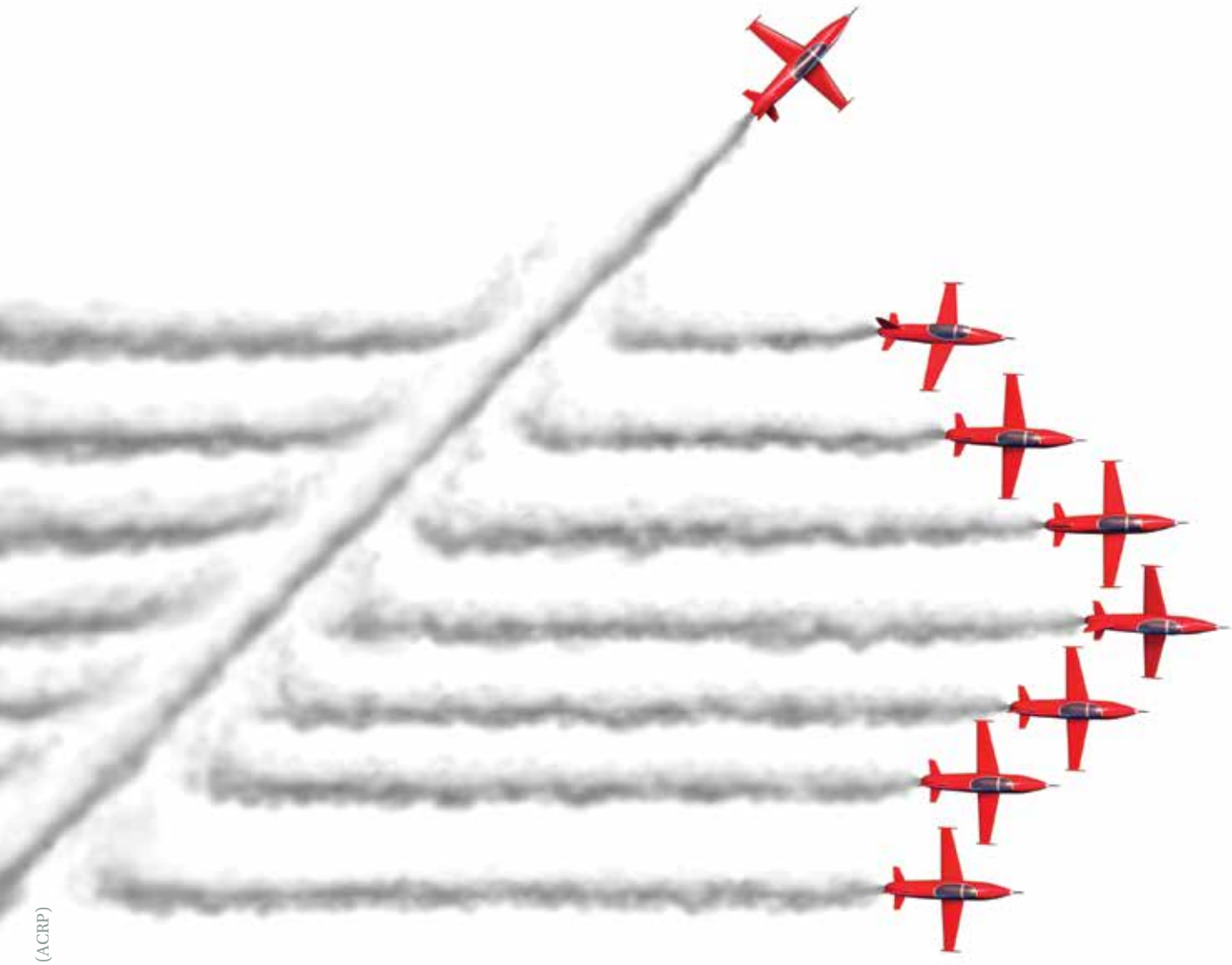
AUGUST 2017

Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research



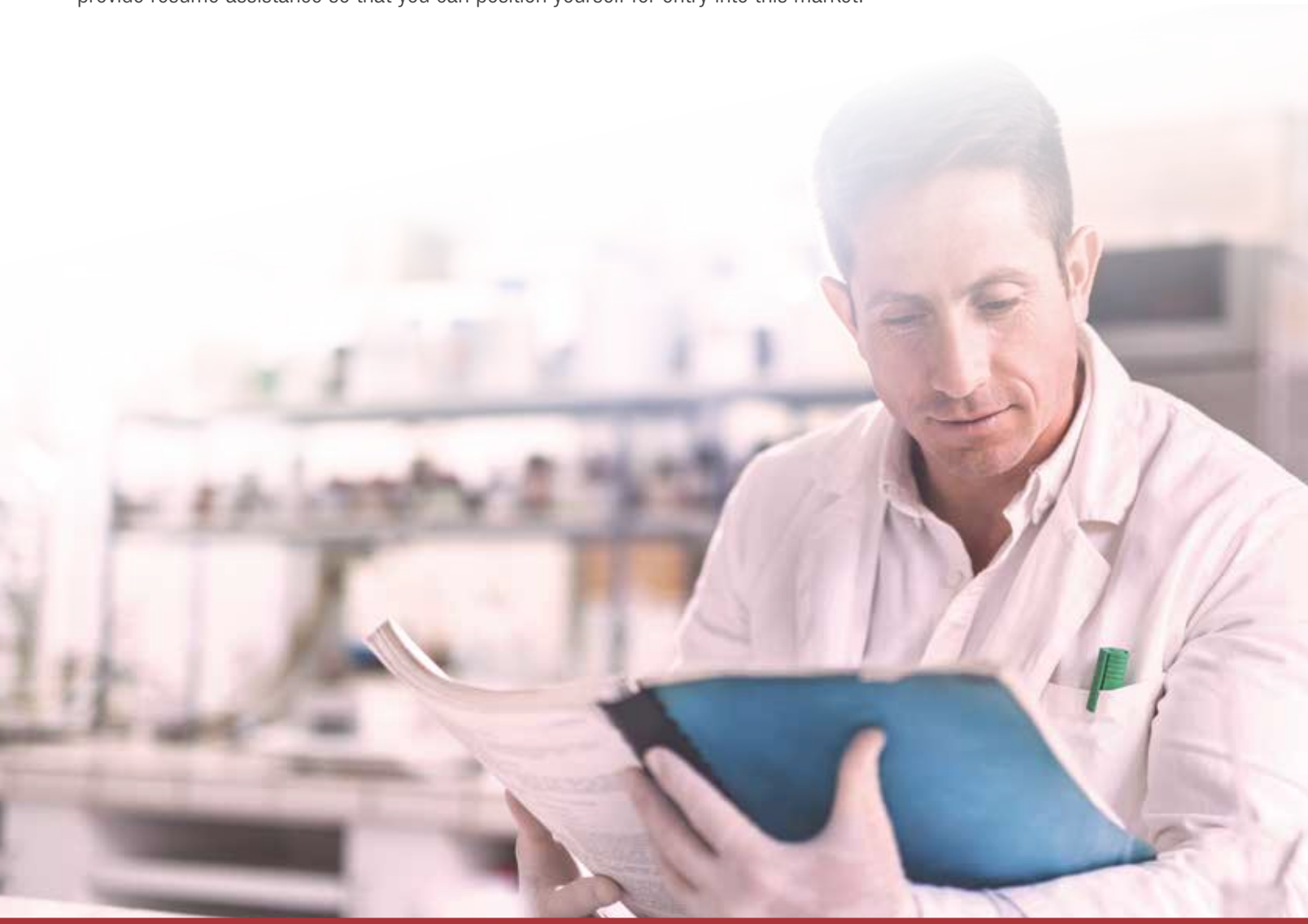
Sites: Tactics and Triumphs from the Front Lines of Clinical Research

Association of Clinical Research Professionals (ACRP)
www.acrpnet.org

BARNETT INTERNATIONAL
Leaders in Clinical Research Training

10-Week CRA & CRC Beginner Program

The online 10-Week CRA & CRC Beginner Program provides a comprehensive introduction to clinical research and the job functions of the Clinical Research Associate (CRA) and Clinical Research Coordinator (CRC) for drug, biologic, and device trials. This program is geared toward individuals seeking a new career or career change into clinical research, but haven't decided which job track to pursue. Case studies and industry best practices are presented to emphasize how the learning objectives apply directly to the responsibilities of the CRA and CRC. Upon completion, Barnett will provide resume assistance so that you can position yourself for entry into this market.



Clinical Researcher™
The Authority in Ethical, Responsible Clinical Research

CONTENTS

August 2017 • Volume 31, Issue 4 • ISSN 2334-1882

Clinical Researcher **is your platform.** Interested in writing a peer-reviewed article or guest column? You'll find our submissions guidelines at acrpnet.org/submit

ACRP
FOR LEARNING FOR LISTENING FOR LIFE

Clinical Researcher ISSN 2334-1882 (Print) and ISSN 2334-1890 (Online) is published bimonthly. It is provided to ACRP members by the Association of Clinical Research Professionals (ACRP).

Postmaster: Send address changes to Clinical Researcher
99 Canal Center Plaza, Suite 200, Alexandria, VA 22314

+1.703.254.8102 (fax)
+1.703.254.8100 (phone)

www.acrpnet.org

DESIGN
TGD Communications
tgdcom.com

"VOICES" FROM THE FIELD

Sharing insights from clinical research professionals as quoted in recent media coverage and press releases.

"[Physicians] don't ask older adults whether they want to participate [in studies] or not. It's a combination of concern that older patients might be unable to comply with a trial's requirements, which are usually quite rigorous, and concern that specified therapies might be too toxic."

—Richard Schilsky, chief medical officer for the American Society of Clinical Oncology

(Source: *Washington Post*, https://www.washingtonpost.com/national/health-science/clinical-trials-for-cancer-could-use-more-older-people/2017/07/21/c015d858-6bc7-11e7-b9e2-2056e768a7e5_story.html)

"The emphasis [in clinical research] on reliable results is not just for academic reasons. It's the results that impact on the care of future patients. If a treatment really works but your trial fails to prove it then you've missed an opportunity. If a treatment is not safe and you miss that because your trial is too small or is badly conducted then that's also bad for patients."

—Martin Landray, professor of medicine and epidemiology with the Clinical Trial Service Unit at the University of Oxford

(Source: *EurekAlert!*, https://www.eurekalert.org/pub_releases/2017-03/esoc-ctr030817.php)

"[Stem-cell] clinics are basically trying to take advantage of the perceived legitimacy and credibility of the [ClinicalTrials.gov] website. They want to suggest that if their studies are on this site, then they must be legitimate. The problem is that anybody can sit at his computer, enter pretty much anything, press submit, and get on ClinicalTrials.gov, because the screening is inadequate."

—Leigh Turner, a bioethicist at the University of Minnesota

(Source: *MinnPost*, https://www.minnpost.com/second-opinion/2017/07/stem-cell-clinics-are-using-federal-website-marketing-tool-unproven-treatment)

ACRP

FOR LEARNING FOR LISTENING FOR LIFE

GUEST EDITOR'S MESSAGE

Jerry Stein, PhD

[DOI: 10.14524/CR-17-4034]

In Search of Perspectives from Sites on the Front Lines

The primary theme of our August *Clinical Researcher* issue is the study site; truly the central axis on the front lines of the clinical research enterprise. Virtually all other organizations are connected to, or dependent on, sites: sponsors, contract research organizations (CROs), institutional review boards, electronic data capture (EDC) vendors, etc.

Not surprisingly, nearly two-thirds of ACRP members work at study sites as investigators, coordinators, or other staff members. At every annual ACRP Meeting & Expo, I am amazed by the proportion of attendees I speak with who are employed at small local or distant study sites seeking to share their experiences, improve their personal skills, or improve the efficiency of their site's operations.

It's lonely out there if your site is not nested in a mega-academic medical center (AMC) or part of a site network. Where do you find the networking opportunities, training, or operational models to follow? ACRP is often a primary resource in these situations.

SKIN IN THE GAME?

An impressive 25% of articles published in *Clinical Researcher* during the last two years had senior authors affiliated with study sites, and another 13% had authors affiliated with site management networks. However, only 11% of authors were affiliated with small sites, and this statistic worsens considerably when we exclude authors who are ACRP Board members.

Most of our recent authors worked as consultants or were affiliated with sponsors, data management firms, or CROs. Clearly the voice of small study sites has been under-represented.

There are some obvious reasons why the leaders or other staff of small sites do not contribute articles. For example, they might be too busy with

of articles published in *Clinical Researcher* during the last two years had senior authors affiliated with study sites

non-study activities, and many investigators may only have experience with one study or one sponsor. Some other reasons may not be so obvious.

I am concerned that the participation of small sites in clinical research is disappearing. This important gap in publications needs to be addressed. If small sites are vital players in the clinical research enterprise, our professional organization needs to encourage these experts to share their knowledge, experience, and challenges.

DISPATCHES FROM THE FRONT LINES

First up as we launch into the sites theme in the pages ahead, Joanne Perry and Elise Levine offer some practical advice on budgeting from the perspective of a large ophthalmology practice that mixes research studies with private patients. Developing the ideal budget is crucial for both sites and sponsors. The authors point out that activities imposed on sites that are frequently not included in budgets developed by sponsors. As a long-term practice, this situation cannot be sustained. Study activities not reimbursed by sponsors increase site dissatisfaction and the willingness of the investigators to participate in future studies.

Next, Ellie Einolhayat and I present our experiences with site noncompliance and the need for onsite monitoring as a detection method. It's not a pretty picture. Some types of noncompliance cannot be detected by edit checks and other electronic data management tools. Despite the increase in automated and remote monitoring practices, the need for well-trained, smart monitors to visit sites will not (or at least, should not) disappear any time soon.

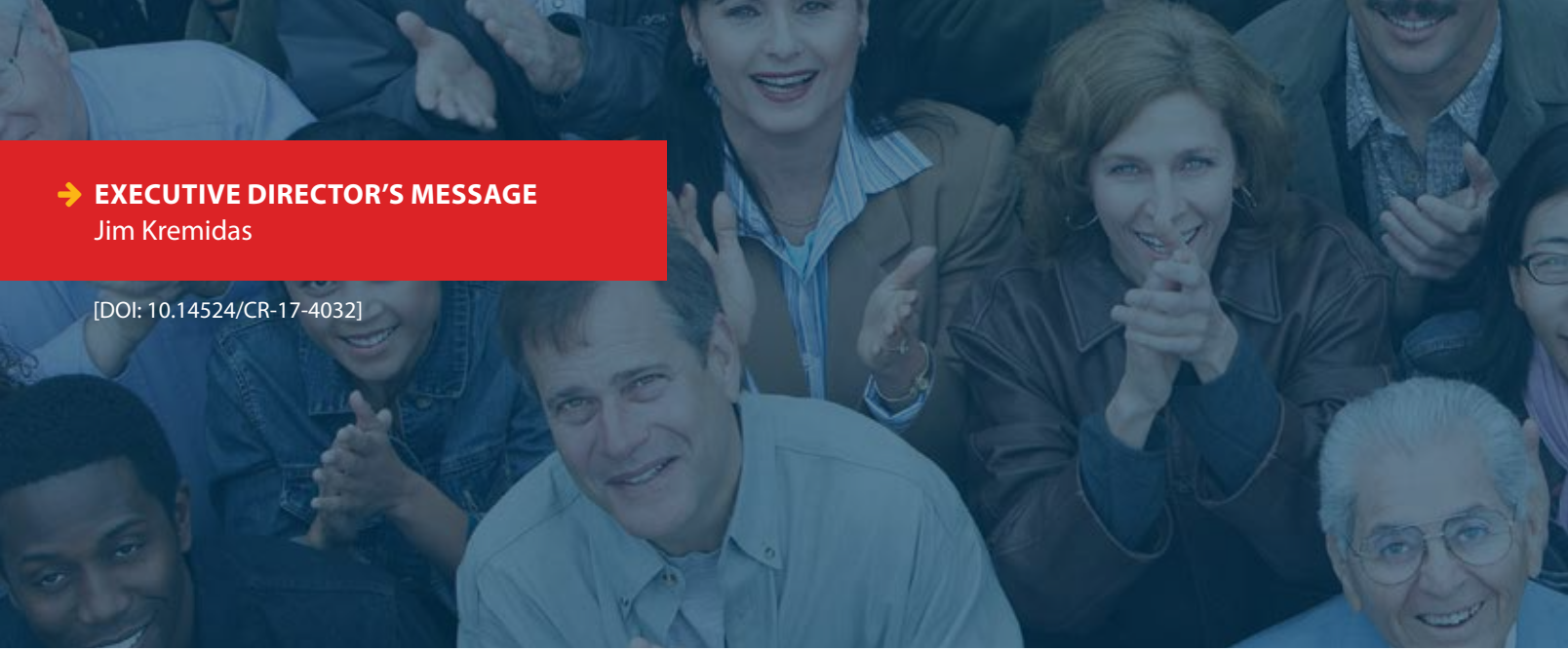
In his opinion piece, Kurt Mussina provides a keen, broad vision of the future of study sites. He sees compelling reasons for the development of standardized processes and easier-to-use electronic systems that are well-integrated at the site level. Working with multiple electronic systems that do not talk to each other when working for the same sponsor closely meets the definition of inefficiency. Industry standards are needed. The study site of the future must use its resources—time, staff, investigators, and patient volunteers—more efficiently. Hold on to your hats! The adoption of revolutionary changes to our operations is accelerating.

Raymond Nomizu discusses the current and future use of eSource at sites. The majority of study sites continue to use paper for source documentation in addition to, or instead of, electronic study records. These are inefficient, redundant practices which are prime candidates for automation. Part of the problem is the inability of most electronic systems to efficiently separate study-specific data and non-study information in a manner that is site-centric and sensitive to protecting personal health information. Even if a well-designed eSource system is available, there may not be good communication with other electronic systems (e.g., EDC) and the requirements of each sponsor may be different. The ideal eSource technology has the potential to significantly improve site and monitoring activities.

In the final article on our theme, Soumya Niranjan discusses the key attributes of well-developed site standard operating procedures (SOPs) from the point of view of a quality unit based at a large AMC. The U.S. Food and Drug Administration's key principles are emphasized: "Say what you do… Do what you say… Prove it… Improve it." The article describes the key SOPs that need to be developed and a set of basic guidelines for SOP development teams. There are many obvious benefits for having a standard set of rules at a single clinic and a common set of rules at large institutions with multiple clinics.

If small sites are vital players in the clinical research enterprise, our professional organization needs to encourage these experts to share their knowledge, experience, and challenges.

Jerry Stein, PhD, (summercreekc@gmail.com) is president of Summer Creek Consulting LLC and the 2017 Chair of the Editorial Advisory Board for ACRP.



EXECUTIVE DIRECTOR'S MESSAGE
Jim Kremidas

[DOI: 10.14524/CR-17-4032]

Doing Our Best for Those Who Deserve It

Let's be very clear. It's about the patients. Always.

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

Sometimes, in the midst of our hectic workdays and meeting the increasing demands on our time, it can be easy to forget why we do what we do.

I recently had the opportunity to discuss the importance of raising the standards of professionalism of the clinical research workforce with our colleagues at CenterWatch. After spelling out why ACRP believes it is so important to help drive this change, and giving some examples of how those new standards could improve workforce performance, we turned to the issue of public trust in the clinical research enterprise.

Thankfully, we are well beyond the days of terrible clinical trial scandals such as the Tuskegee syphilis experiment abomination decades ago. That said, we must continue to demonstrate clinical trial integrity and inspire more patients to join all of us on the shared journey toward treatments and cures.

We need to know that people conducting clinical research protect patients and demonstrate competency and the high standards patients deserve. Unfortunately, that's not always the case today.

The Logic of Standards

If you look at the training programs within sponsors and contract research organizations, there is a vast variance across them. There's really no way to know who is doing a good job and who isn't. The variance is even greater at the site level.

It's Business 101 to say that in any type of quality initiative, the greater the variance, the greater the probability of error. When we set a standard methodology and competency level for clinical researchers who come into the industry, it will reduce the variance and improve workforce quality.

The clinical trials industry would benefit—from a perception perspective, for starters—if patients could see proof that the investigator and the coordinator are not only trained "health" specialists, but also trained "research" specialists. As an industry, we need to find a way to demonstrate each has the appropriate competencies to do clinical research and keep the volunteers safe.

As we all know, the clinical practice of medicine is vastly different than conducting clinical research!

If you get a haircut, the barber cutting your hair must have a license. You need a license to drive a car. Restaurants must have licenses showing they are meeting basic health and sanitation standards. However, if you join a clinical trial, the study coordinator doesn't even need to be credentialed. Frankly, it's a shocking situation.

Properly vetted, a license demonstrates a certain level of competence. It can also inspire those around you.

When we set a standard methodology and competency level for clinical researchers who come into the industry, it will reduce the variance and improve workforce quality.

Monitoring Ourselves

We're not suggesting creating licenses for clinical researchers. However, if we want to improve the quality of research, which has all kinds of benefits in terms of delivering therapies to market faster, with fewer errors along the way, and with better patient safety results, we as an industry must come together to establish standards and monitor ourselves to make certain we have competent professionals conducting these critically important activities.

We are the ones closest to clinical trials. We should be the ones to establish and enforce standards. If we aren't careful, however, it leaves a tempting gap for the government to intervene and legislate something without significant industry input. That's not a good scenario for anyone.

