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EXECUTIVE DIRECTOR'S MESSAGE

Putting "One and Done" in the Rearview Mirror

Jim Kremidas

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It's called the "one and done" phenomena, and it's a problem that has plagued the clinical trial industry for years. It refers to physicians and other medical professionals who are would-be principal investigators (PIs), though completely or relatively inexperienced in clinical trials, and who take one on as PI in hope of adding a new revenue stream to their practice or boosting their academic credentials.

Unfortunately for them, and patients, they quickly find conducting a trial isn't so easy after all. They underestimate the time and personnel needed to get the job done right. So, they struggle to complete their portion of the trial and drop out. Sometimes they drop out before the trial concludes.

There are several other forces at work driving the problem of PI churn. Trial protocols are increasingly complex and sponsor demands increasingly onerous, regulators continue to raise the bar for study conduct, and minus clear, industry-wide standards and certifications, it's incredibly difficult for prospective PIs to do their homework adequately before they decide to become part of the clinical trial process.

In addition, the standards for compensation are murky. For example, a PI may or may not be compensated for activities tied to site selection and initiation for a sponsored study, the investigator meeting to go over the study protocol, ongoing oversight of the trial, review of adverse events and serious adverse events, review of laboratory reports, monitoring visits, site phone calls, and the site close-out visit.

Recognizing the Challenges

It's timely that this month's *Clinical Researcher* looks at the important role of the PI as we join together to address these challenges and to try and put them in the rearview mirror of the research enterprise.

Evidence of the PI turnover problem abounds. A 2014 study by Tufts Center for the Study of Drug Development counted some 40,000 PIs, with half being new to job. In addition, although the highest turnover rates are observed among the least active investigators, turnover rates have been getting progressively worse among more active investigators.

At ACRP, we're working to further professionalize the clinical trial workforce. For example, in January we released the clinical research industry's first-ever competency guidelines for clinical research coordinators (CRCs), a study team role in which professionalism can make a world of difference for PIs' capacities to take on and remain engaged in clinical trials. The groundbreaking guidelines provide a comprehensive roadmap by which individuals and organizations can support the hiring, assessment, and development of entry-level through senior CRCs.

Variance is the enemy of quality. The *ad hoc* manner in which we hire and train CRCs is a root cause of poor quality and inefficiencies in clinical research conduct from the beginning to the end of the trial lifecycle—a span for which PIs take on full responsibility by signing the Form FDA 1572 (Statement of Investigator) to receive U.S. Food and Drug Administration approval to conduct their trials. We are also failing those at the front lines of clinical research by leaving them without an industry-wide consensus on what we expect from them, and how they can grow in their careers.

We hope these guidelines will provide CRCs with the support they need while improving operational quality and trial outcomes for their PIs and for all stakeholders in the clinical research community. And that's just a start. Watch this space for some exciting new developments throughout the rest of 2018.

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MANAGING EDITOR'S MESSAGE

Spreading the Good News

Gary W. Cramer

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In one of my previous lives, I spent the better part of 15 years writing enough press releases about the findings of faculty and student research projects for a major university that you could have lined them up to the moon and back (or so it felt at the time). The goal of this vast output of verbiage was to either get media outlets to share portions or all of the releases with their audiences, or to inspire reporters to contact the researchers and develop their own spins on the significance of the findings, thus spreading the fame of the university's research prowess far and wide.

I rarely dealt with medical topics back then, and knew little about clinical research. These days, I have a better appreciation of how difficult it can be to attract and retain talented researchers—especially those who will serve as principal investigators (PIs)—for the serious business of conducting studies that support the development of new and improved drugs, medical devices, and other therapies with participation from volunteer subjects.

The authors of the peer-reviewed articles and several of the columns in this issue of *Clinical Researcher* bring to the fore some of the challenges and promising avenues facing PIs and their teams in terms of maintaining and strengthening the clinical research enterprise. In the midst of real and feared global health crises, both the challenges and promises have high stakes, considering the rapidly evolving environment we find ourselves in for engaging researchers and patients, adhering to regulations, and disseminating findings.

More to Come

We hope to bring you even more PI-centric insights of this nature in the pages of the journal later this year, and we encourage more PIs and members of clinical trials teams at large to share their knowledge and experiences with the clinical research community by writing for *Clinical Researcher* or by writing or being interviewed for the online *ACRP Blog*. Please feel free to contact me at any time if you have ideas for scholarly articles, informal columns, or opinion pieces that would be of value to our enterprise.

Gary W. Cramer (gcramer@acrpnet.org) is Managing Editor for ACRP.

