiple initiatives in most of these areas already, but meaningful results are rare and usually fleeting.

We live in operational mediocrity instead of operational excellence. Nonetheless, we can no more give up on process change because it fails often than we can give up on early-stage drug research because it fails often. Improving processes is still worthwhile; indeed, it is an unavoidable imperative.

Consequences and Changes

A particularly sad consequence of operational mediocrity is its impact on innovation. If we look at the current appealing innovations in clinical development—things like risk-based monitoring, fully electronic trial master files, exploiting mHealth technologies, next-generation electronic data capture (EDC), professionalized CRO oversight, and so on—each involves significant workflow and responsibility changes that must be as innovative as the technology used.

The industry's long experience with trying to exploit EDC and electronic clinical outcome assessment (eCOA) technologies has taught us this: Underlying every innovation is a change in the way we work; otherwise, there is no innovation. To make that change, organizations and internal thought leaders must understand and respect the nitty-gritty process changes which need to be defined, agreed to, tested, and trained.

Approaching Excellence

How do we steer back toward something approximating excellence? I have seen considerable success in what I call a "pragmatic" approach—one that takes on change step by step. It is grounded on several key essential items:

- Committed and visible executive management
- Traceability to key enterprise goals
- Breaking the task into manageable, iterative pieces which, once achieved, serve as positive examples for breaking the skepticism cycle
- Immediate follow-up to the above items with additional improvement pieces to maintain momentum and convince staff it is "real this time"

One way of thinking of this is akin to "evidence-based" medicine, but as used here, it is an evidence-based method (EBM). EBMs are usefully distinct from JBMs (jargon-based methods), which are used instead all too frequently. It can be generalized that jargon is the refuge of those with little else to offer.

The building blocks of pragmatic process improvement will certainly sound familiar (identifying key business drivers, interviewing stakeholders, designing processes in workshop settings, documenting and implementing the changes, and monitoring first use). This is like saying that basketball is dribbling down the court and putting the ball in that hoop up there. The hard part is overcoming all the typical obstacles that can so easily undermine improvement projects, some of which we have alluded to.

Let's take the ubiquitous "workshop" as an example. Everybody in pharma has been to many workshops. What are the characteristics of those you remember as being productive? The workshop needs to have a crystal-clear purpose achievable in the time allotted. It needs a domain-knowledgeable facilitator. It requires some organizing mechanical technique to make the discussion and results tangible.

Most important is the selection of the participants: 18 people chosen for their political affiliation does not a workshop make. That is better a definition of a circus. Instead, a small group of stakeholders who can truly devote the necessary time to the task will be essential. It all sounds familiar, but the subtlety of applying pragmatism to each step is the heart of the matter.

What Lies Beneath

Underlying the success of pragmatic process improvement is the correct governance—who is in charge, who funds, who decides, who staffs, who is accountable? The answer is always a little different from company to company.

Should the people who do the work being improved be responsible for improving it? (Seems logical and essential to me.) Can process improvement cost less by creating a central, dedicated department (at the risk of separating domain knowledge from the process knowledge)? Should it be outsourced like everything else? Should it be lumped in with the information technology, human resources, or training departments?

Every company will try it differently, but tying performance accountability to the management of the process in question is the most powerful solution.

Change fatigue, change skepticism, wasteful projects, and unmet expectations are all real challenges to improving the way we work. They all can be overcome by a pragmatic approach to process improvement that is properly governed, with visible management commitment, taken in manageable steps that demonstrate success, and featuring improvements grounded permanently in our work environment. This steers us back toward excellence, which is the only direction worth traveling.

Underlying the success of pragmatic process improvement is the correct governance—who is in charge, who funds, who decides, who staffs, who is accountable?

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Dan Dumrauf, director at Medix Scientific, understands the unique challenges of identifying leading resource talent for the clinical research industry, and is not afraid to confront obstacles head on.

Hiring the right talent is one of the toughest things to do, especially when the organization's leaders or the talented prospects don't know exactly what they are looking for.

Q: You majored in business communications and chemistry while in college, and you used your talents to work your way up through a career sector that is mainly comprised of individuals with scientific backgrounds. Can you tell us how you first became interested in clinical research, and describe a little bit about the path you took to get involved with your clinical research career?

A: After graduating college, I started with a recruiting firm that specialized in placing scientific professionals in the pharmaceutical/biotech and medical device industries. Mostly, we were placing talent in the lab, but as our business expanded we began focusing on clinical research; it was at that point that I fell in love with clinical research.

I came across so many fantastic people working for a greater cause than a paycheck. These people were passionate about finding therapies that could help our community.

As I grew in my career, it took me in and out of the clinical research sector of recruiting, and it felt like my purpose had been diminished. Not that I didn't have passion for helping people find the right opportunity, but it wasn't the same. When I came to Medix, I knew I had found the perfect combination of purpose and passion. When I started, we didn't offer recruiting for sites, contract research organizations (CROs), and sponsors, so I knew the chance to grow those areas would make the position a perfect match for me. Five years later, I lead a national team that is passionate about advancing research and positively impacting lives. We offer a variety of national workforce solutions to the research community, along with consulting services to sites.

Q: What do you consider to be the biggest challenge in your business?

A: Hiring the right talent is one of the toughest things to do, especially when the organization's leaders or the talented prospects don't know exactly what they are looking for. Having the right talent on board will either make or break a trial, so it is mission critical that we get the hiring right. The organizations that spend the time to find the right people to match their culture, values, and purpose typically perform at a high level.

Q: What advice do you have for professionals who are interested in entering the industry or advancing their careers in clinical research?

A: I get this question a lot, and I am happy to share:

a. Ask yourself what motivates you. It has been my experience that the people who have a stronger motivation for purpose (advancing research) over money tend to be the happiest in our industry.
b. Do your strengths overlap with what is required of clinical research professionals? For example, attention to detail and the process of management are two strong competencies in top performers in our community.
c. Evaluate clinical research at a site vs. clinical research with a sponsor. Those are two very different career paths.

Q: What do you see as currently being the biggest challenge for clinical research professionals? Any advice on how to approach or overcome barriers?

A: The landscape of healthcare is changing at an epic rate, and it is impacting the guidelines and regulations for our community of practice. This is rippling through our community at lighting speed. It doesn't matter if you work at a CRO, sponsor, or site—we are all impacted. Continuing education is one way to combat that. Also, participating with associations like ACRP is a tremendous way to collaborate and hit these challenges head on.

Q: How about your involvement in ACRP? When did you first get involved, and how has your affiliation affected you professionally?

A: I first started attending local chapter meetings in Chicago in 2005 as a guest. It made a significant impact on me right away: It was a great networking arena for meeting some great people, and it was a huge educational platform for me to learn about the industry. Today, my team is active in multiple communities across the United States, and we attend the annual ACRP Meeting & Expo when we can.

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

A: When I was first introduced to clinical research, my purpose became clear. How can I find the very best talent so that we can advance research, so that we can drive innovative therapies to our families and friends? I am lucky; I have found a platform at Medix that gives me a huge opportunity to positively impact lives all over the United States and the world. I will continue down this path professionally and personally.

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

A: There is no shortage of challenges or drama in our industry, and it is easy to get wrapped up in them. I believe we should anticipate our challenges and hit them head on. Our community, families, and friends are counting on us to get closer to cures.

Jamie Meseke, MSM, CCRA, (jamie.meseke@ppdi.com) is a clinical trial manager for PPD, Inc., and a member of the ACRP Editorial Advisory Board.

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