Yes, it's a big challenge. Yes, it will require a paradigm shift in the way we operate. However, if we are going to fundamentally improve the quality of research, we need to come together and address this issue.

ACRP, working with members like you, plans to be at the center of this important movement to inspire and protect our patients. They deserve our very best.

And the Winners Are...

ACRP would like to thank all the members who took the time to complete the recent ACRP Member Engagement Survey. Six respondents were randomly chosen to receive $100 AMEX Gift Cards: Sofia Keim, Pamela Walker, Hiromi Oda, Diego Ramon Fua, Reema Nayef Haddadin, and Peter Odhiambo. It is with the participation of members like you that ACRP is moving forward, providing new benefits and value to membership, including innovative programs such as the ACRP Mentor Match, ACRP Fellowship, and the new ACRP-CP® certification. Your engagement allows us to pursue our goal of ensuring that clinical research is conducted ethically, responsibly, and professionally everywhere in the world. Please join us in congratulating our winners!

CHAIR'S MESSAGE
Jeff Kingsley, DO, MBA, CPI, FACRP

[DOI: 10.14524/CR-17-4035]

Thoughts on Tactics and Triumphs from the Front Lines of Clinical Research

As one considers that "tactics and triumphs from the front lines of clinical research" is the theme for this issue, one must admit that those "front lines" are pretty ugly. This battle isn't going well. Many of us who are fighting the good fight are getting hit hard. So, as someone with a deeply vested interest in study sites, what are my tactics and what triumphs have I seen?

Sponsors want enrollment to (at least) the contracted number of enrollments. Plus, they want high-quality data and very rapid timelines (e.g., for speed of startup, contract and budget negotiation, regulatory preparation, enrollment of the first patient, query resolution, and database lock), all the while also wanting sites to be responsive and pleasant to work with. I call this EQTCS. It stands for Enrollment, Quality, Timelines, and Customer Service.

Spelling it Out for Sites

The issue, however, is that sites are only contracted and compensated for enrollment—the "E" of the four things our customers want. We receive no compensation for quality, timelines, or customer service.

If we produce exceptional quality, we are paid nearly the same as the sites that all the monitors are talking about behind their backs. If we are the number one enrolling site, we are paid essentially the same as the site that produced merely one patient. If our timelines are the fastest on the trial, we are paid essentially the same as the site that was slowest.

We're simply paid for the data we hand over to the sponsor. Supposedly, we can lose future trial opportunities if our performance on those "Q," "T," and "CS" metrics is poor, but my experience tells me that our performance has to be really poor to receive that outcome.

The unfortunate reality is that, if you're producing high quality, great timelines, and exceptional customer service, that investment is entirely on you. You're not being compensated for it.

Owning Up to What We are Due

So, "tactics and triumphs." We need to help our industry to mature. We can, no longer, remain a commodity. We can, no longer, continue to receive no compensation for the high-quality work we provide. We need to promote a pay-for-performance model where the best of the best are compensated as such.

The fair market valuation model in contract and budget negotiation is dramatically flawed. It is literally a simple average of contracts and budgets from the nation. It is not adjusted for site size, capability, concurrently enrolling trials, staff size, investigator experience, historical results, or current results produced.

This model cannot pertain to the sites that are producing exceptional performance. More to the point, it cannot sustain the sites that are investing in high-level performance for our customers. Ultimately, without improvement in contract and budget terms, we'll be forced to retreat to merely above average, but not exceptional, performance.

So here's what I'm proposing: fight. Make a difference. Change how our industry behaves and performs.

Be All That You Can Be

Make your site the best of the best in terms of EQTCS, and then fight to get paid appropriately. Prove with objective metrics that you are not a commodity. Prove that you are clearly and objectively distinguished as a premium provider.

Interestingly—and unfortunately—this will lengthen your timeline metrics in contract and budget negotiation, but I don't see an alternative.

Put simply, the best of the best cannot be treated as commodities subject to fair market value determination that is an average including the worst of the worst.

Prove with objective metrics that you are not a commodity. Prove that you are clearly and objectively distinguished as a premium provider.

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

In Consideration of Certified Professionals

PI CORNER
Christine Senn, PhD, CCRC, CPI

[DOI: 10.14524/CR-17-4030]

I have the honor this month of writing both the "PI Corner" and the "CRC Perspective" columns. This may well be a first, and I remember the delight I felt when I became dual-certified as a Certified Clinical Research Coordinator (CCRC®) and a Certified Principal Investigator (CPI®).

Now a new opportunity presents itself—one that will make dual certification a lot easier for existing CCRCs, CPIs, and Certified Clinical Research Associates (CCRA®s), and that will be something entirely new for so many more professionals who are part of the clinical research enterprise.

New and…For You?

The new ACRP-CP® credential (ACRP Certified Professional) is awarded to clinical research professionals who meet eligibility requirements, demonstrate proficiency of specific knowledge and skills, and pass the standardized ACRP-CP Certification Exam. The ACRP-CP designation formally recognizes a professional who has met the professional standards set forth by the Academy of Clinical Research Professionals.

The ACRP-CP program provides professionals seeking the credibility and prestige of an ACRP credential with an alternative to ACRP's role-specific, specialized credentials for CRCs, CRAs, and PIs. All professionals involved in clinical studies—regardless of their roles, practice settings, or career stages—can earn the ACRP-CP credential, presuming they meet the eligibility requirements and pass the written ACRP-CP Certification Exam. The applicant should determine his/her own eligibility before submitting an application to the program.

You can learn more about the ACRP-CP credential by visiting the link on the right.

This is Who We Are

Why offer this new credential? Take a mental walk through your work day and consider how many people are working on clinical trials who are not CRCs, CRAs, or PIs; people like:

- Project managers at clinical research organizations
- Physicians, dentists, and ophthalmologists who write protocols
- Statisticians
- Research pharmacists
- Medical monitors
- Site administrators
- Quality assurance personnel
- Institutional review board/ethics committee members
- Budget and contract specialists
- Recruiters of patients who do not perform other CRC duties
- Regulatory affairs specialists
- Data managers
- Medical writers
- The people who create our software systems—electronic data capture, electronic source, electronic regulatory, and clinical trial management systems

It Takes a Village

They say it takes a village to raise a baby. I think that of the clinical trial industry: It takes a village to raise a trial.

A trial cannot happen with only a site's research coordinator and investigators. They would have no protocol, no ethics oversight, and no one to review data and interpret the results for the regulatory authorities. It is only fitting, then, that our industry's primary professional organization would offer a certification for everyone.

I hope to see many ACRP-CP titles on badges at the ACRP 2018 Meeting & Expo. The first exam window is from September 8 to October 7, with an application deadline of August 14, so spread the word while you still can. You should tell anyone who is not an ACRP member already that they will receive one free year of ACRP membership upon successful passing of the exam.

Consider This…

As we consider how poorly clinical trials and medicine in general fare in the news, it is time that we take pride in what we do and assert ourselves to the world as Certified Professionals in clinical research.

ACRP CERTIFIED PROFESSIONAL
ACRP-CP

You can learn more about the ACRP-CP credential by visiting www.acrpnet.org/professional development/certifications/acrp-cp-certification.

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

[DOI: 10.14524/CR-17-0012]

How Much Do I Ask For?

Budget Negotiation for Private Practices

PEER REVIEWED

Joanne Perry, BS;
Elise Levine, MAG

Successfully getting through the process of budget negotiation can be a daunting task. The contract research organization (CRO) wants to meet the sponsor's expectations. The sponsor is trying to keep costs down. The principal investigators (PIs) want to be reimbursed for their time. Essentially, it's negotiating your site's salary for the time frame of the trial.

In this article, we provide tips for making sure the site budget contact knows what to ask for during the negotiation period and gains confidence at doing so along the way. This is important because a lot of work goes into study start-up from the initial Confidential Disclosure Agreement, the Clinical Trial Agreement, the budget, and all the way through the regulatory paperwork. (This does not include preparation done within your site.)

Further, private practices vary in type between large organizations that utilize separate individuals to handle budget, regulatory, and contract issues to smaller practices where personnel may wear several hats. The following material will deal directly with budget contacts, and is more tailored to those with less experience, whether it be with clinical trials in general or with budget negotiation in particular.

Do Your Homework

Before negotiation even begins, the sponsor or CRO hopefully has provided you with a protocol, or at least a synopsis, of the proposed study. Read this thoroughly. Even if you don't participate in study activities, you need to know what is involved. Look for a Schedule of Procedures—a handy table that shows procedures to be performed on participants by visit.

Sometimes the budget template is taken directly from the Schedule of Procedures; or you may just be offered a per-visit fee. Sometimes the sponsor controls the budget negotiation and sometimes it's left up to the CRO. Whatever the manner in which the protocol's procedures and proposed fees are presented to you, site leaders want to know what is expected of their personnel and what kind of compensation will be received.

You may also need to read between the lines; sometimes a procedure is worded quite simply, but when translated into real life it is an hour-long process. For example, "12-lead ECG (electrocardiogram) performed" could be a line item. That can involve lead placement, capturing, re-testing, PI assessment, and transmission to a reading center.

Ask the PI and other study personnel about potential challenges and about any procedures that you do not understand. Also consider what the subjects are required to do—are certain visits easier on them (diary/medication drop-off) or are some more entailed (multiple visit days)?

What Can and Should I Ask For?

The look of a budget proposal can vary from sponsor to sponsor or from CRO to CRO. Sometimes the sponsor/CRO thinks a flat visit fee is acceptable with some ancillary costs. Try to get a breakdown per procedure of the budget. This will especially help in the future, when you're trying to compare past studies. It will also serve as a list of how much the study coordinators' and the doctor's times are worth (see Table 1 for tips on procedures and other key questions site leaders should ask sponsors during budget negotiations).[1]

Do not undervalue your time. Think about regular physician office visits and how those are billed. Typically, costs are fixed per procedure (i.e., vital signs, informed consent procedures), with the exception of investigator fees, coordinator fees, and subject reimbursement. These costs are then laid out for each visit per protocol. Make sure there is a listing for unscheduled visits (including subject reimbursement). Office staff or site personnel fees should be a reflection of time spent by that person on each visit. Some visits may require more time than others—like a screening or end-of-study visit.

Some sponsors/CROs allow an institution to charge an overhead fee; sometimes they do not. What can you do? Try building the overhead into your regular costs. Otherwise, many sites use a 20% overhead to account for the supplies not provided by the sponsor/CRO (e.g., paper and printing supplies) and general operating expenses (e.g., utilities, security, shared administrative expenses).

Please note: Read the protocol carefully for hidden supply costs. Sometimes it can be assumed that the site can invoice for small items like over-the-counter pain medications or ice. If this is not negotiated in advance, the sponsor can refuse to reimburse the site. For example, we had an issue with dry ice that the sponsor had just assumed was included in the visit fees. Depending on how many subjects you have and how many procedures require special supplies, the cost can add up quickly.

More on Paying Participants

Subject reimbursement is similar to site personnel fees, in that it should mirror how involved each visit is for the subject (including time spent in office and types of procedures done). This fee is vital to your study because enrollment may be affected by a low reimbursement rate. Also, once you start developing a database of subjects who return for multiple studies, they are likely to compare rates. Make sure to note who will handle the subject payments (you or the sponsor). You will also need to clarify if the subject stipends are included in your per-subject payment or as a separate item.

Also, there may be efficient and innovative ways to pay your participants. Many sites are using reloadable "debit" cards that can make your bookkeeper's life easier, but come with associated processing/material costs. These cards also make quick work of issuing tax forms for patients who will exceed the Internal Revenue Service (IRS) threshold for payments and must be issued 1099s.

Subjects who are screened but not enrolled are typically classified as screen failures or randomization failures. Sites might be paid a flat fee for all the anticipated screen failures, regardless of the number of subjects actually screened.

Again, consider what work goes into screening and make sure you are compensated for your time. It is in the sponsor's best interest to put a cap on payment for screen failures—usually as a set number or a ratio to enrolled subjects. This system is intended to ensure the sites are taking the time to "pre-screen" these subjects and are choosing their candidates wisely. However, the protocol may suggest a high screen fail rate based on difficult inclusion and exclusion criteria. If you anticipate this, make sure the cap is set high enough.

Ancillary Costs and Other Considerations

As far as ancillary costs go, the start-up fee may be the most important. This covers your site's fees from the time you sign the initial contract until you consent the first subject. This often includes travel time to meetings; it certainly covers initiation visits and any other pre-study meetings.

Occasionally, the meeting expenses are a separate item, but these expenses (beyond paid time) usually are handled directly by the sponsor and the meeting planners. The start-up fee may be the only payment you receive until the study is well under way (be sure to note the payment time in the contract). So, if you consider the overhead expenses and the subject compensation (if your site handles this directly), you may be at a negative balance at the beginning of the study.

Verify with your accountant or business office how monies are allocated. It may be necessary for the practice to "loan" money to the study cost centers to cover subject payment until the monitoring visits occur and the source data are verified.

Be sure and look at when and how often payments will be sent to the site. Payment schedules are usually included in the CTA; just be sure to note how often you will receive payments and compare that to the visit schedules.

If you only see subjects every few months or even less often, a quarterly payment may be acceptable. However, if the study visits end within

Site leaders want to know what is expected of their personnel and what kind of compensation will be received. You may need to read between the lines; sometimes a procedure is worded quite simply, but when translated into real life it is an hour-long process.

Some sponsors/CROs allow an institution to charge an overhead fee; sometimes they do not. What can you do? Try building the overhead into your regular costs.

a quarter and you expect high enrollment, it might be best to try to get monthly payments. If you are responsible for subject payments, you may be paying those out of pocket before you receive compensation. Also, note holdback (may be 10%) and when the last payment is due so there are no surprises.

Other ancillary costs may include archiving fees for keeping records for at least two years following U.S. Food and Drug Administration (FDA) approval of the drug, or for two years after FDA notification of discontinuation of a drug investigation.[2] However, sponsors may require a longer retention period in the contract. Also consider re-consenting fees in your budget, since sponsors may say they have no plans to amend the protocol, but no one can predict the future.

Plan ahead. If your subjects have a long visit, they may require food, so try to include that in the budget as well. Or your site may have fees involving transportation, parking, or any other predictable considerations—don't forget to add those. Lastly, if a sponsor/CRO is prone to sponsor audits or if there is a high likelihood of this (or even an FDA audit), consider asking for compensation. These audits take a lot of time, especially if the study is closed and you are trying to gather records.

It is important to stay on top of the legal status of your sponsors (even when studies close), as many small pharmaceutical start-ups may be purchased by larger companies upon FDA approval. There is no need to warehouse records indefinitely, and by knowing who to contact you can receive permissions as to destruction.

Legal Obligations

Although most of the legal issues will be addressed in the contract itself, there are a several general principles to remember about the terms you've agreed upon in the budget. The biggest thing to remember is if you require compensation for any services or items not specified in the budget, an amendment to the contract/budget must be made before payment can be sent. Sponsors generally do not like to amend contracts unless it is on their own terms so you may be out of luck if extra expenses are found.

Also, consider your obligations for subject payments. The informed consent form (ICF) states the subject compensation. If your payment records do not match the ICF and the budget, this is a red flag for not only the sponsor, but possibly for the FDA.

You also have obligations to the IRS regarding subject compensation. As per IRS instructions,[3] "other income" of $600 or more during a year must be reported with a 1099-MISC. That means you should have the subject fill out a W-9 so you have all of the information needed to file the 1099. Consider using a payment service for subject compensation; the reporting options will make this process much easier.

Communication with the CRO or Sponsor

Now that you know what to expect and how to prepare, we'll go over communicating with the start-up team. Once your site has been selected for a study, you may have three different contacts beyond the monitoring team—these are budget, contract, and regulatory personnel. Some companies may combine teams, and it will be up to your site to set guidelines on your contacts.

Our site allows for the steps involved in study start-up to be completed concurrently. Some sites, however, will not even allow the regulatory process

TABLE 1:
Sponsor/Site Contract Negotiations—Key Questions Sites Should Ask

STUDY PROCEDURES:

- Do the proposed fees adequately compensate the site for personnel time and resources?
- Do the proposed fees cover non-routine activities (e.g., investigator meeting, training time, regulatory audits, data entry/data corrections, adverse event management)?
- Does the proposed fee schedule address protocol amendments and re-consent activities?
- Does the proposed compensation schedule cover long-term costs (record storage expenses, changes in sponsor ownership)?
- Does the contract provide for institutional overhead expenses?

STUDY RECRUITMENT:

- Is the proposed subject compensation schedule adequate?
- How does the proposed level of subject compensation compare to other studies of a similar nature?
- How will the site be compensated for screen failures?

PAYMENT SCHEDULE:

- How does the anticipated payment schedule match the site's anticipated expenditure schedule?

Source: Adapted from The Center for Cancer Care and Research of St. Louis, Mo.[1]

to begin (including development of the investigator files) until the contract is finalized. Such sites may concede a few items asked for by sponsors, but consider that "good faith" cooperation. If you are just starting out or if your study contacts seem irregular, you may want to push for the contract first.

Conversely in competitive enrollment, the faster start-up happens, the faster your site can be approved to start enrolling. Our site has not had issues where negotiations fell apart in the start-up process, so we are content to begin developing regulatory documents at the same time. However, subject compensation is usually included in the institutional review board submission, so technically you cannot complete that without signing the contract/budget.

How quick can you turn this around? This is usually asked in feasibility/pre-trial questionnaires. If you have a committee to work with, these timelines may already be set. Otherwise, it depends on your site's team members to meet and review the numbers.

Our site prefers to send back responses as soon as possible—it's better to be waiting on responses from the sponsor/CRO than holding up the process on your end. Generally, we don't want sponsor queries to sit in our inbox for more than a week; the sponsor may be less inclined to agree with your changes if left alone for long.

Our site has a small team for budget negotiations, but you may have many people who want to review everything. Still, try to be timely with your responses to sponsors. In addition, try to think ahead about what the sponsor's rejoinder will be. Did you ask high enough so that, if the sponsor returns with slightly lower amounts, that is acceptable? Did you ask for unreasonably high amounts? Be prepared to re-negotiate based on whatever counter-offer is returned.

Standing Your Ground or Settling?

Speaking of the sponsor response, your budget team needs to consider if and for what you would settle. As in any monetary endeavor, think about a list of needs and wants. If you need a certain amount for medical exams, place that high up on the list. If archiving is not a large cost, put that lower on the list.

Discuss which items necessitate standing your ground. For our site, the biggest emphasis is often placed on subject compensation. A recent budget came across our desk that suggested subject payments of 50% of our usual schedule for that type of study. We told them this would adversely affect subject enrollment, and that we could not absolutely guarantee we will enroll at our usual standards.

Often, a little explanation will go a long way.[4] Also think of the big picture (e.g., what is the overall visit compensation, and is that more agreeable in comparison to the procedural costs?).

Building Your Future Budget Templates

Once your site team has gained experience through a few studies, especially those evaluating similar indications or procedures, start making your budget template. Reflect on each line item to see if the costs were undervalued for the time and effort put forth. Assess the overall compensation to see if past payments were fair. Remember those individual fees and which best apply to your site. Then, when you receive a new budget, you can compare your rate schedule to the proposal; it's a bonus, of course, if the sponsor's numbers are higher. If not, then you can back up your negotiation with your prior experience.

Conclusion

Sites have wide variations in how they operate, but preparation is the most important key to any type of research practice. Obviously, site compensation is just like employee salaries, in that they aren't usually shared amongst private practices, so it's up to site leaders to establish their own guidelines.

Consider the value of time and effort on behalf of the site team as well as the subjects participating. Think about ancillary costs that may not occur to the sponsor. Be respectful of timelines and your responsibilities with start-up work. Lastly, be smart about your negotiation tactics.

When the study gets under way, everyone involved at your site wants to feel they are being compensated for what they are worth.

Once your site team has gained experience through a few studies, especially those evaluating similar indications or procedures, start making your budget template. Reflect on each line item to see if the costs were undervalued for the time and effort put forth. Assess the overall compensation to see if past payments were fair.