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PEER REVIEWED

Opinion: Approaches to Set Up Principal Investigators for Success

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Show of hands—how many people believe that principal investigators (PIs) are not currently set up for success? Odds are that not many hands would go up with confidence after that question.

As the perception of this role in the drug and device development industry currently stands, it is not surprising that the number of active PIs continues to decline.{1} This can gut enthusiasm for opportunities in the field, which is a shame, because being a clinical research investigator used to be a coveted role. What happened, and how can we turn the tide to encourage young clinicians to seek out opportunities to lead clinical research?

What is the Problem?

The problem is the lack of PI oversight and engagement in clinical research. Over the last decade, the number one cause of Form FDA 483s (Inspection Observations) leading to Warning Letters from the U.S. Food and Drug Administration to PIs was protocol compliance issues, such that "an investigation was not conducted in accordance with the signed statement of the investigator."{2}

By signing Form FDA 1572, PIs agree to take on full oversight of the clinical trial, including the investigator agreement, adherence to the protocol and investigational plan, and ensuring the rights, safety, and welfare of all clinical trial participants. This is a daunting task, considering most PIs are *not* directly responsible for the hiring, training, and allocation of available resources

for the research team members within their oversight who are delegated to complete various clinical research tasks.

The conundrum is the incongruence between the government regulations requiring full responsibility of oversight to be owned by the PI, versus the operational practice most often owned by a healthcare administrator. To be honest, I prefer the PI to be the scientific and medical expert on the clinical trial and leave administrative functions to the professionals with expertise in that area.

Let's not forget that the list of additional stressors on the economic healthcare landscape contributing to the decline in investigator oversight and engagement includes:

- Decreased National Institutes of Health grant funding available to support academic careers.{3}
- Increased regulatory requirements regarding adherence to International Council for Harmonization guidelines, the U.S. Health Insurance Portability and Accountability Act mandates, and U.S. government Meaningful Use standards for using electronic health records.{4}
- Study budgets have remained static, despite trends of greater study complexity and requirements, including exponential increases in terms of electronic data capture systems each requiring lengthy training and unique logins.{4}
- Lack of adequate supporting research staff.{5}
- Lack of dedicated time for research activities.{6}
- Lack of financial incentives and/or recognitions.{6}
- Lack of PI orientation or training for the responsibilities for clinical research, despite those in this role having the most responsibility for complete oversight of the clinical trial activities per the 1572.{6}

In summary, as an investigator, you're faced with less funding, less time available, fewer resources, lack of training on clinical trials operations, and 100% responsibility of oversight on a team you with many members whom you neither hired nor trained. Sign me up!

However, there are obviously sites full of professionals that conduct clinical trials very well, indeed. These sites have institutional support to ensure the above issues are addressed in their organizational infrastructure.

With severe limitations in the availability of grant funds, site administrators have the difficult job of balancing their clinical trial portfolios amongst industry-sponsored, grant-funded, investigator-initiated, and cooperative group trials, all while meeting the community needs for innovative treatment options. These site administrators dig deep to find their true costs of running trials, and justify the amounts in their study budgets.

Truly thoughtful administrators will turn down trials with inverse expense to revenue ratio if the trial provides no other value to their sites. These site leaders understand the need to operate like a business; not accepting revenue losses simply because it is research. The culture and expectation at these sites is that adequate investigator time and resources are given for research and, in return, the sites meet research and accreditation standards. Standout sites include Duke Clinical Research Institute, clinical trials units at such other academic medical centers as the ones based out of Northwestern University and Baylor University, the Sarah Cannon Research Institute, and the HonorHealth system in Arizona.

How to Make the PI Role Attractive Again

Sharing Success Stories

The first thing I would do is highlight successful investigators in a variety of therapeutic areas and share their success stories. What are the common denominators that they share? My educated guess is that these PIs have been influenced by great mentors, have dedicated time for clinical research activities, and are part of a site that invests in the infrastructure required to execute clinical trials well, instead of demanding to financially break even on day one.

All of the above-mentioned qualities allow exceptional PIs to focus on their research and practice responsibilities, instead of on the types of administrative duties that can be handled by non-physicians on site. Further, both new and ongoing PIs who want to reach and remain on the

leading edge of trials will seek out other successful investigators and network with them at industry events or other opportune moments.

An example of a defined and successful mentoring program is HonorHealth's Drug Development Scholar program. This program recruits young oncologists and hematologists with a passion for drug development. The one- to two-year program focuses on early-phase clinical trial development, patient recruitment and follow up, statistical analysis, bioinformatics and regulatory affairs.