References

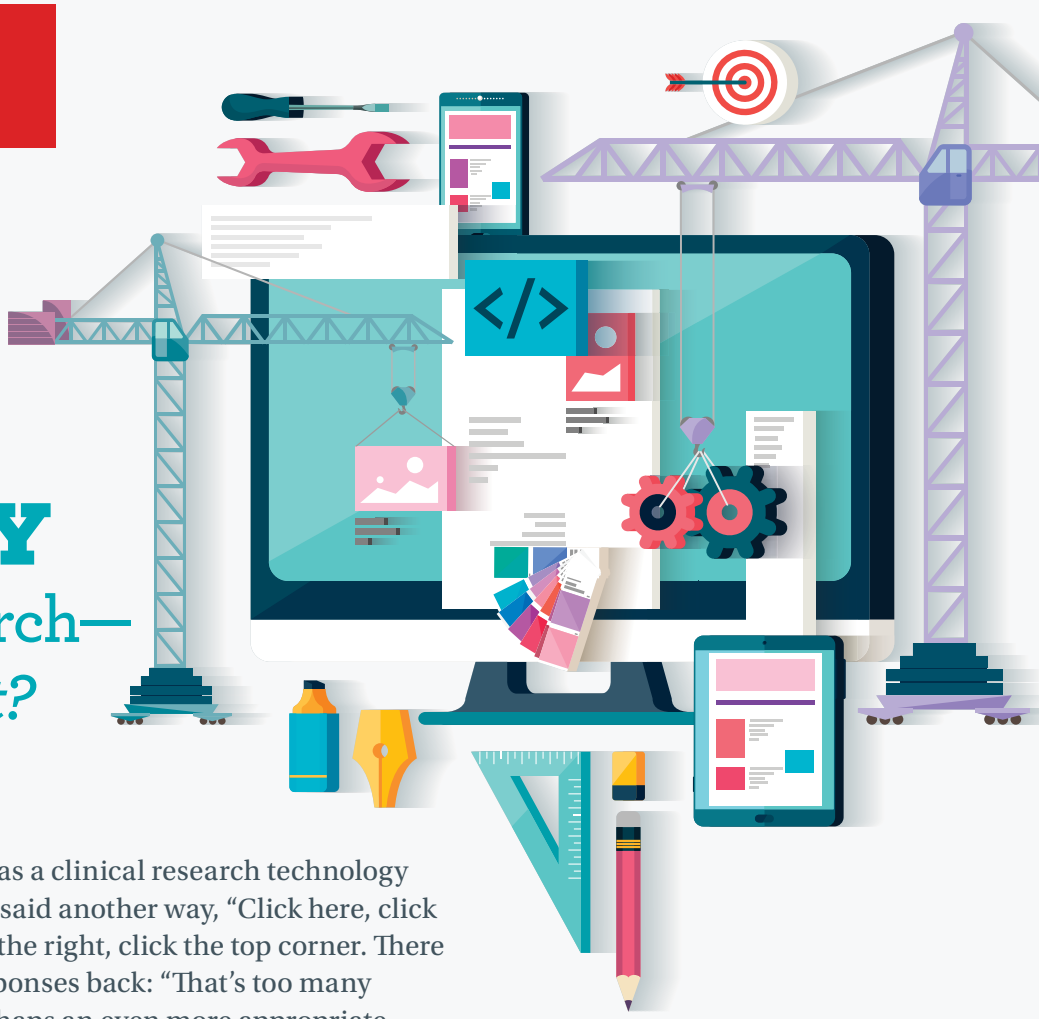
1. The Center for Cancer Care and Research of St. Louis, Mo. 2007. Developing an investigator site budget for clinical trials. *J Oncol Practice* 3(2):94–7. http://ascopubs.org/doi/full/10.1200/jop.0724604
2. *Code of Federal Regulations*. Title 21, Volume 5. Revised as of April 1, 2016. Part 312 (Investigational New Drug Application) Subpart D (Responsibilities of Sponsors and Investigators), Sec. 312.62 (Investigator Recordkeeping and Record Retention) [21 CFR § 312.62]. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62
3. Department of the Treasury/Internal Revenue Service. 2017. Instructions for Form 1099-MISC. https://www.irs.gov/pub/irs-pdf/i1099msc.pdf
4. Parke J. 2013. Negotiating effective clinical trial agreements and study budgets with research sites. *App Clin Trials* 22(4). http://www.appliedclinicaltrialsonline.com/negotiating-effective-clinical-trial-agreements-and-study-budgets-research-sites?id=&pageID=1&sk=&date=

Joanne Perry, BS, (joanne@northvalleyeye.net) is a clinical research manager with North Valley Eye Medical Group.

Elise Levine, MAG, (elise@northvalleyeye.net) is administrator and director of clinical research with North Valley Eye Medical Group.

Paula Smailes, RN, MSN, CCRC, CCRP

[DOI: 10.14524/CR-17-4027]



USABILITY in Clinical Research—*Are We There Yet?*

I often hear myself saying in my role as a clinical research technology educator, "It's a deep link." Or maybe said another way, "Click here, click there, click over on that side, click on the right, click the top corner. There it is!" In turn, I get a whole slew of responses back: "That's too many clicks!" or "Where do I find that?" Perhaps an even more appropriate response, "How will I remember this?"

As technology becomes a necessary entity in our clinical research work environments, maintaining the quality of the end-user's experience in putting these tools to work has become a priority.

Everyone comes with different learning curves that may impact his or her relationship with technology, but the ease of use that technology provides also contributes to the experience. If it works, we love it. If it doesn't, we really hate it.

As technology becomes a necessary entity in our clinical research work environments, maintaining the quality of the end-user's experience in putting these tools to work has become a priority. Technology serves as a convenient means to execute our daily workflows, but what may also happen is an inconvenience that hinders productivity. An analysis of the human-computer interaction is important for system success.

Usability

There is a science to this clicking and navigating through technology that has been studied in clinical research environments. The idea is to create an improved end-user experience that facilitates system workflows that are understandable and user friendly.

Usability, simply stated, is the degree to which technological devices and systems can be used. The International Organization for Standardization (creator of the ISO standards applied in many industries) has established three goals for usability:

- **Effectiveness:** How accurately and completely the user achieved the goals in specific environments;
- **Efficiency:** The resources expended in relation to the accuracy and completeness of the goals achieved; and
- **Satisfaction:** The perception of comfort and acceptability that users and other people associate with the product or work system.[1]

Translating to Clinical Research

The use of technology across the clinical research enterprise is vast. How research teams manage technology is crucial for study and business success. We see it in areas such as electronic data capture (EDC), social media, recruitment search engines, and electronic medical records, just to name a few.

The importance of usability has been studied in clinical research, and the results are significant to the ergonomics of our workplace. One example is data collection, which can be accomplished in a variety of ways in clinical research. When it comes to usability for EDC, it has been found that handheld computers may double the duration of data entry and increase the risk of typing errors and missing data.[2]

Usability considerations also expand to research participants, who may be savvy users of technology or have limited to no experience. For this reason, there may be cause for concern. Clinical trials with patient-facing technologies may need to have research staff spend considerable time educating participants if usability or their comfort with the technology is low.

One example may be how our potential subjects navigate technology as they search for studies to join. A team of researchers at Northeastern University looked at search engines geared toward patient recruitment, and found that low health literacy contributed to challenges using clinical trial search engines, along with unusable keyword-based searches that were prone to issues with misspellings.[3] The team suggests using an autocorrect feature for spelling, to aid the user who may be unable to spell complicated diagnoses.

Usability Testing

Before technology is implemented in clinical research, it should undergo usability testing. Testing will be able to reveal how well the technology works, and how satisfied the end-user is who uses it.

Usability testing is a subset of the field of human-computer interaction that involves applied psychology, computer science, and information science.[4] A usability assessment could be focused on one or several aspects of system usage, such as what tasks are involved for the user; does the user understand how the system works; what are the end-users' preferences of the methods and technologies used in the system; do changes intended to improve the usability of a feature or system actually do so; and do the added changes achieve a satisfactory level of usability, or do problems remain that need to be addressed?[5]

The use of technology across the clinical research enterprise is vast. How research teams manage technology is crucial for study and business success.

The importance of usability testing in clinical research should not be ignored. In the usability testing of three clinical trials management systems, Byungsuk found that ease of use was more valued than functionality.[6]

I participated in usability testing for a clinical research system earlier this year that may lead to improved clinical research applications. I was placed in front of a computer with an instruction sheet and asked to carry out the tasks, while speaking my thoughts out loud for what was good and not good about the system to an observer who kept notes. I had four scenarios total, and my feedback was to be added to others who had undergone this experience. Those who are experts in the field can give important insight through usability testing that can impact users across the enterprise.

Conclusion

More attention should be paid to the concept of usability in clinical research. How users across the clinical research enterprise interact with technology will ultimately impact study success.

Next time you execute workflows with technology, ask yourself if you are efficient, effective, and satisfied with the experience. If you find you aren't, then consider how you can be part of the solution to making that system better.

References

1. Health Information Management Systems Society. 2011. *Promoting Usability in Health Organizations: Initial Steps and Progress toward a Healthcare Usability Maturity Model*. HIMSS: Chicago, Ill.
2. Haller G, Haller DM, Courvoisier DS, Lovis C. 2009. Handheld vs. laptop computers for electronic data collection in clinical research: a crossover randomized trial. *J Am Med Inform Assoc* 16(5):651–9. doi: 10.1197/jamia.M3041
3. Dina U, Bickmore T, Barr B, Paasche-Orlow, M. 2014. Health literacy and usability of clinical trial search engines. *J Hlth Comm* 19:190–204. https://www.ncbi.nlm.nih.gov/pubmed/25315593
4. Staggers N. 2002. Usability concepts and clinical computing. *Nursing Informatics: Where Caring and Technology Meet. 3rd ed.* Ball M, Hannah K, Newbold S, Douglas J, eds. Springer: New York; 95–109.
5. Kushniruk AW, Patel VL, Cimino JJ. 1997. Usability testing in medical informatics: cognitive approaches to evaluation of information systems and user interfaces. *Proc AMIA Ann Fall Symp* 218–22.
6. Choi B, Drozdetski S, Hackett M, Lu C, Rottenberg C, Yu L, Clauw D. 2005. Usability comparison of three clinical trial management systems. *Proc AMIA Ann Symp* 921.

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

[DOI: 10.14524/CR-17-0020]

The Hidden Value of **Onsite Monitoring**

PEER REVIEWED
Jerry Stein, PhD
Elham Einolhayat, RN

Electronic data capture (EDC), central monitoring, and risk-based monitoring (RBM) have been disruptive to the entire clinical research enterprise. These new technologies and processes offer the potential to increase efficiency while reducing onsite monitoring and data management costs. Sponsors and contract research organizations (CROs) are crafting standard operating procedures (SOPs) which will allow these changes to occur in their organizations, and they have been discussed extensively at professional meetings and in publications

Rarely discussed, however, is the role onsite monitoring plays in detecting high-level problems with the design of investigational test products, with the clinical protocol, and with site noncompliance or fraud.

Onsite monitoring is often responsible for identifying high-level issues that impact the outcome of entire projects, and which often are only discussed behind closed doors.

Given recent and ongoing developments in monitoring practices, is traditional study site monitoring an historical anachronism? Would it be better if onsite monitoring were only applied to a few unique situations? These provocative questions are being discussed throughout the clinical trial enterprise. Indeed, with the growing adoption of EDC in conjunction with the increase in computer-assisted centralized monitoring and RBM processes, one might logically raise the question whether onsite monitoring should be significantly scaled back or totally abandoned.

Our view is that clinical monitoring operations have been significantly disrupted by the acceptance of these new and partially automated processes by regulatory bodies and their growing adoption by sponsors, CROs, and sites. In this article, we describe aspects of the overall topic that are rarely discussed, with special focus on the risks that accompany these trends and the underestimated value provided by onsite monitoring.

Purpose of Traditional Monitoring

Traditionally, a significant proportion of onsite monitoring has been devoted to ensuring that central site study files and source documentation are in place to safeguard human rights and verifying that all study information is accurate and properly documented.[1] Checking every datapoint in the sponsor's database against patient charts and other records is a major activity of traditional monitoring models representing a large proportion of the work done during most site visits.

In addition, monitors perform verification and accountability of study drugs or devices to confirm protocol adherence. Ultimate goals include confirming that the study was conducted per protocol, gaining an increased assurance that the safety and human rights of subjects were protected, and ensuring a diminished likelihood that auditors will find deficiencies in the study conduct.

Evolution of the New Processes

Given the intentions stated above, what are the key advantages offered by the new processes and technologies impacting monitoring styles? The Clinical Trials Transformation Initiative (CTTI) has addressed many of these factors with one key conclusion from this source being that the amount of effort required in traditional onsite monitoring did not justify the resources applied to this activity. Part of this conclusion was based on economic and statistical arguments. Specifically, it was asserted that the occasional random error that occurs during a large clinical study should not make an appreciable or statistical significant difference to bottom line determinations of safety and efficacy.[2–5]

These conclusions, along with public comment, were incorporated into the 2011 U.S. Food and Drug Administration (FDA) guidance on RBM.[6,7] The guidance states that there are "a variety of acceptable approaches to fulfill monitoring responsibilities," and that monitoring should be focused on critical, higher risk clinical sites and data that impact subject safety and data reliability. Also, it emphasizes that monitoring plans should be dynamic and reflect the discovery of new information.

The implications of the guidance on monitoring, as well as those of similar International Council for Harmonization and International Organization for Standardization documents, have been published extensively in this journal and elsewhere.[1,8–17] Sponsors are slowly implementing changes that have the potential to significantly impact long-held practices, and monitoring organizations are carefully adjusting their SOPs and (hopefully) watching out for unintended consequences.

We are in the midst of a "formative" period—one in which sponsor/CRO processes can be influenced; therefore, before the new monitoring practices become standardized across the industry, it is important to raise concerns, some of which have hardly ever been discussed or published.

This new paradigm envisions a monitoring and database validation process with a higher level of efficiency and reduced cost, as well as the following advantages:

- If site personnel are responsible for entering data directly into electronic systems, transcription errors will be reduced significantly, compared to the process of using paper case report forms (CRFs) and other hard copy study documents as source documentation.
- Out of range or inconsistent data values can be proactively rejected prior to data being saved, as they would be identified by automated, pre-identified edit checks and/or centralized data reviews.

Since clinical monitoring is one of the most time-consuming and expensive product development activities, even a small change in the amount of onsite monitoring will have a large impact on product development costs.

- Essential study documents can be stored in central repositories that provide site personnel, monitors, and sponsors with remote electronic access.

Since clinical monitoring is one of the most time-consuming and expensive product development activities, even a small change in the amount of onsite monitoring will have a large impact on product development costs.[1,18,19] Monitors will have more time to concentrate on problematic subjects or entire sites identified remotely by the new systems. On a higher level, RBM and properly applied centralized monitoring has the potential to identify anomalies at both the site and study levels that might not be apparent without automated processes.

Benefit of Onsite Monitoring

While the new processes have several important advantages, those already provided by traditional onsite monitoring models must be addressed. The following sections expound on these advantages, which are summarized in Table 1.

PROBLEMS TO BE DISCRETE ABOUT

Onsite monitoring is often responsible for identifying high-level issues that impact the outcome of entire projects, and which often are only discussed behind closed doors. Frequently, these tales concern inadvertent noncompliance, known but uncorrected errors, or outright fraud by site personnel. These incidents are not often discussed publicly for obvious reasons, as the reputations of sponsors, clinical research associates (CRAs), and sites are at risk.

A false accusation or the promulgation of a rumor can have significant consequences on organizations and individuals. There are often moral, legal, and financial implications, including delays in or rejections of regulatory marketing approvals when data from a single site are excluded.

For example, if a study site's data are suspect, a company may elect to present two analyses of the study results—one with the suspect data included and one without. Preparation of two analyses requires a significant amount of additional resources. There is also the possibility that the smaller database will have an insufficient number of study subjects to meet *a priori* statistical objectives. In this case, the sponsor may be forced to re-open enrollment to recruit additional subjects for meeting the needs of statistical analyses.

PROBLEMS DIFFICULT TO DETECT

Seasoned monitors often identify significant issues that can never be detected in databases. Three problems are particularly difficult to detect from a distance:

- First, there can be problems encountered by subjects or site personnel when attempting to use investigational products. Ease of use, malfunctions, or other investigational product–related difficulties encountered by end-users are often important factors not sufficiently captured in electronic or paper questionnaires. Crafting the perfect CRF or patient-reported outcome questionnaire is often very difficult until the investigational product has been used by hundreds of subjects. In the case of rare events (e.g., 0.01% incidence), an observation might not occur during the entire clinical development program. Basically, you don't know what you don't know. If a drug is too hard to mix or apply, or if a device is too difficult to operate, compliance can be significantly impacted. Perhaps the greater risk is that poor product design will be tolerated in the clinical study setting, but will be rejected once the product is approved, released, and marketed.

TABLE 1: Relative Effectiveness of Monitoring Technique

Type of Issue	Relative Effectiveness (★ = minimum; ★★★★★ = maximum)	
	Electronic Data Capture/ Central Monitoring/ Risk-Based Monitoring	Traditional Onsite Monitoring
Inconsistencies within the database	★★★★★	★★★
Inconsistences between source documents, study site trial master file, and database	★★★★	★★★
Noncompliance by end-user conduct	★★	★★★
Noncompliance by site personnel	★★	★★★★
Detecting problems with the protocol or investigational product	★★★	★★★★
Clinical supply accountability	★★★★★	★★★

- Ironically, the second type of problem that is not easily detected remotely involves site personnel and study participants dutifully executing the procedures as described in the protocol. The number of procedures mandated in each protocol has increased, and study visits have become longer and more complicated.[1,18] This has several potential effects, including how, for study subjects and site personnel, excessively long study visits can lead to fatigue and inaccuracies in both objective and subject test results. The duration of office visits can make recruitment more difficult and inadvertently impact the type of subjects who elect to enroll. For the study monitors, more errors lead to excessive time devoted to reconciling databases with source documentation, which poses an unnecessary distraction. An increase in data variability, especially if concentrated in one of the treatment groups, makes it more difficult for sponsors to detect important safety and efficacy signals. Onsite monitoring is a very effective method for recognizing that study visits are too long or procedures too complex.
- The third type of issue that is difficult to identify from a distance covers insufficient investigator oversight, fraud, and noncompliance. This includes confirmation that the principal investigator (PI) understands and is properly carrying out his/her responsibilities. The same applies to sub-investigators, study coordinators, and other site personnel. Too many monitoring visits (and FDA inspections) reveal that PIs have inappropriately delegated key activities to site personnel or not maintained active control. These important noncompliance incidents can be detected by the good detective work provided by experienced monitors.

AN INSPECTOR CALLS…

The FDA's website[20] has many examples of issues discovered at study sites by their inspectors; however, these reports have been heavily edited and do not emphasize the impact on study sponsors. Here are some real-life examples from our personal experiences that may help communicate these concerns:

- Several years ago, we learned about a study that seemed to be progressing quite nicely based on the receipt of CRFs and periodic remote contact. The PI was conducting the study at two urban offices. Enrollment had progressed reasonably well and the number of database errors was proportionately appropriate. While the source documentation matched the CRFs, a routine monitoring visit uncovered some serious concerns. An examination of the front desk calendar revealed that the PI, the only individual authorized to perform several key medical procedures, was at the wrong office on several study visit days. The CRF visit days did not match the front desk calendars. This was a significant deviation that invalidated a significant number of datapoints and raised concerns about all study data. Ultimately, the site's participation in the study was prematurely terminated.
- In another case, a six-month study had progressed well with a good start-up visit followed by good enrollment. Overall, the responsiveness of the site to phone calls and other contacts with the sponsor was outstanding. CRFs were unremarkable. At the Month-3 milestone, a routine monitoring visit uncovered a significant problem. The study coordinator pulled the monitor aside and demonstrated that the investigational medical device malfunctioned when the instructions for use were followed. Specifically, the combination of two investigational products led to excessive foaming that spilled the investigational solution out of the designated vial and left it puddled on the table. This had not been previously reported to the sponsor because there was no place on the CRF to report this type of event, and the site had not reported it in any communication to the sponsor. The study was terminated early and the project abandoned.
- In another occurrence, a large study was close to meeting its enrollment goal when sponsor audits revealed that many adverse events and serious adverse events found in source documentation had no follow-up documentation and/or had not been reported. This caused a significant delay in the study timelines and raised many quality issues that had to be ironed out.

Our view is that clinical monitoring operations have been significantly disrupted by the acceptance of these new and partially automated processes by regulatory bodies and their growing adoption by sponsors, CROs, and sites.

We are in the midst of a "formative" period—one in which sponsor/CRO processes can be influenced; therefore, before the new monitoring practices become standardized across the industry, it is important to raise concerns, some of which are hardly ever discussed or published.

- Elsewhere, six weeks after institutional review board (IRB) approval and receipt of investigational products, an onsite visit revealed that no one had enrolled in a study despite frequent dialog with the site personnel claiming that 12 subjects had been enrolled and randomized (Note: The new processes cannot totally eliminate this problem, since the availability of an EDC system does not guarantee timely data entry by site personnel).
- Then there was the case in which an onsite visit revealed that the duration and complexity of the office exams was excessive—twice as long as planned—and may have led to excess fatigue and data variability.
- An onsite visit regarding another study revealed that site personnel had prepared their own set of in-office written instructions for site personnel and subjects that had not been vetted by the IRB or the sponsor.
- During an onsite visit elsewhere, it was noted that a site staff member with many years of clinical research experience used pencil to document all study data. Per the study coordinator, this would allow her to erase "mistakes" and write over the correct data with a pen.

Remote communication processes between the site and the sponsor/CRO that would detect these types of incidents are often not in place, or are inadequate. The same can be said with cross-checks within electronic databases. In addition, once these deviations are detected, the processes used within sponsor or CRO organizations to manage these events are of potential concern.

Sponsor/CRO organizations typically have well-developed SOPs that specify that noncompliance or suspected fraud must be immediately reported to management and quality assurance departments. Such SOPs mandate many well-defined steps to protect all parties: the monitor, the sponsor, the site, and the subject/public good. However, critics can easily identify conflict of interest factors.

These study site incidents are often complex and rarely receive external visibility due to confidentiality and liability concerns. Feedback to sites suspected of significant noncompliance is often kept intentionally vague. Perhaps more importantly, bad apples often remain in the barrel. The original sponsor may not use the site again, but a competitor may. Confidentiality concerns and the competitive environment are often barriers to the free exchange of this information.

Best Practices

What is the ideal? What are best practices? The potential for improving our processing using EDC, central monitoring, and RBM is extraordinary. It is a significant modernization that needs to move forward. The clinical research enterprise needs to leverage the use of automation to improve efficiency and reduce costs.

However, practical experience accrued from years of traditional monitoring indicates that these new technologies and processes only make sense when used in conjunction with monitoring and data management plans that allow for customization. The customization needs to address:

1. the challenges presented by each specific protocol (e.g., complexity; development stage; project criticality; safety risk);
2. the experience and skill of the site personnel (e.g., certified personnel or novice);
3. the experience of the sponsor or the sponsor/CRO's organization with this type of study;
4. the experience of the specific personnel assigned by the sponsor/CRO to the project; and
5. any new evidence of major noncompliance found during the course of the study.

Frequent onsite monitoring with 100% source data verification should be required at all sites unless evidence is presented to support another approach. Essentially, clinical study managers should build their plans by assuming that noncompliance will occur if the site were allowed to operate without intense intervention (guilty unless proven innocent). Less intensive onsite monitoring should occur only when it is justified, and all monitoring plans periodically reviewed based on available evidence.

Finally, the quality and frequency of site visits needs to be addressed. Quality is highly dependent on the detective work provided by CRAs who have a strong foundation of extensive training and experience. ACRP's Certified Clinical Research Associate (CCRA®) program has recognized the requisite skill sets, and most organizations impose a field-training element.

These study site incidents are often complex and rarely receive external visibility due to confidentiality and liability concerns. Feedback to sites suspected of significant noncompliance is often kept intentionally vague. Perhaps more importantly, bad apples often remain in the barrel.

The full utilization of a CRA's skills requires a good relationship between the monitor and the site personnel; however, the concern amongst many clinical research professionals is that the new monitoring models will reduce the number of site visits and contact time with key site personnel.[13,21] Success building professional relationships may be adversely impacted if visits are inappropriately reduced.

Many of the noncompliance incidents described above were uncovered when CRAs asked questions that were not specified in monitoring plans. The discoveries relied on personal relationships developed over time. Sponsors and CROs should be concerned that the pressure to reduce onsite monitoring time combined with high turnover rate amongst monitors will spur unwelcome consequences in product development.

Summary and Conclusions

The potential for efficiency improvements using the new data monitoring tools and processes is significant. There is an opportunity to significantly reduce development costs and improve data quality. However, the clinical research literature has rarely focused on the problems that cannot be detected without the onsite presence of a skilled monitor.

While the safety risk to individual subjects or the risk to the project may appear to be small, the hidden, underestimated value provided by onsite monitoring is significant. Companies should seek the appropriate balance between remote and onsite monitoring that will take advantages of new technologies while maintaining the benefits provided by site visits.

Jerry Stein, PhD, (summercreekc@gmail.com) is president of Summer Creek Consulting in Fort Worth, Texas, and the 2017 chair of the ACRP Editorial Advisory Board.

Elham Einolhayat, RN, (Ellie@lexitaspharma.com) is a clinical research associate with Lexitas Pharma Services, Inc. in Durham, N.C.

References

1. Kulkarni N, Bhatt A, Dalal J. 2016. Challenges and training needs for clinical research associates—a survey. *Clin Res* 30(2):28–33.
2. Clinical Trial Transformation Initiative. June 2008 Conference (Washington, D.C.).
3. Baigent C, Harrell FE, Buyse M, Emberson JR, Altman DG. 2008. Ensuring trial validity by data assurance and diversification of monitoring methods. *Clin Trials* 5:49–55.
4. Einstein EL, Collins R, Cracknell BS, Podesta O, Reid ED, Sandercock P, Shakhov Y, Terrin ML, Sellers MA, Califf RM, Granger CB, Diaz R. 2008. Sensible approaches for reducing clinical trials costs. *Clin Trials* 5:75–84.
5. Einstein EL, Lemons PW, Tardiff BE, Schulman KA, Jolly MK, Califf RM. 2005. Reducing the costs of phase III cardiovascular clinical trials. *Am Heart J* 149(3):482–8.
6. U.S. Food and Drug Administration. 2011. Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (Draft Guidance). https://www.fda.gov/downloads/scienceResearch/SpecialTopics/criticalPathInitiative/UCM277529.pdf
7. U.S. Food and Drug Administration. 2013. Guidance for Industry: Oversight of Clinical Investigations—A Risked-Based Approach to Monitoring. https://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf
8. Patkar S, Dalal J. 2016. Challenges to the implementation of risk-based monitoring. *Clin Res* 30(3):57–60.
9. Castle C, Bell A, Gwirtz P. 2016. The rise of electronic data capture and its greatest obstacle. *Clin Res* 30(3):30–3.
10. Causey JM. 2015. Risk-based monitoring: hope or hype? *Clin Res* 29(5):59–63.
11. Ferrer FM. 2014. Risk-based monitoring in clinical trials: an opportunity for quality and efficiency. *Clin Res* 28(4):39–43.
12. Halbe VS, Dalal J. 2016. Risk-based monitoring: changing roles, changing mindsets. *Clin Res* 30(6):16–9.
13. Hamrell MR, Mostek K, Goldsmith L. 2016. Monitoring of clinical trials—are remote activities helpful in controlling quality? *Clin Res* 30(5):18–21.
14. Manasco PK. 2016. Quality remote monitoring: the tools of the game. *Appl Clin Trials* 25(6).
15. Meseke J. 2015. No man is an island: the CRA's role in the production of shared knowledge systems: adaptive monitoring and risk management. *Clin Res* 29(3):12–3.
16. Sharma N. 2016. eSource and risk-based monitoring: a favorable union for future clinical trials. *Clin Res* 30(3):26–9. www.appliedclinicaltrialsonline.com/quality-remote-monitoring-tools-game
17. Shukla BK, Khan MS, Nagak V. 2016. Barriers, adoption, technology, impact and benefits of risk-based monitoring. *Int J Clin Trials* 3(3):9–14.
18. Getz KA, Stergiopoulos S, Marlborough M, Whitehill J, Curran M, Kaitin KI. 2015. Quantifying the magnitude and cost of collecting extraneous protocol data. *Am J Theraps* 22(2):117–24.
19. Artyomenko A. 2015. Effective risked-based monitoring: the CRO perspective. *Clin Res* 29(3):16–9.
20. U.S. Food and Drug Administration. Inspections, Compliance, Enforcement, and Criminal Investigations. Warning Letters. https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
21. Rosenberg R. 2014. Investigative sites' eye view of the clinical trial industry. *The CenterWatch Monthly* 21(9):1–4.

[DOI: 10.14524/CR-17-0025]

Qpinion:
The Investigator Site of the Future

The perspectives offered in this opinion piece come from the author, who works in a contract research organization (CRO) with a site alliance; from two investigators and a study manager who conduct clinical research; and from personnel at a CRO-like organization with a new hybrid approach that offers staff and processes to help investigators conduct clinical research.

PEER REVIEWED
Kurt Mussina

The investigator site of the future will look dramatically different than it does today. To a great extent, investigator frustration with the current environment will drive change as the industry seeks to eliminate inefficient processes that create redundant activities, slow patient recruitment and enrollment, and complicate trial execution. Such processes are harmful in that they distract physicians from patient care and discourage others from considering clinical research.

The frustration experienced by investigators and other site personnel often stems from their increased responsibility for activities tied to contracts, budgets, new software, training, and other mundane, though necessary, tasks, when they would prefer to focus primarily on patients. For example, they must navigate multiple levels of government and private-payer policy to determine which study treatments and services are (and are not) eligible for insurance coverage, often creating uncertainty that can complicate billing.[1] Meanwhile, delayed reimbursement and inaccurate payments reportedly contribute to a 40% investigator turnover rate, fostering the "one (trial)-and-done" investigator phenomenon.[2]

Moreover, growth in global clinical trial grant spending—by both government and industry—has slowed significantly in recent years, even as industry-sponsored clinical trial activity has continued to increase.[3] Given the average per-patient cost of $36,500 for clinical trials of any phase or condition,[4] such financial and administrative volatility can significantly impact site revenue streams and resource planning.

Trial sites are further burdened by the proliferation of multiple technologies. The typical site uses 12 different systems for data collection[5] and has increasing responsibility for deploying devices and wearables for patient use. While these technologies are meant to increase efficiencies, the lack of standardization across the industry, in fact, often makes their use a hassle.

All these factors—combined with increasingly stringent regulatory and administrative requirements—serve to drive up costs and increase the burden on investigators and sites, dissuading many from participating. This situation must change.

ENVISIONING THE SITE OF THE FUTURE

Overcoming the challenges of the current site environment will entail extensive consultation and rethinking among trial sponsors, CROs, and regulators about how they can reduce investigator turnover and encourage more physicians to participate in clinical research, while also streamlining patient

The typical site uses 12 different systems for data collection

recruitment and retention. Certain aspects of site operations will therefore need to be optimized to accelerate and improve clinical research.

"To be successful, sites will need both the right resources and the right processes," said Ravi Thadhani, MD, MPH, chief of the Division of Nephrology at Massachusetts General Hospital and adviser to various healthcare organizations. "There isn't going to be one solution, but multiple solutions. There will need to be modifications in processes, incentives, and organizational activities."

RUNNING THE SITE AS A BUSINESS

For sites to truly become better centers for high-quality clinical research, each site should be professionally managed as a proper business.

"Sites need to change the way they operate to become more efficient and profitable, especially during study startup, and they can do so by streamlining ideas and establishing a sound infrastructure," said Manuel Montero, MD, who serves as a principal investigator at Eastern Nephrology Associates.

CROs can facilitate this by helping sites implement professional financial systems as well as new tools, technologies, and services to expedite payments and provide more transparency for sponsors and investigators. Sites also can make greater use of resource planning tools to optimize resources, possibly transitioning from the decentralized (silo) operational and administrative model to one in which some or most research activities are standardized and controlled by an umbrella core organization.[6,7]

"It is very difficult to redirect medical providers to a business mindset," Montero said. "We need them to understand that research is not just about medical care, but about helping patients in the future."

While the concept of patient centricity is nearly ubiquitous in the current environment, it needs to be incorporated into strategies and value propositions, helping sites to sell their services and expertise to sponsors and/or CROs. Having an experienced study manager on staff with project management expertise will enable sites to prioritize study demands and oversee the adoption and implementation of new technologies.

THE POWER OF CLINICAL SITE NETWORKS

The future may see the rise of clinical investigative site networks, which are groups of independent clinical sites that function as one entity. In one model, the typical network is managed by a central administrative staff that oversees and streamlines financial, regulatory, safety, data management, business processes, quality assurance, and site selection matters for each trial.

Unless affiliated with a CRO, these networks typically require sponsor monitoring, are regionally structured, and further divided by disease state, with each region assigned a lead investigator for a specific disease state.[8] Whether structured in this manner or in some version of this model, networks offer value by centralizing services.

"There's a need for independent research sites to group together to reduce their overhead costs," said John Potthoff, PhD, CEO of Elligo Health Research. "Technology, systems and training applied to one site per year is a heavy cost. If the same processes and infrastructure can be leveraged across many sites, it eases the burdens of study conduct."

It remains to be seen whether site networks can take over such tasks as overseeing general feasibility assessments, licensing, annual Good Clinical Practice (GCP) training, and internal audit programs to eliminate redundancies and optimize site qualification visits. However, networks can be particularly effective in leveraging recruitment campaigns—even those not specific to a study, but which target patients expressing a general interest in participating in clinical research.

Such networks may be able to obtain more studies through competitive pricing, making it harder for non-affiliated sites to compete. Some of the larger networks may also be able to negotiate better payment terms.

ADOPTING AND OPTIMIZING NEW TECHNOLOGIES

The site of the future will almost certainly feature new technologies that dramatically improve management of data, documentation, workflow, and compliance. When sites effectively use the technology available, patients can benefit.

"We can begin to utilize remote consenting with live chat and remote monitoring to include more patients in clinical trials," said Thadhani. "When patients have the opportunity to be more involved—in activities like filling their own kits, for example—they feel like they are actively participating in the research."

Another advance that can be implemented is to automate the processes for sharing trial performance–related information with sponsors, which can potentially save 40 hours a month alone for CROs per study[9]—a benefit that can result in shortened trial timelines and significant cost savings.

To a great extent, investigator frustration with the current environment will drive change as the industry seeks to eliminate inefficient processes that create redundant activities, slow patient recruitment and enrollment, and complicate trial execution.

However, efforts to optimize the drug development process may backfire if these new technologies do not fully integrate with each other. Multiple technologies can be more burdensome because of training requirements at the site level, along with the added weight of managing sign-on credentials across a large number of platforms. Even investigator portals—specifically meant to ease investigator burden—can be troublesome.

"From a technology perspective, we continue to see the deployment of investigator portals to accommodate study startup and data collection, but it's very challenging to maintain sign-on credentials for each individual sponsor," said Morgan Moore, CCHT, CCRC, clinical research site operations manager at Eastern Nephrology Associates.

As new platforms are developed and tested, the number of adopted technologies will likely consolidate over time, with some clear winners emerging, especially given the favorable valuations of technologies in the clinical space. The site of the future will benefit from this consolidation with fewer, more powerful tools such as mobile-friendly electronic data capture systems, clinical data management programs, clinical endpoint adjudication software, genetic analysis software, online risk assessment tools, and cloud-based clinical trial management systems.

Nevertheless, even with consolidation, sites will need to overcome lingering "technophobia" if they are to take full advantage of new technologies. In a 2006 survey of representatives of academic institutions, drug and device companies, CROs, clinical research sites, consultants, and third-party service providers, investigators and their staffs were the least accepting of Big Data and innovative processes in clinical trials, and were the second most resistant group to paperless trials and wearable mHealth technologies; their resistance was largely due to concerns about cost and data integrity.[10]

Technophobia is not limited to trial site personnel. "In our patient population, participants frequently have device limitations, or a lack of familiarity with technology or Internet access," Moore observed. "They prefer the additional one-on-one interactions with our staff during clinical studies."

In the future, patients and site staff alike will benefit from new technologies that work more like apps, require little or no training, and use plug-ins to integrate multiple technologies. There will also be increasing use of telemedicine and wearables to collect and track vital signs and facilitate ongoing monitoring.

Additionally, consumer advertising and retargeting technologies will facilitate patient recruitment, allowing sponsor companies and CROs to drive more patients to sites, while reducing the recruitment burden at the site level. Other advances such as home-based video conference equipment to enable "virtual" physician visits/examinations and drone-delivered medication may yield further efficiencies.[11]

> Overcoming the challenges of the current site environment will entail extensive consultation and rethinking among trial sponsors, CROs, and regulators about how they can reduce investigator turnover and encourage more physicians to participate in clinical research, while also streamlining patient recruitment and retention.

"Patients want to feel engaged and connected with the research," Thadhani said. "These are technologies that can connect patients to investigators and improve connections among research staff and administrators."

EFFECTING DISRUPTIVE CHANGE

The site of the future will be the product of disruptive change that transforms the industry and eliminates redundant activities; it is almost ridiculous the way current practices needlessly ask investigators to do certain things over and over from trial to trial. Rather, by centralizing and standardizing key processes, disruptive change can accelerate study startup and drug development, while also cutting costs.

To a great extent, disruptive change can ameliorate many of the inefficiencies in the current site environment, particularly those pertaining to patients. "Having a streamlined process to screen patients would greatly assist the whole industry," said Montero. However, getting patients in the door can be a resource-intensive pursuit.

"While ongoing patient engagement and education programs can be instrumental in getting more patients interested in clinical research, a comprehensive program that includes 'lunch and learns,' educational materials, slide shows, collateral, etc., as well as database maintenance, requires a lot of resources—and resources at sites are limited," said Moore. "At industry conferences, there is a lot of talk about Big Data, but right now, we are not seeing it effectively translated to the site level."

To get more patients involved in clinical research, Elligo Health Research is improving the accessibility of studies in terms of potential participants. The company is using electronic health records and other data to first identify patients. Once patients are identified, the company provides their physicians with the infrastructure to conduct the studies with their own patients in their own clinics.

"We need to look at healthcare and where the patients are really treated—not where should we run the trials," said Potthoff. "Patients want the familiarity and consistency of their trusted clinician."

This approach is a new way to tackle the problem of low patient and physician participation

levels. In addition, the industry must evaluate many options and implement those that truly help us meet our challenges. Some disruptive changes that can be considered include:

- U.S. Food and Drug Administration or other centralized organization takeover of responsibilities for collecting licenses and conducting annual GCP training, as well as development of an audit program to enable research sites to eliminate redundant per-study requirements and site qualification visits.
- Improvements to ClinicalTrials.gov to make it more user friendly, up to date, and compatible with other tools.
- Streamlining insurance cost analysis so that the sponsor can conduct a single analysis for the largest providers, rather than requiring each site to expend time and resources on multiple analyses across the sites.
- Centralization and expansion of site data to reduce the volume of feasibility questionnaires for every study.
- Collaboration between industry and regulators to improve guidance on "serious and unexpected" adverse events, and to reduce the burden of over-reporting of all adverse events.
- Adoption of centralized, risk-based monitoring to lessen the burden on the entire system.

CONCLUSION

Although forecasting change is an inexact science, it is possible to envision how trial sites will evolve into more efficient engines of clinical research. Indeed, many of the procedural and technological advances described in this article are already under way and are expected to yield benefits in the not-so-distant future. As these benefits are realized, skeptics and others reluctant to adopt new technologies and practices may become proponents of change in order to capture labor and cost savings.

As Thadhani said, "Research complements and can enhance clinical care." This is at the heart of our efforts—the desire to complement clinical care now and to enhance it in the future. To truly succeed, all stakeholders—sponsors, CROs, investigators, site personnel, and even patients—must be willing to embrace the changes necessary so that we can realize the broader benefits of more streamlined and more efficient clinical development.

The future may see the rise of clinical investigative site networks, which are groups of independent clinical sites that function as one entity.

References

1. Vose JM, Levit LA, Hurley P, Lee C, Thompson MA, Stewart T, Hofacker J, Bruinooge SS, Hayes DF. 2016. Addressing administrative and regulatory burden in cancer clinical trials: summary of a stakeholder survey and workshop hosted by the American Society of Clinical Oncology and the Association of American Cancer Institutes. *J Clin Oncol* 34(31):3796–802. http://ascopubs.org/doi/full/10.1200/JCO.2016.69.6781
2. Corneli A, Pierre C, Hinkley T, Lin L, Fordyce CB, Hamre G, Roe MT. 2017. One and done: reasons principal investigators conduct only one FDA-regulated drug trial. *Contemp Clin Trials Comm* 6:31–8.
3. CenterWatch White Paper: study grants market breaks $13 billion. 2015. *CenterWatch Monthly* 22(2):1–6.
4. Battelle Technology Partnership Practice. Biopharmaceutical industry-sponsored clinical trials: impact on state economies. http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf
5. New CenterWatch study finds that e-clinical technologies are increasing investigative site work burden and performance inefficiencies. 2016. https://www.centerwatch.com/press/pr-2016 -05-17.aspx
6. Stevens E, Autry S, Eberhart C. 2016. The clinical trials unit: defining, staff assessment and scheduling restructuring for operational efficiency. www.fticonsulting.com/~/media/Files/us-files/insights/white-papers/ctu-trial-white-paper.pdf
7. Rubin E, Lazar D, Gaich N, Haray D. 2007. The clinical trials landscape: limitations, strengths and promise. www.aahcdc.org/Portals/41/Series/Issue-Briefs/Clinical_Trials_Landscape_Limitations_Strengths_and_Promise.pdf
8. Russell DR, Brinkman KJ, Scheible LS. 2005. The clinical investigative site network. *Appl Clin Trials*. www.appliedclinicaltrialsonline.com/clinical-investigative-site-network
9. Regan B. 2017. Can technology foster better collaboration? *Appl Clinl Trials*. www.appliedclinicaltrialsonline.com/can-technology-foster-better-collaboration
10. SCORR Marketing and *Applied Clinical Trials*. 2017. Technological innovations survey report. https://www.scorrmarketing.com/resources/act-scorr-technological-innovations-report/
11. Alsumidaie M. 2017. How healthIT can change the clinical trial landscape. *Appl Clin Trials*. www.appliedclinicaltrialsonline.com/how-healthit-can-change-clinical-trial-landscape

Kurt Mussina is vice president for clinical studies operations and general manager of Frenova Renal Research in the Greater Boston area.

Christine Senn, PhD, CCRC, CPI

[DOI: 10.14524/CR-17-4029]

Failing to Embrace Our Potential

Scan. E-mail. Re-scan. Set weekly reminders.

Scan. E-mail. Answer questions. Resend e-mail.

Defend self, stating that the documents have already been scanned and e-mailed.

Re-resend e-mail anyway.

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

I had occasion for the past few months to return to where I started in research—being a clinical research coordinator (CRC). It is the job that holds the entire site operation together.

Coordinating is, indeed, what a good CRC does best. For every trial under their domain, CRCs coordinate the patients, investigators, sponsor representatives, regulatory authorities, and data managers. At larger sites, such as hospitals and academic medical centers, add to this coordination of the laboratory, patient schedulers, pharmacy, and quality assurance personnel.

I have always held great respect for high-quality CRCs because they are the unspoken heroes of most sites and many trials. Returning to such duties after six years in management, though, forced me to recognize that the amount of wasted time is…what's the technical term?…*mind-blowing.*

The Solution Presents Itself…

More patients could be enrolled, protocols better attended to, trials covered per CRC, and profit margins improved for sites and sponsors alike if the industry committed to doing what every other service industry has done—get off of paper!

My calendar looked like this, and the example is from only one trial (let's be honest, no CRC ever has only one trial):

Recurring events

- Every Monday: Scan and e-mail the pre-screening log to Person A.
- Every Tuesday: Remove the drug accountability log from each subject's binder individually, then scan and e-mail the logs to Person B. Re-file each log.
- Every Wednesday: Remove the patient questionnaires from each subject's binder individually, then scan and e-mail the logs to Persons C and D. Re-file each log.
- Every Thursday: Scan and e-mail the screening log to Persons A, D, and E.

As-needed events

- After enrollment: Print digital imaging files in color and de-identify each page three times (because that's how many places the subject's name is noted). Scan the de-identified files to a USB drive. From a computer, compress the file due to size, so it can be e-mailed all at once, or split the file into multiple parts and multiple e-mails.
- Also after enrollment: Complete an enrollment form. Scan and e-mail it to Persons A, C, D, E, F, and G (not kidding).
- Re-scan all patient questionnaires (Wednesday's task) because Person C claims not to get most of them.

It is entirely without exaggeration that I tell you that this singular trial cost me two hours per week in scanning, e-mailing, and re-e-mailing. Another hour or more would be added per enrollment. I assume the workload was similar on the contract research organization (CRO) side.

Let's Think This Through

Does this seem logical? How can we be scientists and be this illogical and redundant in our processes?

Pre-screening and screening logs can be entered into an online system just as easily as they can be entered on a paper log, but with the benefit of real-time review. This is also true for drug accountability logs—and what is especially odd about having to e-mail these is that the data have already been entered into the electronic data capture (EDC) system by the time the weekly deadline rolls around.

The patient questionnaires are likewise already entered into the EDC. Electronic source documents would help even more, but the site cannot implement its own electronic source documents because the sponsor insists on use of its specific paper form. The enrollment form also has to be the sponsor's paper-based form, even though all of the information summarized on the form comes from the screening visit data that are in the EDC.

Which Leaves Us With…

Until sponsors and CROs allow or foster electronic source documents, and until they utilize the data in EDCs for more than just data analysis, we as an industry will always be underperforming compared to our potential.

[DOI: 10.14524/CR-17-0022]

The Real Reason Sites Need *eSource*

PEER REVIEWED

Raymond Nomizu, JD

Most discussion about electronic source (eSource) documentation in the clinical research enterprise starts from a sponsor standpoint, with eSource being viewed as an extension—almost a mobile version—of electronic data capture (EDC). In this view, sponsors provide sites with eSource systems that the sites use to collect data, which are then transmitted to the EDC system. This is a sensible view, but it misses a bigger opportunity. Independent of a sponsor mandate, sites need eSource technology for one fundamental reason: to manage complex operations in an efficient and high-quality manner.

Clinical research is a complicated business. Research protocols are nuanced, with numerous requirements for patient compliance, investigational product administration, clinical procedures, and data capture. To execute protocols properly requires extensive and rigorous project planning, task management, and data collection processes.

However, to date, few good technology options have existed that enable sites to manage these processes efficiently. Electronic health record (EHR) systems, for instance, are not optimized for clinical research and lack critical features sites need, such as the ability to easily build research-specific templates, pre-program visit windows, or provide isolated, study-specific views to clinical research associates (CRAs). As a result, 96% of site staff recently surveyed report using paper, and not EHR, as their primary data collection tool.1

Without good technology, sites end up spending too much time on inefficient and error-prone pen-and-paper processes. This misallocation of time limits the attention site staff can devote to patient recruitment and retention, and serves as a drag on the financial health of the industry.

Without good technology, sites end up spending too much time on inefficient and error-prone pen-and-paper processes. This misallocation of time limits the attention site staff can devote to patient recruitment and retention, and serves as a drag on the financial health of the industry.

TABLE 1: Average Metrics for Phase III Protocols

	2001–05	2011–15
Endpoints	7	13
Eligibility criteria	31	50
Procedures	110	187
Visits	12	15
Number of sites	124	196

Source: Tufts Center for the Study of Drug Development[2]

The Growing Complexity of Research Protocols

The complexity of clinical research seems to be an ever-growing trend. As Table 1 indicates, Phase III studies have more visits, procedures, endpoints, and eligibility criteria than they did 10 years ago.[2] All of this complexity leads to greater data collection requirements, which in turn lead to more complex research procedures.

It is hard to execute many clinical trial procedures accurately using pen and paper. Take, for instance, a "simple" procedure such as contraception. The purpose of this procedure is to ensure that subjects do not become pregnant or cause pregnancy during the course of a study. Nearly every interventional drug study will have a requirement that women of childbearing potential agree to use contraception during the life of the study.

Table 2 depicts actual variations across study protocols in how the contraception requirement is to be fulfilled. As the table shows, protocols differ in their definition of "post-menopausal," what procedures are considered surgical sterilization, how much and what kind of contraception is required, and what is required of male subjects.

This complexity is difficult to manage using paper templates. Figure 1 shows an actual example of a paper source template written by a research site against one of the "female contraception requirement" protocols above. Note how easy it is to miss checkboxes or branching logic. For example, a harried coordinator could check off "N/A [Male]" at the top, but then miss the requirement that the male subject be educated about refraining from sperm donation.

Coordinators routinely miss required data fields because paper is not interactive and does not provide the real-time alerts to ensure accurate data at point of capture. CRAs may come to visit a site weeks after the fact and catch a mistake, which means the coordinator then has to update the missing data field (often requiring a call to a patient for follow-up). Because the paper source was not adequately completed in the first place, a coordinator has to spend precious time on data correction down the road.

This "simple" procedure isn't so simple then! The average study could easily have more than 20 procedures. Picture a small research site with five coordinators who manage 15 studies at any given time and have to collect data against 300 complex and unique requirement sets.

Collecting Data Outside Visits is Also Challenging

The above example is about data collected during a visit; however, research trials require extensive management of tasks before and after visits. For instance, coordinators have to schedule visits within precise visit windows (e.g., the Week 8 visit must be eight weeks from Baseline Visit, plus/minus three days). Coordinators must keep track of new informed consent form (ICF) versions and re-consent patients before conducting procedures at their next visit, and keep track of central lab results, ECG interpretations, third-party medical records, and other documents that come in between visits, and which are critical to determining eligibility.

TABLE 2: Sample Protocol Language on Childbearing Potential/Contraception

	Protocol 1	**Protocol 2**	**Protocol 3**
Female contraception requirement	1 from pre-defined list	2 from pre-defined list	2, including 1 from "highly effective" sub-list
Surgical sterilization	Includes tubal ligation	Excludes tubal ligation	Includes tubal ligation
"Post-menopausal" defined as	12 months	24 months	12 months
Male contraception requirement	1 from pre-defined list and cannot donate sperm	None	2, including 1 from "highly effective" sub-list

Research staff have to manage patient compliance; they often have to schedule offsite procedures, train patients how to use diaries, and check online patient portals to track compliance. They must remind patients prior to certain visits of visit-specific requirements, such as medication wash-out, fasting, or exceptions from their normal study routine (e.g., skip the morning dose of study medication).

Here's an example of a *single protocol* that had differing visit requirements within the same study:

- Visit A: Fasting visit
- Visit B: Fasting visit and skip morning dose
- Visit C: Take morning dose but time visit so pharmacokinetic sample can be done within two to four hours of dose
- All other visits: No fasting; take morning dose on the day of the visit

With all this complexity, before, during, and after a visit, is it any wonder that sites struggle to keep up with the demands of modern protocols?

The Research Industry Needs Operational Technology

Every modern industry utilizes technology to streamline and automate operations. Can you imagine a bank balancing its ledgers with paper books? Or a major retailer managing inventory from paper logs?

Just like banks or retailers, research sites are running complex *operations,* but unlike other industries, too many sites are running these operations using pen-and-paper processes. Inventory is kept on paper logs (the "investigational product [IP] logs"); design specifications (the source templates) are done in Word and then printed out and delivered by hand to the production staff (the research teams); production (data capture) is done manually, with no technological guardrails.

In such an environment, quality of output rises and falls with the individual skill and commitment of the person doing it. This is why site-centric eSource technology can significantly improve operations. Well-designed eSource technology allows sites to construct and put in place technological guardrails against protocol deviations, and to automate processes that are routine, such as ICF version tracking, visit window calculation, or body mass index and other calculations. It standardizes workflow and makes output less dependent on the individual coordinator's skills.

Site-centric eSource technology features should, at minimum, allow sites to:

- design and manage all of their own studies in a single platform;
- house research-specific templates and create their own for future use;
- collect data and receive real-time alerts to ensure accurate data collection;
- provide CRAs with study-specific, anonymized access to view and quality control subjects and visits;
- enables routing, digital annotation, and e-signature of lab reports, ECG tracings, and other documents; and
- take advantage of research-specific workflows such as visit scheduling, ICF version tracking, internal quality control, patient reminders, and task management.

What would be the impact of a technology like this on site operations? Technology like this should:

- Save significant time by reducing the need to print and manage paper binders, populate data fields that can be automated, reduce re-work, and eliminate the need to transport binders. A site that recently adopted eSource, in fact, reported productivity gains of 20% compared to its previous paper-based process.[3]
- Enhance principal investigator (PI) oversight by allowing them to access and modify source data at any time. For instance, if a patient has a high-risk adverse event (AE) while the PI is offsite, the PI could log into the eSource record to review the AE and related information, thus facilitating timely assessment and action.

FIGURE 1: Sample Paper Source Template

CONTRACEPTION [BIRTH CONTROL] ❒ Not Done

Is the subject of Childbearing Status? ❒ Yes ❒ No ❒ N/A [Male]

If no, which of the following applies to the subject:

❒ ***Post Menopausal***

❒ ***Surgically Sterile*** ➡ **Select One:** ❒ **Hysterectomy** ❒ **Bilateral Oophorectomy** ❒ **Tubal Ligation**

What method of birth control does the subject *[MALE OR FEMALE]* use and agree to continue to use throughout the study?

- ❒ **Hormonal contraceptives (ie, oral, patch, injection, implant)**
- ❒ **Male condom with intravaginal spermicide**
- ❒ **Diaphragm or cervical cap with spermicide**
- ❒ **Vaginal contraceptive ring**
- ❒ **Intrauterine device**
- ❒ **Vasectomized partner**
- ❒ **Sexual abstinence**
- ❒ **MALE SUBJECTS ONLY: Male participants should refrain from donating sperm during study**

Coordinator Signature: _____ _____ / _____ / _____

Well-designed eSource technology allows sites to construct and put in place technological guardrails against protocol deviations, and to automate processes that are routine.

The biggest challenge comes from the learning curve faced in the adoption of any new technology and workflow. Every member of the site must adopt the technology and accompanying process changes.

- Improve quality through the use of real-time alerts to guide investigators and coordinators as they complete data entry. A third-party auditor, for instance, found that well-designed eSource provides safeguards against 50% of the most commonly cited deviations.[4]
- Enable more rapid onboarding of new employees by standardizing their workflow, and enable more coverage among site staff. For instance, back-up coordinators are much more likely to be successful if they can work with interactive eSource, and not to have to rely on soft knowledge of a protocol that the prime coordinator has through extensive training.

What are the Challenges and Caveats to Implementation?

The biggest challenge comes from the learning curve faced in the adoption of any new technology and workflow. Every member of the site must adopt the technology and accompanying process changes.

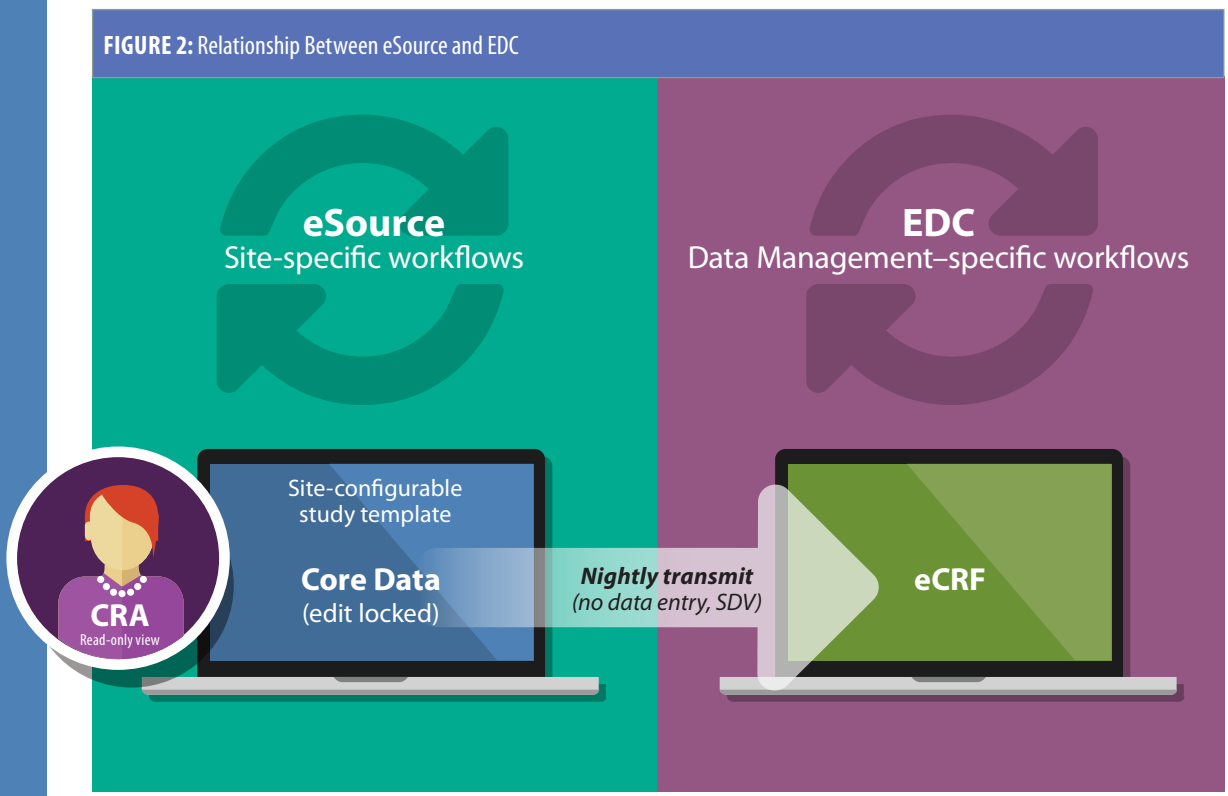
For many, real-time EDC will be a new experience. It may not feel as "real" or as substantive as handwritten paper templates. The templates will likely present themselves differently than on paper; there will be new features and workflows to master.

To overcome these challenges, site management needs to implement a staged roll-out accompanied by extensive staff training and communication.

Sites must also develop, or outsource, a strong eSource design capability. As with paper source templates, eSource templates need to be thoughtfully designed and tailored to protocol requirements. In addition, they should incorporate appropriate use of technological features such as alerts and branching logic. Only when the templates are well designed will the site realize significant efficiency and data quality gains, so site management should identify, at the outset, who will be designing their eSource templates and how they will be trained. They should also develop robust processes for eSource template design and quality control.

In addition, site leaders must ensure that any eSource system used complies with local regulations. The PI is ultimately responsible for compliance (not the vendor), and this means that sites should have in place an eSource standard operating procedure governing the use of the technology as well as documentation concerning the system's compliance with regulatory requirements. For the U.S., this means compliance with expectations regarding electronic records and electronic signatures found in 21 CFR Part 11 of the *Code of Federal*

FIGURE 2: Relationship Between eSource and EDC



Regulations. For the European Union, this means compliance with Annex 11 to Volume 4 of the Rules Governing Medicinal Products in the European Community, Computerized Systems.

Sites also may need to manage other stakeholders. For large healthcare networks, that may mean the engagement and approval of groups tasked with procurement, compliance, technology, or governance. If site leaders anticipate that only staff members and not patients will use the system, they will likely not need local institutional review board (IRB) approval, although they should check their IRB's requirements first.

For industry-funded trials, sites need to develop a policy on how and when to notify sponsors and provide access to, and train, the CRAs. While the PI has the absolute right to use electronic instead of paper source, site management must factor in the sponsor's right to ascertain compliance and the CRAs' need for access.

Finally, site personnel should understand that while there are basic regulatory requirements that govern the use of eSource, the technology is new and no standards have emerged. Since eSource is an internal workflow tool, sites do not need interoperability with other systems to reap the benefits. However, site leaders may want to consider how eSource can or will integrate with other systems, such as sponsor EDC systems. If using an outside vendor, they may ask about interoperability with EDC systems and the vendor's adherence to Clinical Data Interchange Standards Consortium (CDISC) standards, which are a set of protocols that govern the transference and presentation of data within the clinical research industry.

How Would This Work with EDC Systems?

Many eSource systems start with the needs of the EDC system; however, as discussed above, a good eSource system should start with the needs of the site. Ideally, the two systems "talk" to each other to enable seamless flow of data from eSource to EDC.

Figure 2 depicts the ideal relationship between eSource and EDC. The left-hand side depicts eSource as a workflow tool optimized for research sites. The right-hand side depicts EDC as a workflow tool optimized for the sponsor's data management group.

The eSource template contains all the data required to populate the electronic case report form (eCRF) *plus all the compliance data* required to document protocol compliance. For example, while eCRF might require that only the systolic and diastolic blood pressure be entered, the equivalent eSource might include documentation on the patient's position (e.g., sitting), the time of position, the time of vitals, and the arm used. All of these data elements are important to document that the vitals were obtained in a manner consistent with the protocol.

In this model, a subset of the eSource data fields are mapped to their eCRF-equivalent data fields. These data fields should be edit locked, so that the user does not "break" the integration by modifying them. The rest of the eSource data fields relate to protocol compliance and site workflows, and have no analogous eCRF fields. These fields can be configured by the site.

This arrangement has numerous advantages:

- It preserves site independence since the site's data are housed in a separate database.
- It allows sites to configure source templates to match site workflow requirements, while standardizing the fields that are required to preserve the integrity of the eCRF mapping for sponsor analysis.
- It enables an "opt in" strategy, in which sponsors can standardize their data collection on a single, global platform across the trial, while individual sites can opt to use an eSource system or traditional manual data capture with subsequent data entry.

A data model like this ensures that site staff can use a workflow tool that meets their needs, while realizing the efficiency of EDC integration. When free to choose their own system, site leaders are incentivized to select one that maximizes their own staff productivity.

Conclusion

Increasingly, sites are recognizing the advantages of technology and incorporating it into workflows. Many have adopted the recent spate of purpose-built eRegulatory or eSource solutions provided by vendors, without waiting for data integrations that will take longer to mature. In going paperless, these sites are furthering the evolution of the industry to a more technology-centric approach, which will be critical to manage the ever-growing complexity of clinical trials.

References

1. Milam D. 2017. Society for Clinical Research Sites presentation. eSource – A Research Site Perspective. www.cbinet.com/sites/default/files/files/Milan_Dan_Pres-updated.pdf
2. Bolten B. 2017. Sites wrestle with protocol design complexity. *CenterWatch Monthly* 24(3) (citing Tufts Center for the Study of Drug Development). https://www.centerwatch.com/news-online/2017/03/01/post-june-sites-wrestle-protocol-design-complexity/
3. Clinical Research IO case study.
4. Audit letter provided to Clinical Research IO from ClinPharm Networks.

Raymond Nomizu, JD, (raymond@clinicalresearch.io) is cofounder of Clinical Research IO, owner of Beacon Clinical Research, and cofounder of Bench Core LLC, all in Massachusetts.

Clare Grace, PhD

[DOI: 10.14524/CR-17-4031]

ICH E6(R2)—Impacts on Investigator Responsibilities

The International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) dates back to 1996, when clinical trials were largely managed with paper documents. Since then, the scale and complexity of clinical trials have greatly increased. This has given rise to the need to revise ICH E6 to better reflect advances in technology, including the Internet, electronic data capture (EDC), cloud computing, and real-time review of clinical data, and how these impact oversight of people and documents as well as recording and reporting procedures.

ICH E6(R2) now mandates sponsor oversight of contract research organizations (CROs), and requires that investigators document and oversee any delegated tasks such as essential document control or study-specific procedures.

Therefore, ICH E6(R2) was introduced in November 2016; it was adopted in the European Union on June 14, 2017, but there is no specified date for adoption in the U.S. or Japan yet.

Understanding the Revisions

While it is important to educate investigators and their teams about the salient aspects of ICH E6(R2), it is essential that they grasp *how* the revised guidance will affect both their workflows and the tools they use to do their work.

For instance, in the old days a clinical research associate (CRA) would regularly travel to study sites to manage quality. Now, under the most recent revision to ICH E6, there will be a mix of onsite and centralized monitoring. Investigators should be aware that not only will CRAs do more by telephone and e-mail, they will also likely visit the site less frequently, freeing them up to go into greater detail regarding verification of procedures and how specific tasks are carried out. In addition, other sponsor staff such as data managers, statisticians, and medical monitors will monitor data remotely.

In particular, the latest revisions to the tenets of GCP are meant to address deficiencies at the site and investigator level—in record keeping, lack of rigorous oversight of individuals charged with conducting study tasks, deviations from trial protocols, inadequate storage and archiving of essential documents and data, and poorly documented assessment of third-party providers.

For instance, ICH E6(R2) now mandates sponsor oversight of contract research organizations (CROs), and requires that investigators document and oversee any delegated tasks such as essential document control or study-specific procedures. It is critical that this oversight is ongoing and documented.

Where clinical trials used to be managed by a single study nurse who executed most of the trial activities, now many more individuals and professionals are involved in trials. Investigators are now responsible for ensuring that third-party suppliers to whom they delegate trial-related duties and functions are qualified. They should also implement procedures to ensure the integrity of those parties' duties and functions, and of the data they generate.

Prior to implementation of ICH E6(R2), investigators would delegate a task and not revisit it, assuming it was satisfactorily completed unless told otherwise by a study monitor. Now, beyond simply delegating the task, investigators must supervise and moreover document that ongoing supervision and oversight throughout the life of the study. Document control (e.g., case reports, medical images) and standard operating procedures (SOPs) should be adapted to the demands of this new regulatory environment.

This new ICH revision will put a lot more focus on how sponsors and CROs interact. It will require that sponsors be able to manage risk and be clear about which risk management tasks they want to retain, and which ones they want to delegate to the CRO.

Targeting Technology and Clear Communications

Study teams now have the technology needed to review clinical data in real time. This can be critical in the case of a dose-escalation trial, where investigators must track safety data across trial participants in real time in order to know when to go to the next dose.

Sites should be staffed by people skilled in data integrity, including system access, version control, and audit trails. In addition, source data should be attributable, legible, contemporaneous, original, accurate, and complete.

Sites also must now ensure that communications with staff regarding studies are documented—particularly communications between investigators and individuals to whom tasks have been delegated. This could encompass telephone calls, study meetings, eligibility discussions, and so forth.

Sponsors and investigators will need to maintain records of the location of all records, including but not limited to essential documents and communications that would enable the reconstruction of the study. In many cases, documents such as medical records or CVs are stored offsite, and will require a documented method to be accessed when required. This underscores the importance of noting their specific location in an SOP.

Rising to the Challenge

In its own words, the ICH E6(R2) addendum "encourages the implantation of improved and more efficient approaches to clinical design, conduct, oversight, recording, and reporting." These new responsibilities fall on lead investigators and their key staff, and the changes will usher in a new era in how clinical monitoring and trial management are conducted.

If investigators are prepared for the new tasks they will have to execute and the new ways that their sites will be monitored—and how these will impact their workflows and responsibilities—then they will have no trouble in meeting the challenge.

Clare Grace, PhD, (clare.grace@incresearch.com) is vice president for site and patient access with INC Research.

[DOI: 10.14524/CR-17-0023]

STANDARD OPERATING PROCEDURES

Critical Components of Quality at Clinical Research Sites

PEER REVIEWED | Soumya J. Niranjan, BPharm, MS, CCRP

The U.S. Food and Drug Administration (FDA) expects clinical researchers to abide by standards of Good Clinical Practice (GCP), and when they are not in compliance, investigators are subject to receiving a Warning Letter from the FDA. Between January 2005 and December 2010, 129 Warning Letters were issued to investigators, with the most common deviations at study sites being noncompliance with the investigational plan, failure to maintain accurate and adequate case histories, and informed consent issues.[1] The frequency of these deviations and, consequently, the receipt of Warning Letters can be greatly minimized if standard operating procedures (SOPs) are in place for all study-related activities at research sites.

In clinical research, SOPs are detailed instructions that help define and standardize how and by whom a unit's procedures are conducted to assure execution of research tasks in accordance with institutional, state, and federal guidances. According to the International Council for Harmonization (ICH) Guideline for GCP E6 2.13, "Systems with procedures that assure the quality of every aspect of the trial should be implemented." This is generally accomplished through the implementation of an SOP program.[2] The ICH GCP guideline is upheld by regulatory authorities in the U.S., Canada, European Union, Japan, and Switzerland.

Quality in clinical research starts with a systems approach.[3] In this context, "systems" include training programs, role definition, organizational structure, responsibilities and accountability, SOPs, and metrics. All clinical research sites should have quality systems to ensure that the clinical trials conducted are of the highest quality and in compliance with the tenets of GCP, study protocols, and local and federal requirements. In essence, SOPs answer the who, what, when, where, and how questions of all clinical trial activities and its management.

Thus, SOPs serve the following objectives:

- Improve and maintain quality of operations
- Standardize working practices
- Ensure high-quality, consistent, and reproducible results
- Define best practices
- Define roles and responsibilities of the individuals involved
- Ensure compliance with GCP guidance and regulatory guidelines
- Save time

FDA Recommendations

A key part of quality is consistent performance of procedures producing a consistent result. A critical part of these quality actions is developing SOPs, so that anyone performing the procedure will complete it in the same way and produce the same result. In addition to providing a standard for procedures, SOPs provide training information for new hires on what kinds of clinical trial activities are ongoing at their new workplace.

Further, SOPs set the measure for quality results so staff performance can be measured to the standard required.[4] Establishing and improving quality of clinical trials requires the use of the systems approach, tools, and models. In this regard, FDA recommends a four-step systems approach[5]: (a) Say what you do (b) Do what you say (c) Prove it (d) Improve it.

SAY WHAT YOU DO

The site should have a qualified and responsible management team to provide governance of the clinical trial process in its entirety. SOPs should define procedures and responsibilities for all key clinical trial processes, from site qualification to site close out.

DO WHAT YOU SAY

This step largely describes uniform education and training of all site staff regarding the trial protocol, study requirements, policies, and procedures. All site staff need in-depth training in regulatory requirements, ethics, consent process, and protocol compliance.[6] Needless to say, it is imperative that site staff are aware of their responsibilities.

PROVE IT

This step utilizes risk-based monitoring and trend analysis, which would be functions of an institution's internal quality assurance unit.[7] Risk-based monitoring focuses on process management and verification of critical activities, including quality control, to ensure that they are carried out as planned.[4] Trend analysis looks at data as compliance intelligence, and employs such approaches as statistical monitoring to assess data trends across the sites and trials with an objective of proactively identifying and evaluating compliance signals and unanticipated risks.[4]

IMPROVE IT

Improving quality will require actions—namely, effective corrective and preventive actions (CAPAs). For a CAPA plan to be effective, there should be an in-depth analysis of the root cause of any issue that is degrading quality at a site, and a search for an action plan that can provide long-term and sustainable solutions.[5] The system and processes should be reassessed to ascertain how the problem occurred in the first place.[6,8]

Get Your Studies Off to the Right Start

Take control of your processes and ensure compliance with your organization's SOPs and study regulatory requirements. The central feature of mapping out the required SOPs is a list of the steps or activities that constitute the required task. One way to do this is to begin by creating a flowchart of the clinical research process (cradle to grave); identify the individual steps (what to do) and place them in logical order.[9]

Based on the author's perspective, here are the three most important SOPs that any site should develop and apply to the conduct of clinical research:

1. **SOP for Preparing and Maintaining SOPs**—This is the primary SOP, as it helps in preparing, maintaining, numbering, and formatting SOPs. It helps the research team to prepare SOPs that comply with the guidelines set by ICH GCP and regulatory authorities.
2. **SOP for Responsibilities of the Research Team**—This SOP defines the responsibilities of the research team, such that all conditions defined by the relevant regulatory authority on the use of investigational articles are followed. The principal investigator acts as the head of the team and is responsible for implementing the guidelines. This in turn will help in preparing SOPs detailing each of the tasks under site staff responsibility. For example, it is the responsibility of the investigator to assess adverse events. This will help in preparing an SOP detailing toxicity evaluations, as just one example.
3. **SOP for Training and Education**—This SOP defines the standard training procedures that must be adopted to ensure that clinical research is carried out in a responsible manner. The purpose of the SOP is to define guidelines for GCP at the site in compliance with regulatory expectations.

In essence, SOPs answer the who, what, when, where, and how questions of all clinical trial activities and its management.

Accordingly, the most common SOPs present at research sites in the author's experience are:

- GCP Training
- Authority and Delegations of Responsibilities of Research Staff
- Subject Screening and Recruitment
- Informed Consent Process and Documentation
- Eligibility Confirmation
- Source Documentation
- Data Management
- Protocol Deviations
- Adverse Events and Serious Adverse Events Reporting
- Drug/Device Storage, Accountability, and Management
- Regulatory Document Submission Process (Initial Submissions, Amendments, and Continuing Reviews)
- Sample Processing and Shipping Procedure and its Training
- Monitoring Visits
- Sponsor, Contract Research Organization, and Internal Audits
- FDA Audits
- Writing SOPs
- Record Organization and Retention
- Sub-Site/Ancillary Site Management

Indeed, FDA's 2009 guidance on investigator responsibilities[10] recommends that sites have procedures for many study activities, including ones to ensure high-quality source data, protocol compliance, and proper adverse event reporting.

Who Writes SOPs and How Should They be Written?

The process of developing an effective SOP is critical to its successful implementation, and the process should be inclusive.[11] Highly successful managers actively engage their teams, and it is human nature that people support what they help create. Thus, managers who write SOPs without input from workers run the risk of upsetting them, while those who enlist the talents of their workers increase buy-in.

Apparently, the most convincing reason to involve others is that individuals who participate in the process are positive about generating ideas, accept the SOPs, and feel a sense of ownership in them, which is not the case when workers feel that management is imposing an SOP without regard to their input.[12]

As suggested above, start with an overall view. Once the process is mapped, improvisations, revisions, and edits must be expected. Then, turn the flowchart into a narrative that assigns process steps to roles (who will do it) and includes details as necessary (how to do it).[9]

Highly successful managers actively engage their teams, and it is human nature that people support what they help create. Thus, managers who write SOPs without input from workers run the risk of upsetting them, while those who enlist the talents of their workers increase buy-in.

Zimmerman[13] discusses an eight-step process for writing SOPs that involves the following:

- Process Mapping
- Authoring
- Formatting (includes language considerations)
- Editing
- Authorizing
- Training
- Implementing
- Revising and Archiving

During SOP development, start with an understanding of such sections of the *Code of Federal Regulations* as 45 CFR 46 (pertaining to research overseen by the Office for Human Research Protections [OHRP]) and 21 CFR 50, 56, and 312 (pertaining to research overseen by FDA); the ICH GCP guidelines and other pertinent guidance from OHRP and FDA; and applicable institutional policies. As written previously, include representatives from every impacted institutional area in the process.

SOPs should not merely duplicate regulations or guidelines; rather, they should be instructive as to how the regulations and guidelines will be followed in a consistent manner. Each procedure should be clearly and concisely written with little room for interpretation, while ensuring that the procedure is compliant with applicable laws and regulations. A good SOP should clearly identify the scope, be separated into easily identifiable sections, and include responsibilities for specific tasks, detailed procedures to perform tasks, and any associated documents/forms/tools to support the work governed by the SOP, such as checklists and templates.[14]

The benefits of SOPs are obvious, in that they provide a level of formal accountability for team members and prevent noncompliance on a systemic level. They help to ensure that all research conducted as part of the clinical trial follows federal regulations, ICH GCP, and institutional policies. They ensure processes have been examined, optimized, and standardized.

If used right, SOPs can provide valuable sustenance to new employees in need of details on how activities are required to be performed. Most importantly, SOPs allow for continued operations if a key staff member is unavailable. By referring to the SOP, someone can handle an urgent task and do it correctly the first time. This becomes necessary especially if research sites are experiencing high turnover rate.

Further, SOPs may in some cases support institutional practices that sponsors may dispute.[15]

Last, but not the least, SOPs help reduce errors or variations and improve the quality of the data collected.[9] Thus, an effective SOP should:

- Be written in a simple, easy-to-understand language
- Be a comprehensive document
- Differentiate between instructions and general information
- Describe procedures thoroughly
- Contain a descriptive title
- Contain an indication of the SOP's position among other SOPs

Writing SOPs Isn't Enough: Challenges Ahead

Although SOPs are invaluable, they can be burdensome—especially when one considers the elaborate steps involved in such tasks as document control, revision, review, and training, and the high levels of scrutiny for strict adherence that come with established SOPs. It would be wise to consider the following before writing an SOP:

- Can the SOP be consistently followed?
- How will all staff be trained on the SOP initially, as new staff are added, and as the SOP is revised?
- How will compliance to SOPs be assessed?
- What are the added regulatory burdens and costs of compliance?

Thus, writing SOPs is simply the beginning in achieving quality results. As written previously, everyone must be trained on the SOPs, and performance must be measured against the standard to ensure the correct results. Metrics must be collected on a regular basis to ensure staff are following the SOPs; if metrics and performance measurements are not undertaken, SOP compliance, standardization, and quality will inevitably decrease and the efforts taken in designing and writing the SOPs will prove to be futile.

In short, for standard processes leading to quality to be effective, there must be written SOPs, training on the SOPs, and metrics and measurement on the compliance to the SOPs—this, in effect, is the trifecta for quality in clinical research.

The Future of SOPs

Traditionally, SOPs are documented in unwieldy manuals; however, this need not be the case if resources permit the use of documentation applications to build a database of information. Most software systems will not only be able to support creation and maintenance of SOPs, but can manage organizational charts, instructions, and checklists in a centralized domain.

Conclusion

SOPs make it simpler for the research team to carry out trials in compliance with the standards set by regulatory authorities, sponsors, and institutions. The twin objectives of quality—data integrity and subject projection—can be met by a systematic approach to the conduct of clinical trial process.

Research relies on repeatable, reliable, accurate data; a breach or compromise in any of these facets can be disastrous to the research study. Compliance to quality requirements is the foundation of a scientifically valid and ethically sound clinical trial. The recent regulatory approaches of risk-based inspections and real-time oversight, combined with a specific focus on quality systems, demand continuous vigilance and continuous process improvement, from scientific and operational design to the conduct and monitoring of clinical trials.

References

1. Gogtay N, et al. 2011. A study of warning letters issued to clinical investigators and institutional review boards by the United States Food and Drug Administration. *Indian J Med Ethics* 8(4):211–4.
2. U.S. Department of Health and Human Services. 1996. Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance. https://www.fda.gov/downloads/drugs/guidances/ucm073122.pdf
3. Zon R, et al. 2008. American Society of Clinical Oncology Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites. *J Clin Oncol* 26(15):2562–7.
4. Bhatt A. 2011. Quality of clinical trials: a moving target. *Persp Clin Res* 2(4)124.
5. Meeker-O'Connell A. Enhancing clinical trial quality: CDER perspective. www.fdanews.com/ext/files/Conference/FIS10Presentations/MeekerOConnell-HarmonizingRegulatoryApproaches.pdf
6. Kleppinger CF, Ball LK. 2010. Building quality in clinical trials with use of a quality systems approach. *Clin Infec Dis* 51(Supplement 1):S111–6.
7. Niranjan SJ. 2016. Building an internal quality assurance program: from the ground up. *Clin Res* 30(6):52–3.
8. Niranjan SJ, Saleh M. 2014. Lessons learned from audits past. *Clin Res* 28(4)54–8.
9. Manghani K. 2011. Quality assurance: importance of systems and standard operating procedures. *Persp Clin Res* 2(1):34.
10. U.S. Food and Drug Administration. 2009. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors—FDA Inspections of Clinical Investigators. www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf
11. Amare G. 2012. Reviewing the values of a standard operating procedure. *Ethiopian J Hlth Sci* 22(3).
12. Stup R. 2001. *Standard Operating Procedures: A Writing Guide*. Dairy Alliance, Penn State University.
13. Zimmerman JF. 1999. The importance of standard operating procedures for investigators. *SoCRA Source*. www.readbag.com/impactcg-docs-socra-11-99-sops
14. Sajdak R, Trembath L, Thomas KS. 2013. The importance of standard operating procedures in clinical trials. *J Nuc Med Tech* 41(3):231–3.
15. Goldfarb NM. 2005. Something for everyone: standard operating procedure products for the investigative site. *J Clin Res Best Pract* Vol. 1, No. 4.

Soumya J. Niranjan, BPharm, MS, CCRP, (souyma14@uab.edu) is a quality assurance manager with the University of Alabama at Birmingham's Comprehensive Cancer Center.

Adam Butler

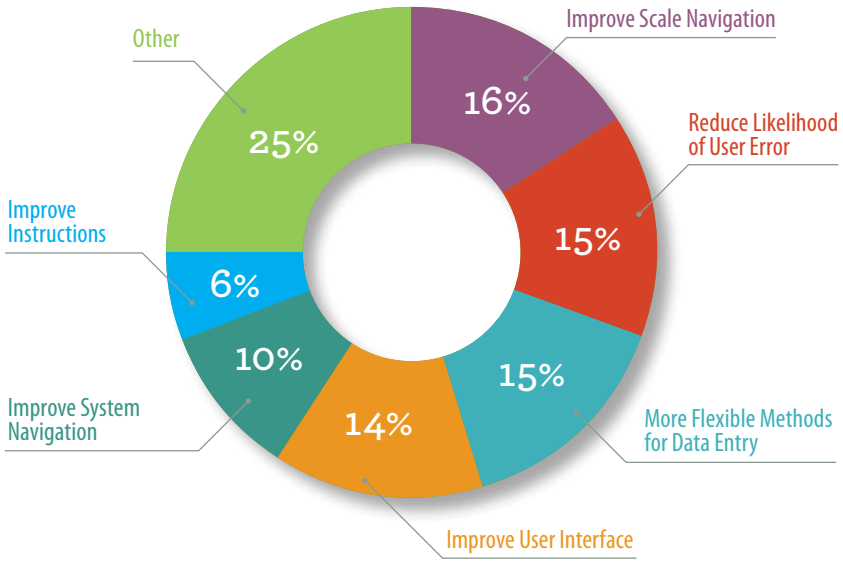
[DOI: 10.14524/CR-17-4033]

Sites as Partners: A Better Way to Develop Clinical Technologies

The rise in the adoption of new clinical technologies in pharmaceutical research is exponential. Many tools considered novel or untested just a few years ago, such as electronic data capture and interactive response systems, are now considered requirements. However, as the use of these technologies has expanded, stakeholders in clinical trials have struggled to ensure a seamless introduction of these beneficial tools.

Increasingly, the burden for introducing new tools in clinical trial sites has fallen on the investigators, research coordinators, and other staff at clinical trial sites who are on the front lines of research studies, yet sites are often left out of the design and development process. Sponsors, contract research organizations, and technology vendors collaborate well to determine which technologies are the best fit for each study or program. Historically, clinical trial sites are often the last to find out about something new.

FIGURE 1: MOST REQUESTED AREAS OF IMPROVEMENT



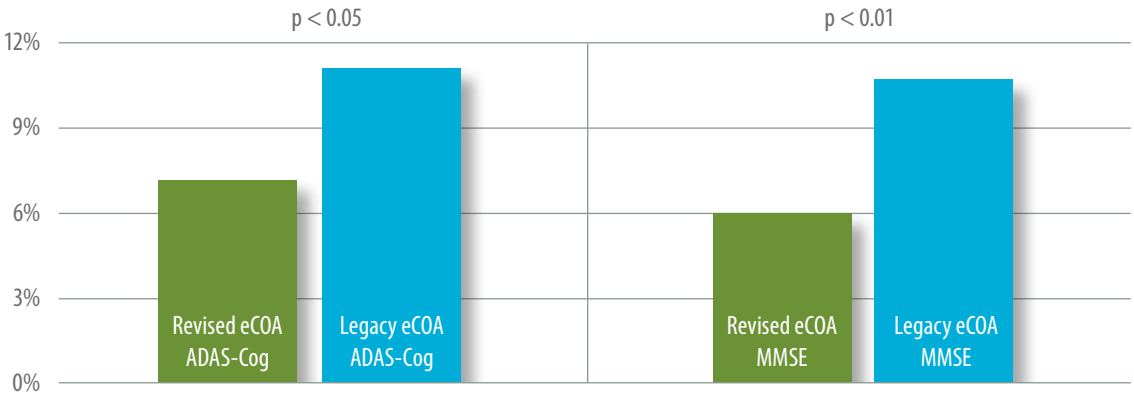
Site-Focused Development

Many services provided in support of clinical trials by vendors revolve entirely around the research sites themselves. For example, vendor-created randomization and trial supply management and clinical interactive response technology platforms are used mainly by investigators and research coordinators who need to screen and randomize patients and identify the correct drug kit or investigational product to give to a subject. Site-based electronic clinical outcomes assessment (eCOA) platforms from vendors are used by site clinicians to collect information from patients. Clinical raters for trials may complete their training and certification with a vendor directly.

After a 2014 product launch, the author's company heard feedback from numerous sites who were frustrated that its eCOA tools, designed to make collecting clinical outcome data from patients easier, were becoming a burden. Site staff complained that many features of the platform slowed down their work, made patient visits longer, and made entering and correcting data more difficult. Many of the people who worked to develop these technologies had previously worked at clinical trial sites, and while it was disappointing to hear about these frustrations, it was clear that the sites hadn't had enough of a say during the platform's design process. The solution was to initiate a formal process to redesign the entire platform, starting with discussions with several investigators.

A prospective user focus group was made up of researchers who had experience with the company's tools in past clinical trials. This group included investigators, clinicians, and study coordinators. One-on-one sessions were conducted with a panel

FIGURE 2: ERROR RATES



References

1. Butler A, Feaster T, Gaughan S, Friedberger G. 2016. Incorporating user experience design into electronic clinical outcome assessment (eCOA) system design. Poster presentation at the 21st International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting in Washington D.C.
2. Feaster T, Solomon T, Barbone J, and Miller D. 2017. Using iterative user experience design to improve electronic clinical outcomes assessment data quality. Poster presentation at the 22nd International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting in Boston, Mass.

that included a clinician and a user experience researcher who would observe an untrained user navigating in the platform. Feedback was collected regarding the challenges that arose during use of the tool.

These observations were organized across the respondents and categorized to identify the areas of greatest need. Once this prioritization was complete, the product development team set out to revise the technology based on collected feedback (see Figure 1).[1]

User Experience Matters

As primary users, clinical trial site staff played a critical role in ensuring the new technology satisfied their direct needs. Throughout the new product development process, beta versions of the tool were tested with individual sites. Once the final version was complete, sites who participated in the original round of focus groups were given a first look of the new platform.

Most of the feedback had to do with the appearance of the interface and the feel of the user experience. In the initial rollout, the number one complaint from sites was that the interface confused users by being too simple. Suggested improvements included larger screen font size, smoother navigation between screens, better instructions, and more flexible methods for entering data. One common request was to make the display of the remaining battery percentage on the tablet computer more visible, in order to prevent loss of power during a patient visit.

When all of these adjustments were incorporated, a completely new version of the product was released for use in clinical trials.

Increasingly, the burden for introducing new tools in clinical trial sites has fallen on the investigators, research coordinators, and other staff at clinical trial sites who are on the front lines of research studies, yet sites are often left out of the design and development process.

Improving Data Quality

Following the product launch, the company periodically surveyed sites to ensure that the revised platform worked well for users. Although areas for improvement continue to be identified, many of the core revisions have been well-received by site staff.

The primary goal of such technologies is to improve the functions of collecting and analyzing data. Because of this, the company also took the time to compare the quality of data collected on the old platform to that of the new platform, and found that the new platform enabled a significant improvement in data quality. The revisions made to this technology contributed by reducing error and ensuring standardized administration and scoring (see Figure 2).[2]

In short, by re-focusing product development priorities to directly address the needs of trial sites, vendors can produce products that better serve all stakeholders in the clinical trial process.

Adam Butler (adam.butler@bracketglobal.com) is senior vice president for strategic development and corporate marketing with Bracket, a company focusing on clinical research data services and technology based in Wayne, Pa.

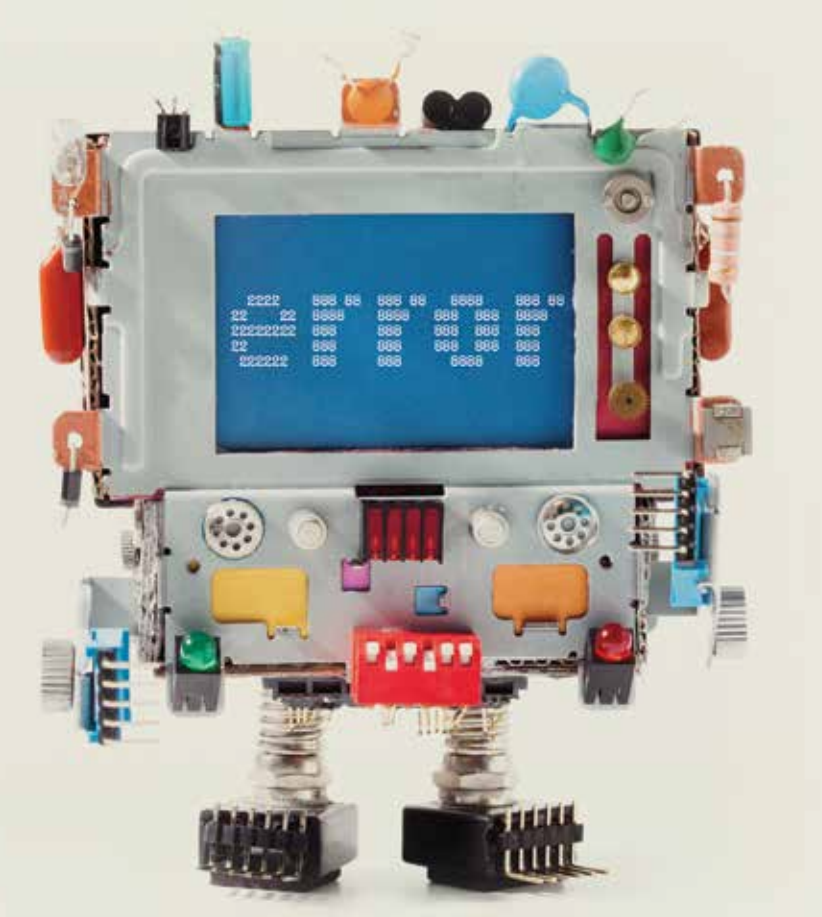
[DOI: 10.14524/CR-17-0002]

Medical Device Recalls: A PRIMER

PEER REVIEWED | Pranali M. Wandile, MS, CCRP

For the purposes of this article, a "recall" is the process of removing or correcting medical device products deemed to be in violation of U.S. Food and Drug Administration (FDA) regulations.

In most cases, manufacturers and distributors voluntarily recall a problematic product out of a sense of responsibility for protecting public health from a defect that poses a risk of injury or gross deception. Guidance for recalls is described under 21 CFR Part 7 in the *Code of Federal Regulations.*[1]



The most common causes for recalls fall under the areas of device design, software, and nonconforming material or component issues. FDA has stated that approximately 400 recalls each year can be prevented through joint efforts of industry and the agency's Center for Devices and Radiological Health (CDRH).[2]

FDA legally can ask a firm to recall a device if the firm refuses to recall a device associated with significant health problems or death on its own initiative. However, in actual practice, FDA has rarely needed to recall a medical device as the process is described under 21 CFR 810 Section 518(e) of the Federal Food, Drug, and Cosmetic Act.[3]

This article provides an overview of the types of individual device recalls, the process of recall, and what exactly FDA would like to implement when medical devices are recalled.

Background

FDA data indicate that a 97% increase in recalls of medical devices occurred between fiscal years 2003 and 2012 due to stepped-up public safety efforts by regulators and by industry.[4] The agency publishes an Enforcement Report on a weekly basis containing all enforcement actions, including recalls, field corrections, seizures, and injunctions.

When a product violates FDA regulations, manufacturers and distributors do two things[5]:

- Recall the device (correction or removal of device at or from the places it is used or sold)
- Notify FDA

Patients in possession of a recalled device are to stop using the product; sometimes it must be removed and returned to the company, sometimes it just needs to be checked, adjusted, or fixed.

Moreover, the device companies inform doctors regarding how to discuss various options with affected patients. For example, if manufacturer companies found that an implanted device has the risk of failing unexpectedly, they inform doctors to contact their patients to discuss the risk of removing the device compared to the risk of leaving it in place.[6]

What Actions May be Involved in Recalls?

A recall may involve inspection of the device for problems, re-labeling the device, destroying the device, notifying patients of a problem, monitoring patients for health issues, repairing the device, and adjusting settings on the device. Further, when a company has concerns about a group of devices, but is not sure which individual device is affected, it recalls the entire lot or product line.

FDA describes recall procedures and assessments of the adequacy of a firm's actions in recall in 21 CFR 7. A recall can be disruptive of a firm's operation and business, but there are several steps a firm can take in advance to reduce these effects. Having these procedures in place prior to any recall can make the recall process more efficient for everyone involved; apart from quality system regulations (21 CFR 820), a firm can take the following measures:

1. Make contingency plan for initiating and effecting recalls in accordance with 21 CFR 7.
2. Use sufficient coding of regulated products for product lot identification.
3. Maintain product distribution records containing the location, shelf life, and expected use of the product, and retain these records for at least the time span specified in the applicable regulations.

Categories of Individual Recall

a. **Medical device design**—Beyond the overall design of a device, since significant numbers of devices are developed with software components, software design failure is becoming the leading cause of recalls.[4]

b. **Change control**—This includes component, labeling, vendor, process, packaging, software, and finished-device change control.

c. **Process control**—This includes process, packaging process, process design, or reprocessing controls.

d. **Material/component**—Including for reasons of nonconforming materials or components, component design or selection, material contamination, material mix-up, and removal or release of material prior to testing.

e. **Packaging/labeling**—For reasons of labeling mix-up, packaging, packaging design/selection, expired dating, labeling design, false and misleading labeling, or errors in labeling.

The Most Common Cause of Recall—Design Failure

A medical device may be software in and of itself, or may contain software, or may be manufactured through use of software. In any of these cases, a minor deviation in software design can cause a significant effect on a device's function and clinical performance.

Failure to implement software design controls can lead to software variance. Software design failures often require recalls of, improvements in testing procedures for, or changes that increase the complexity of the next version of the affected medical device.[4]

Development of complex medical device software and early availability of high-risk medical devices to patients can also lead to increases in recall frequencies. As reported by FDA researchers, in fiscal years 2010 to 2012, software design failure was the most common cause of recall, contributing to approximately 15% of all device recalls.[7]

In the aforementioned 21 CFR 820 on quality systems, section 820.30 on design controls states that, each manufacturer of Class I devices (low-risk) or any Class II/III (high-risk) devices should establish and maintain procedures to control the design of the device, in order to ensure that specified design requirements are met.[8]

Apart from Class II/III devices, Class I devices subject to design controls include those whose manufacture is automated with computer software and such devices as catheters, tracheobronchial suction providers, surgical gloves, restraints, protective systems, applicators, and items involving radionuclides.

FDA has also provided design control guidance for medical device manufacturers.[9] This guidance is designed to assist manufacturers in understanding the intent of the regulations. However, the guidance does not spell out the practices that must be used; instead, it establishes a framework

A recall may involve inspection of the device for problems, re-labeling the device, destroying the device, notifying patients of a problem, monitoring patients for health issues, repairing the device, and adjusting settings on the device.

that manufacturers must use when developing and executing design controls.

Design controls are focused on quality assurance and engineering principles, and must be applied to a wide variety of devices. The guidance provided by FDA supplements the regulations by describing the agency's intent from a technical perspective, using practical terms and examples.

Withdrawals and Health Hazards

A market withdrawal is when a firm removes or corrects an already-distributed product due to reasons involving a minor violation or no violation, and which are not subject to legal action by the FDA (e.g., normal stock rotation practices, routine equipment adjustments and repairs).[3]

Software design failures often require recalls of, improvements in testing procedures for, or changes that increase the complexity of the next version of the affected medical device.

Meanwhile, FDA conducts evaluations of the health hazards presented by products that have been or may be recalled, and this process include some of the following factors:

- Evaluation of any diseases or injuries that occurred due to the use of the product.
- Evaluation of possibilities of incidences of hazard.
- Evaluation of the consequences (immediate or long-term) of hazard incidences.
- Evaluation of any existing conditions that could aggravate clinical conditions in exposed device users. Any such finding should be supported completely by scientific documentation.

- Evaluation of hazard in various sections of population (e.g., children, surgical patients, pets, livestock, etc.) who may be exposed to the recalled product, with specific attention to hazard in individuals at greatest risk.
- Evaluation of the grade of seriousness of the health hazard in the population at risk.

Recall Strategy

Recall strategy is developed by considering a variety of factors,[6] including health hazard evaluation results, easiness in identifying the product, extent of product's deficiency that is obvious to the consumer, unused product extent in the marketplace, and continued availability of essential products.

The FDA will review a firm's proposed recall strategy, suggest changes, and approve it. A recalling firm should only use an approved recall strategy to conduct a recall, and it should factor in the following elements:

1. **Depth of recall—**This depends on the product's degree of hazard and extent of distribution (i.e., is the product available to consumers at large or used only by physicians, etc.).
2. **Public warning—**A decision must be made regarding whether a public warning is needed, for example, in terms of an urgent alert about a recalled product presenting a serious health hazard. Such warnings need to be submitted to FDA for review before being issued, and may be distributed through the general news media or through specialized news media, such as professional or trade press, to physicians, hospitals, etc.
3. **Effectiveness checks—**These verify that all buyers have received notification about the recall and have taken appropriate actions. A recall strategy should mention the level of effectiveness checks that need to be conducted according to the following definitions:
   - » **Level A—**100% of the total number of consignees are to be contacted
   - » **Level B—**More than 10% and less than 100% of the total number of consignees are to be contacted
   - » **Level C—**10% of the total number of consignees are to be contacted
   - » **Level D—**2% of the total number of consignees are to be contacted
   - » **Level E—**No effectiveness checks

If the firm believes that its product is in violation of FDA regulations, and if it wants to remove or correct the distributed product, then it should notify the appropriate FDA district office. If FDA thinks the product is subject to legal action, then such removal or correction will be considered a recall. In this case, the firm needs to provide FDA the following information, and the agency will assign a recall classification after its review: product identification; reason for the removal/correction; date and circumstances when product deficiency was discovered; risk evaluation; total amount of such products produced and/or the time span of the production; total quantity of such products estimated to be in distribution channels; distribution information (including the number and identity of direct accounts); and, if necessary, a copy of the firm's recall communication or purposed communication, recall strategy for conducting the recall, and official contact information regarding the recall.

FDA has classified recalls to indicate the relative degree of health hazard due to a recalled/suspected recalled product:

- **Class I Recall**—A situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health effects or death.
- **Class II**—A situation in which use or exposure to a violative product may cause temporary or medically reversible adverse health effects, or where the probability of serious adverse health effects is remote.
- **Class III**—A situation in which use or exposure to a violative product is not likely to cause adverse health effects.

Recall Conduct

A firm may decide to recall a product found to be in violation of FDA regulations[6] by means of sending a recall letter to all parties that received the affected product. The recall letter should be brief and to the point. Best practice is that the recalling firm will discuss the recall letter with the FDA district office's recall coordinator prior to sending it to anyone else.

A follow-up communication should be sent if there is a lack of response to the initial recall communication. Device buyers who received recall communication should immediately follow instructions given in the recall letter.

The recalling firm also needs to submit periodic recall status reports to the appropriate FDA district office until FDA terminates the recall. Generally, a recall status report should contain the following information: number of consignees notified of the recall; date and method of notification; number of consignees responding to the recall communication and the quantity of products they had at the time it was received; number of consignees that did not respond (identification of nonresponding consignees may be requested by FDA if needed); number of products returned or corrected by each consignee contacted; number and results of effectiveness checks that were made; and estimated time frames for the completion of the recall.

FDA will terminate the recall only when it is confirmed that all rational efforts have been made to remove/correct the product as per the recall strategy, and that the recalled product has been removed/properly disposed of/corrected. The appropriate FDA district office may issue a recall termination notification to the recalling firm on its own, or the recalling firm may inform the office of the details of the recall completion and request such termination notification.

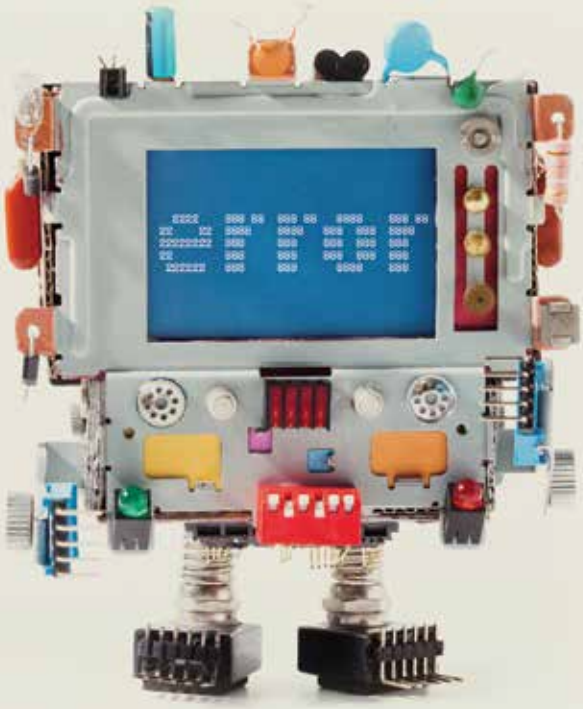
The appropriate FDA district office also assists the firm in determining the exact nature of the product problem and appropriate solution to the problem. Each recall has only one recall cause determination, and this uses FDA's current terminology and processes.[10]

In light of such recall actions, medical device design teams need to understand the requirements of the design controls standard. The right team, tools, and quality assurance are the main contributors to a successful medical device design and, with due diligence and perseverance, design flaws and recalls can be avoided.

Guidance from FDA

Additionally, FDA has developed guidance (paraphrased details of which are shared below) to offer transparency for FDA staff and industry regarding the benefit-risk factors in compliance and enforcement efforts to maximize medical device quality and patient safety. This guidance outlines the general framework for medical device decision making in terms of product availability, compliance, and enforcement actions. FDA believes that this can maximize benefits to patients, improve medical device quality, and reduce risk to patients.

Recall strategy is developed by considering a variety of factors, including health hazard evaluation results, easiness in identifying the product, extent of product's deficiency that is obvious to the consumer, unused product extent in the marketplace, and continued availability of essential products.



FDA will terminate the recall only when it is confirmed that all rational efforts have been made to remove/correct the product as per the recall strategy, and that the recalled product has been removed/properly disposed of/corrected.

FDA's "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions"[9]

FDA initiates a benefit-risk assessment of applicable (violative) medical devices by evaluating benefit-risk information and by considering the relevant benefit-risk factors, as described here in sections 1, 2, and 3.

1. **The following relevant factors may be considered in the assessment of *benefit* for a (violative) product's availability, compliance, and enforcement decisions:**
   - **Type of benefits**
     The following information can be verified by using available global data: the medical device's impact on clinical management and on patient health; confirmation of the expected benefits of the product; and whether additional benefits are reported for the product.
   - **Magnitude of benefits**
     Assessment of expected benefits covers such details as the possibility of patient survival, prevention of loss of function, and expected relief from symptoms of the disease.
   - Assessment of global data is performed to verify if the results are consistent with the aim of successful diagnosis or treatment being provided by the medical device, and to verify any new benefits, increases/decreases in benefit scale, and device impacts on patient health, quality of life, and clinical management.
   - **Likelihood of patients experiencing one or more benefits**
     With the help of available real-world data, this involves verifying the proportion of patients who benefitted from the device, verifying if there are any changes in the benefit across the different population, and verifying how use of the medical device causes variation in public health in different populations.
   - **Duration of effects**
     This covers verification of whether the duration of the medical device's effect is compliant with the expectations or if there are any changes in it.
   - **Patient perspectives on benefit**
     This concerns verifying the severity and chronicity of the disease state, and if alternative treatments or therapies are available. Even if only a small portion of the population benefits from the device, verification is sought about whether patients value those benefits and to what extent, and whether the product improves the overall quality of life of patients.
   - **Benefit factors for healthcare professionals or caregivers**
     This covers verification of whether there is any impact of real-world experience in terms of understanding the product's benefits for healthcare professionals/caregivers.
   - **Medical necessity**
     The availability of different alternative treatments and their effectiveness and tolerance should also be verified, as well as if there are any changes in the treatment options since the medical device was developed and how important the product is to patients.

2. **The following relevant factors may be considered in the assessment of *risk* for a (violative) product's availability, compliance, and enforcement decisions:**
   - **Medical device–related deaths and serious injuries**
     Verify if real-world/or other available data show expected or unanticipated deaths, or serious injuries due to the medical device. Verify if there are any changes in serious adverse events.
   - **Medical device–related nonserious adverse events**
     Verify if medically reversible injuries occur at expected severity, frequency, and duration, or if any unanticipated temporary injuries occurred as well. Verify if there are any variations in serious adverse events and if those events are still reversible, or require intervention.
   - **Medical device–related events without reported harm**
     Verify if medical device malfunctions are reported at anticipated/unanticipated frequencies, and if there are any changes in harmless device-related events.
   - **Likelihood of risk**
     Verify frequency of medical device failure or defect, and check if it has increased or decreased. Verify the information about the number of nonconforming medical devices, number of patients exposed, and proportion of patients harmed due to exposure to such devices.
   - **Distribution of nonconforming devices**
     Verify if violative product is distributed in the market and to what extent.
   - **Duration of the exposure to the population**
     Check the amount of time passed between initial exposure to risk of harm and removal of that harm.
   - **Risk from false-positive or false-negative results for diagnostics**
     Verify if the consequences of diagnostic errors/practices related to diagnosing the problem have changed and, if they have increased or decreased the risk.
   - **Patient tolerance of risk**
     Verify if the patients fully understand the risk, and if they are ready to accept the risk to achieve the benefit of the device.
   - **Risk factors for healthcare professionals or caregivers**
     Verify if there are any changes in frequency/severity of risks for healthcare professionals and for caregivers, and if those changes affect the patients.
3. **FDA completes the benefit-risk assessment by considering the following factors for a (violative) product's availability, compliance, and enforcement decisions:**
   - Uncertainty, mitigations, detectability, failure mode, scope of the device issue, patient impact, preference for availability, nature of violations/nonconforming product, firm compliance history.
   - Before making a decision that can affect the product's availability, FDA may also consider the extent of issues affecting the device's manufacturers, the impact of availability/nonavailability of the device on patients, and caregivers' preferences for availability of the affected device.
   - Generally, if FDA's benefit-risk assessment shows that a violative device has high benefit to patients with little risk, the agency may decide to work with the manufacturer to address the core issue without commencing a formal compliance or enforcement action. If FDA's benefit-risk assessment shows that a violative device has low benefit to patients with high risk, the agency would likely take formal compliance or enforcement action to address the problem.

Conclusion

To summarize, in this technologically advanced era of medical devices, public health is protected with the help of FDA regulations, guidance, and the joint efforts of both industry and CDRH, along with major public input.

References

1. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=7
2. https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/
3. https://www.fda.gov/OHRMS/DOCKETS/98fr/990260SS.pdf
4. www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhtransparency/ucm388442.pdf
5. www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm329946.htm
6. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=7&showFR=1
7. https://www.emergogroup.com/blog/2014/03/fda-report-us-medical-device-recalls-nearly-100-2003
8. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=820.30
9. www.fda.gov/RegulatoryInformation/Guidances/ucm070627.htm
10. www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm506679.pdf

Pranali M. Wandile, MS, CCRP, is a site manager with the DC Research Network in Georgia.

ON THE JOB
Joy Jurnack, RN, CCRC, CIP

[DOI: 10.14524/CR-17-4028]

Tackling Waste in Clinical Research

I tried to tally them all, but there were just too many. I stopped counting at 153 pre-packaged laboratory kits that had expired before we ever had a reason to use them in the latest ongoing trial at our study site.

Receiving a shipment of such kits from a central lab is a routine occurrence for sites like ours that run research trials. Many are the study coordinators who have worked with the big-name labs—the ones whose kits come in bags or boxes, stuffed full of tubes, needles, vacutainer connections, and various bags and labels for packing and shipping.

Yes, they provide a convenient way to ensure proper blood collection at scheduled protocol visits. Yes, they make our lives easier as coordinators at busy sites…but at what cost to the sites and to the environment?

A Sisyphean Task, Among Many Others

Recently, I spent two hours breaking down the pictured mountain of now-useless kits. Completing this task gave me time to think specifically about protocols and the practices surrounding such lab kits. I considered the complexity of the protocol our site had at hand, the contracted number of subjects we had agreed upon with the sponsor, and the amount of work it had taken to agree on a budget.

This is an early-phase trial with strict entry criteria, and the kits I broke down were for bloods to be drawn at specific time points. Our site has been open since last September, and we have only drawn screening samples on a participant's first visit on two occasions. Even if we had enrolled more subjects earlier, a large majority of the kits shipped to us last year would have expired by now. Why such a large volume of kits for the initial shipment? How much money was wasted on the ones that expired?

Collectively, as an industry, we must address the issue of waste. Let's consider study start-up; why not begin with a smaller number of start-up kits? Why not consider initial rate of enrollment and the length of time between visits?

In the past, I have asked a large central lab not to include 18 gage needles because we don't use them; we draw bloods with a butterfly, which provides a more comfortable experience for the subject. The response I received was that the kits are pre-packaged and this was not going to change. Why could we not compromise or have site-specific kits based on need?

Looking for a Challenge?

There must be companies who would love to take input on this challenge from all sides and synchronize this basic aspect of drug research and development between sites, sponsors, and central labs. Possibly the way to go is to use an online portal through which sites can resupply in smaller quantities, or an automatic resupply program to keep sites up to date for whatever time period is decided upon once a subject is enrolled. Whatever the means, let's keep it simple and easy to navigate, with the shared goals of cutting down on expenses and being environmentally conscious.

I would be happy to work with a central laboratory or sponsor or vendor firm on such a project, and I am sure there are others in our industry who would lend their expertise.

As I mentioned, I stopped counting at 153 pre-packaged laboratory kits that had expired. Just look at that picture and try to tell me that this doesn't represent a significant amount of waste when you consider that it happens at sites everywhere. Fiscal and environmental responsibilities should be shared between sponsors, central laboratories, and the sites.

Who wants to work on a project?

Feedback (or Not) from the Real World

In fact, since I first raised this topic for discussion by posting the preceding text on the ACRP Blog site in June (https://www.acrpnet.org/2017/06/19/tackling-waste-clinical-research/), I am reminded of how George Bernard Shaw said, "Progress is impossible without change, and those who cannot change their minds cannot change anything." Let us consider these wise words as we move into further discussion on waste in clinical research.

It seems the site where I work is not the only one that has tremendous waste. I was pleased to have responses from many of you, and I appreciate all your comments and suggestions. I heard from research nurses and coordinators who are now known as "the office recycling person" who splits expired kits to "donate our extra or expired lab tubes to a school for phlebotomists."

"This all takes time, and it is by no means a money-making venture," says one Certified Clinical Research Coordinator. She can sleep better at night knowing at least she has done something to "save the environment."

Another respondent said, "I have felt the same frustration with breaking down those expired lab kits" and yet another added, "It is a lot of waste and must (increase) the cost of developing new drugs."

I applaud these research professionals who break down, separate, donate, and recycle, and I do not blame those who throw kits in the trash. On the other hand, I'll admit I was disappointed I did not hear from industry.

The study that had those 153 expired kits involved a small company. I sent my blog to their medical director with an invitation to discuss how planning can minimize waste in future projects. I'm waiting to see if I get a response.

Not one sponsor or laboratory company responded to my blog with comments, defenses of their purchasing practices, or thoughts on how customization might increase budgets. We—those who do clinical research—are part of a tripod; in my humble opinion, the sponsor, the monitoring team, and the research team must look at this challenge as an industry.

Hope for the Future

Each response I got offered to be part of the solution. Even in my own institution, a group of research nurses wants to start a program for recycling.

The thing is…I want change. As I said, I think all parts of the clinical trials tripod need to work together on this. By no means do I believe this is an easy issue to tackle, but if the tripod worked together and made progress, we would be taking the lead in innovation for cost saving in clinical research.

As British architect Richard Rogers said, "The only way forward, if we are going to improve the quality of the environment, is to get everybody involved."

There must be companies who would love to take input on this challenge from all sides and synchronize this basic aspect of drug research and development between sites, sponsors, and central labs.

Joy Jurnack, RN, CCRC, CIP, (jjurnack@northwell.edu) works in the research program of the Division of Kidney Diseases and Hypertension at Northwell Health and is a member of the Academy Board of Trustees for ACRP.

[DOI: 10.14524/CR-17-4036]

ACRP's New Workforce Innovation Officer Speaks to the Need for Competencies

Beth Harper, president of Clinical Performance Partners, Inc., a clinical research firm, has worked to enhance patient recruitment and retention and improve sponsor and site relationships for more than 30 years.

Last month, the Association of Clinical Research Professionals (ACRP) named Harper its new Workforce Innovation Officer. She will spearhead ACRP's initiatives to lead innovation in clinical research workforce development, including development of a competence-based Entry-Level Assessment for clinical research professionals and promotion of industry-wide adoption and implementation of ACRP's recently published Core Competency Framework for Clinical Study Monitoring.

Clinical Researcher Editor-in-Chief James Michael Causey recently spoke with Harper about the state of the industry—and how ACRP can help drive important change.

James Michael Causey: Why do we need to establish professional competencies?

Beth Harper: A lot of work in the last five years has been done with the harmonized competencies from the Joint Task Force for Clinical Trial Competence. However, I think we still have far to go in terms of creating overall career maps for professional development, as well as really clarifying expectations for what different roles at different levels of maturity require.

JMC: How will doing this improve the industry's performance?

BH: I think it will help set expectations for the hiring, further training, and career development of professionals across many different domains; not just coordinators or investigators or monitors, but across a broad range of roles that people can take on in the industry, such as data management, project management, quality assurance, and so forth.

JMC: Where do you think we are in the process right now? This is a big paradigm shift.

BH: We just published the Core Competency Framework Clinical Study Monitoring for the different levels of clinical study monitors/clinical research associates. As it is so new, we're just in the process of working with the companies who helped support that initiative in terms of implementing those standards within their organizations, and getting industry stakeholders at large more aware of the framework and how it can benefit them.

In addition, we're trying to build on all the work that went into the framework and take it to other job roles, as well as develop a new Entry-Level Assessment (ELA) that goes in a different direction than certification. When employers are bringing people in who are not certified, they need to know that they have some minimum level of competency for the job roles—at least entry-level roles—in clinical research. Having an ELA creates a baseline knowledge assessment from which gaps can be identified, and training and career plans developed to help further the growth and professionalism of the individuals working in clinical research.

JMC: It sounds like we need to get away from the tenure aspect. We want it to be more about skillsets and demonstrated competencies.

BH: Absolutely. Instead of focusing solely on tenure and job descriptions, let's go for KSAs—Knowledge, Skills, Abilities—and competencies.

JMC: What do you see as ACRP's role in this, and how you might be able to help more in this new position?

BH: I think ACRP is really driving this change in focus to the people part of the equation, and is really taking the leading role to operationalize the competencies into something practical for employers and employees.

I'm interested in taking my experience and applying it to this more pragmatic workforce development. There's the academic view of how you grow clinical research professionals, which I have been involved with, and there's this practical arm. That's where I'm really excited about taking all of my passions in clinical research operations, training, and education and helping to drive this to the next level of practical application.

JMC: In terms of the landscape, what would be your hopes/expectations for where we might be in the near future?

BH: Within a few years, I would hope that the nomenclature of competencies is well-established and common language. That we all start referring to the competency domains and competency statements as part of our normal vernacular of speaking about requirements and expectations for clinical research professionals. Also, that we would have better tools for helping employers and employees understand the different job-level competency requirements.

ACRP Announces Clinical Research Training Participants

In recent months, the Association of Clinical Research Professionals (ACRP) has been proud to announce that the National Association of Veterans' Research and Education Foundations (NAVREF), Science 37, Inc., and JDRF have signed on as subscribers to ACRP's Site License program for clinical research training.

The program provides the organizations' employees or members access to ACRP's full catalog of online clinical research training programs. With 20-plus programs included in ACRP's eLearning curriculum delivered on a state-of-the-art Learning Management System, they now have direct access via a site license to one of the most well-respected and highest quality suite of training programs available on the market. The proprietary, organization-branded hosting environments not only provide cutting-edge clinical research training, but administrator control of user and learner records.

"We are thrilled to work with these outstanding organizations to license the full suite of ACRP eLearning training programs," says ACRP Executive Director Jim Kremidas. "They have demonstrated their true commitment to quality, and we're honored that they trust ACRP to provide an additional element of training for their members."

"We're excited to partner with ACRP to provide this terrific learning opportunity to clinical research professionals associated with NAVREF and our member nonprofit corporations," said Rick Starrs, NAVREF's chief executive officer. "NAVREF is offering this free training to ensure site staff have the tools they need to conduct safe and high-quality research focused on improving the health of veterans."

"Our Clinical Operations team is a critical part of managing Science 37's end-to-end clinical research process," says Susan Ko, a vice president with the company. "ACRP's Learning Management System will help ensure that our team is given thorough foundational training so that they may provide the highest level of support while supervising patients' care during research studies. Additionally, we will be using ACRP's intro course to provide a common language across our entire company."

"We're pleased to be working with ACRP to create an eLearning program on clinical trial management for select clinical trial sites funded by JDRF research grants," said Malavi Madireddi, PhD, head of clinical trials management for JDRF, the leading global organization funding type 1 diabetes (T1D) research. "JDRF is offering this free training to ensure site staff members have the tools they need to conduct safe and high-quality research, and to accelerate the development of life-changing breakthroughs to cure, prevent, and treat T1D and its complications."

ACRP's eLearning programs are developed with the distinct goal to drive performance improvement for those engaged in clinical research. Each program delivers interactive material aimed at enhancing human subject protection, data quality, and regulatory compliance for organizations of all size within the clinical research space.

NAVREF
National Association of Veterans' Research and Education Foundations

Science 37

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

"We are thrilled to work with these outstanding organizations to license the full suite of ACRP eLearning training programs."

– JIM KREMIDAS

The Latest News from the World of Workforce Innovation

CTTI CHALLENGES CURRENT INVESTIGATOR TRAINING REGIMEN

Good clinical practice (GCP) training has become the standard for qualifying investigators to conduct clinical trials, but little evidence has been collected to determine whether this training is providing the necessary knowledge and skills, says Jennifer Goldsack, MA, MBA, CPHQ, project manager of a team conducting in-depth interviews of contract research organizations (CROs), sponsors, and investigators.

Rather than accepting GCP training as the default solution for qualifying investigators, the Clinical Trials Transformation Initiative (CTTI) has launched a project on "Qualifying Investigators to Conduct Sponsored Clinical Trials" (https://www.ctti-clinicaltrials.org/projects/investigator-qualification). Project leaders hope to gain a broader, evidence-based perspective that can inform the efficient and effective qualification of site investigators to advance the high-quality conduct of clinical trials.

CTTI hopes its findings will be "disruptive," Goldsack says. To achieve it, CTTI's commitment to evidence-based recommendations will be key. The project team working on this effort already boasts a diverse, multistakeholder group of experts. They are insistent on digging deeper, though, conducting expert interviews with dozens of investigators and sponsor experts, and planning for a large, expert meeting in the fall.

"We didn't want a 'check the box' kind of survey," Goldsack explains. "We want to get to the heart of [the issue] and come up with ways to fix it."

While full recommendations aren't likely to be published until Spring 2018, CTTI hopes to have some preliminary results in the next few months.
(Source: ACRP Blog, https://www.acrpnet.org/2017/06/27/ctti-challenges-current-investigator-training-regimen/)

CAN CROs TAKE THE STING OUT OF CRA TRAVEL?

Remote monitoring tools and other technologies aside, travel will remain a basic requirement for clinical research associates (CRAs) for years to come, says Joe Mills, senior director for the Global Recruitment Center with inVentiv Health Clinical. "It's a core necessity and you can't get away from it," he notes.

The demands of travel are also among the biggest factors contributing to elevated levels of CRA turnover and burnout. However, there are ways to mitigate the travel burdens faced by CRAs, Mills says.

Some travel-oriented tactics might be more difficult for small or even medium-sized contract research organizations (CROs) to replicate. Still, Mills has enjoyed great success with a few basic travel tips:

- Transportation Security Administration (TSA) PreCheck: Help your CRAs sign up for this opportunity to be classified as low-risk travelers who can enjoy expedited security screening, especially if they do a lot of domestic or overseas plane travel. It's an inexpensive perk with a big return.
- Airline Membership Clubs: Help CRAs join these where possible. They'll make layovers much more pleasant. Some offer separate, concierge-type, private lounges where it's easier to relax and be more productive writing up trip reports during the various legs of journeys.
- Bag Tags: Sounds simple, but CROs might be surprised how much traveling CRAs appreciate a distinctive tag to help them find their luggage as it circles a crowded baggage claim carousel.
- Luggage Expense Reimbursement: CROs can provide their CRAs some financial assistance to replace travel bags that are reaching the ends of their lifespans.
- Travel Algorithms: Help CRAs plan smart, efficient travel itineraries that build in as many day trips and regional travel routes as possible.

(Source: ACRP Blog, https://www.acrpnet.org/2017/06/13/can-cros-take-sting-cra-travel/)

SITES MUST EMBRACE TECHNOLOGY OR FACE THE CONSEQUENCES

It's not always hard to predict the future, according to John Neal, founder and chairman of Network LLC. For example, increased use of wearables and remote monitoring means fewer onsite clinical trial visits. Fewer clinical trial visits means a decrease in demand for site locations.

In these early days of advanced technology usage, sponsors are looking for trusted site partners "at the front of the parade," Neal says. Sites that resist could find their business operations threatened as more and more sponsors look to the sites that demonstrate they can leverage tech innovations for increased efficiency in studies, he explains.

The adoption of mobile data collection, mobile visits, smartphones, and wearables means trial participants don't always need to trek out to a site.

The result? According to Neal, it'll mean fewer sites with more centralized subject populations.

"Complacent sites should be concerned about this trend," Neal says. Sites that wait too long to work with sponsors to get up to speed with their tech "won't have a chance" to keep their current level of business, he warns.
(Source: ACRP Blog, https://www.acrpnet.org/2017/07/10/sites-must-embrace-technology-face-consequences/)

ARE RESEARCHERS KEEPING PACE WITH WEARABLE DEVICE PRIVACY REGULATIONS?

Regulations aren't keeping pace with technology when it comes to security and privacy issues and wearable medical data devices, and that can spell trouble for researchers in clinical trials, warns Marti Arvin, vice president of audit strategy with Cynergistek and a former chief compliance officer for an academic research center.

It isn't as if researchers aren't concerned about complying, Arvin stresses. The bigger issue is helping researchers understand how to comply. "If you don't make it easy for them, they are less likely to make it a top priority," she says, in part because they won't recognize when they might be veering out of regulatory compliance.

Meantime, the Clinical Trials Transformation Initiative (CTTI) has released a new set of recommendations (https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/novelendpoints-recs.pdf) for how best to develop novel endpoints generated by mobile technology for use in clinical trials. It outlines how doing this right will enhance patient centricity, efficacy, and overall efficiency.
(Source: ACRP Blog, https://www.acrpnet.org/2017/07/11/researchers-keeping-pace-wearable-device-privacy-regulations/)

PIs STRUGGLE WITH INCREASINGLY COMPLEX OVERSIGHT DEMANDS

Lack of adequate oversight and improper delegation of authority continue to dog clinical trial operations. One or both of those problems are frequently cited by U.S. Food and Drug Administration (FDA) investigators in Form FDA 483s ("Inspectional Observations") after inspection of a study facility, notes Mariette Marsh, MPA, CIP, director of the Human Subjects Protection & Privacy Program for the University of Arizona.

According to the FDA, the buck stops with the principal investigators (PIs); however, Marsh says it's getting tougher and tougher for PIs to provide direct oversight for personnel working complex trials. That means it's imperative for PIs to learn how—and when—to delegate.

It's critical to implement a system to document delegation of authority in a regulatory-compliant manner. However, that documentation must be based on a clear understanding of the investigator's responsibility for study conduct. "You need to know how to obtain and maintain ethically responsible delegation of authority," Marsh says.
(Source: ACRP Blog, https://www.acrpnet.org/2017/06/26/pis-struggle-increasingly-complex-oversight-demands/)

TRANSFORMING CLINICAL TRIALS THROUGH INDUSTRY COLLABORATION

Heading into 2017, it was widely held that the biggest trend in life sciences would be increased industry collaboration. With the midpoint of the year now past, it would seem indeed that collaboration has risen to a top strategic priority for many pharmaceutical and biotech companies whose leaders are working together more closely to overcome the many challenges facing the industry from the clinical to commercial stages.

One example of technology that is enabling the trend comes in the form of the recent integration of the Shared Investigator Platform, an initiative of the nonprofit TransCelerate BioPharma Inc. to facilitate investigative site collaboration with multiple clinical trial sponsors, with Veeva System's Vault SiteExchange, a cloud application for helping sites consolidate study document requests, alerts, and notifications across sponsors enrolled in the platform.

Other examples of collaboration include the European Lead Factory of the Innovative Medicines Initiative, which aims to create new chemistry based on crowd-sourced ideas and boost applicants' drug discovery programs at no upfront costs, and the public-private Accelerating Medicines Partnership linking the National Institutes of Health and the U.S. Food and Drug Administration with 10 biopharmaceutical companies and several nonprofit organizations.

What's driving such efforts? According to Rik van Mol, vice president of research and development strategy in Europe for Veeva Systems, in an article published June 19 in *Journal for Clinical Studies,* "Finding patients and investigators to participate in studies is harder, and competition is intensifying among sponsors seeking to collect more data and differentiate their products in the marketplace. Consequently, data [are] collected from a variety of sources—in different formats—placing a heavier burden on companies to manage it all."
(Source: ACRP Blog, https://www.acrpnet.org/2017/06/15/transforming-clinical-trials-industry-collaboration/)

HOME STUDY

HS

Sites: The Front Lines of Clinical Research

HOME STUDY TEST

Earn 3.0 Continuing Education Credits

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

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

ACRP DISCLOSURE STATEMENT

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

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

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

CONTINUING EDUCATION INFORMATION

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

Contact Hours

The Association of Clinical Research Professionals (ACRP) provides 3.0 contact hours for the completion of this educational activity. These contact hours can be used to meet the certifications maintenance requirement. (ACRP-2017-HMS-008)

Continuing Nursing Education

The California Board of Registered Nursing (Provider Number 11147) approves the Association of Clinical Research Professionals (ACRP) as a provider of continuing nursing education. This activity provides 3.0 nursing education credits. (Program Number 11147-2017-HMS-008)

Continuing Medical Education

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

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

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

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

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

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

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

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

Explore our open job opportunities at DiscoverYourPRA.com

PRAHEALTHSCIENCES

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.

TO CONTACT US

Francisco Moncada, R.N., B.S.N., C.C.R.C., President
Email: info@fxmresearch.com • www.fxmresearch.com

FXM Research Corp.
Hector Wiltz, M.D., CPI.
(305) 220-5222 Office
(305) 220-5779 Fax

FXM Research Miramar
Francisco Flores, MD
(954) 430-1097 Office
(954) 430-5502 Fax

FXM Research International – Belize, Central America
Julitta Bradley, MD & Ines Mendez-Moguel, MD
(305) 220-5222 Office
(305) 220-5779 Fax