The scholar functions as a specialist physician, performing duties involving direct care of patients with advanced malignancies and those receiving treatment on clinical trials, evaluating new patients, and formulating treatment plan under supervision of the assigned faculty member.{7} The Drug Development Scholars are fully immersed in the program, with interaction with all of the research staff.

The American Association for Cancer Research and the American Society of Clinical Oncology also support an annual educational workshop on "Methods in Clinical Cancer Research." The July 2018 event is described as an "*intensive workshop in the essentials of effective clinical trial designs of therapeutic interventions in the treatment of cancer for clinical fellow and junior faculty clinical researchers in all oncology subspecialties, including radiation and surgical oncology and radiology."{8}*

Encouraging Nurse Practitioner Participation

My second recommendation is to encourage experienced nurse practitioners (NPs) to participate in clinical research as principal and sub-investigators. NPs are currently underutilized in clinical research, despite many of them having followed research curricula in advanced degree programs.

There is no regulation that requires PIs to be physicians. Per the *Code of Federal Regulations* in CFR 312.53 and 812.43, sponsors of clinical investigations are required to select investigators who are qualified by education and experience as appropriate experts to investigate the test article, whether investigational product or device.{9} Not only does the inclusion of NPs as PIs and sub-investigators increase the pool of investigators to execute trials (thus helping more

patients and advancing science), it also may raise the bar on the quality of the execution of clinical trials due to their holistic training.{10}

Major pharmaceutical companies such as Celgene, Eli Lilly, Aveo, Nektar, and AbbVie have all sponsored studies run by NP PIs. Central institutional review boards such as Western IRB have and will approve qualified NPs to be PIs on industry-sponsored trials. While physician PIs are far more common than NP PIs, there is an established precedent to build upon.

Emphasizing Training

Regardless the educational background and professional licensure of investigators, they all need adequate training on the responsibilities of being a clinical investigator. Do they understand the requirements on Form FDA 1572 and the consequences of not fulfilling the relevant duties?

Clinical investigator training programs are offered by the Association of Clinical Research Professionals, the National Institutes of Health, the Collaborative Institutional Training Initiative, and academic and private organizations. Site leaders can take the training further and pay for their investigators to become certified as PIs; this demonstrates to sponsors their dedication to the role.

Sites also need a thorough investigator orientation process and competency checklist. The site orientation helps investigators understand how the site operations support their responsibilities in clinical trials oversight. An orientation should lead to routine meetings with the research staff to review and discuss research participants and documentation, and to provide guidance on reporting adverse events, updates on performance status, clinical significance of assessments, and standard operating procedures on training for new protocols and amendments.

Conversely, when taking a role at an institution, physicians and NPs should be turning the tables to ask what resources are available to be successful in the investigator role. Does the site have adequate staffing (including a low turnover rate on staff), a positive reputation in the industry, and administrators who understand the unique needs of running clinical trials? Are financial payments designed to incentivize or de-incentivize participation in clinical trials? Investigators

are obviously going to have better engagement and oversight when they choose to work at sites where the leadership understands the requirements and value of conducting clinical research.

Conclusion

Without a team effort, we will continue to see the number of investigators decline. Sites need to seek sustainability, conduct high-quality training and mentoring for new PIs, and explore expanding the talent pool with experienced NPs. Site leaders need to ensure sites are set up for success for all employees—including investigators.

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PEER REVIEWED

Embedding Clinical Research into the Continuum of Care

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Clinical research is the frontline of medical innovation. Through research projects, scientists and physicians make medical breakthroughs that directly impact the lives of patients and their families. However, what many patients and physicians don't realize is that when clinical research is integrated into the continuum of patient care, it represents a valuable care option.

When patient volunteers participate in clinical research, they get access to leading-edge research treatments or devices, generally at no cost, and a network of healthcare providers who are focused on making sure their overall experience is positive, and meets the highest quality medical standards. Such care excellence is a critical component of the clinical research experience for a patient volunteer. Study leaders are deeply invested in each participant, and go to great lengths to ensure trial volunteers adhere to strict care protocols. That translates to greater adherence, and often results in patients, as healthcare consumers, being more educated and invested in their care.

Such dedication to patient care doesn't just benefit the researchers. Patient engagement has become an increasingly important measure of success in the healthcare space. Mounting evidence confirms the influence of patient engagement on improved health outcomes and on reduced costs.{1} This directly drives the coveted value-based healthcare delivery of improving the patient experience of care, improving overall population health, and reducing the per-capita cost of healthcare.

Participation as a Positive Experience

A recent study shows that people can be far more engaged in their care when participating in a clinical trial, perhaps because they see the connection between their participation and the greater good of the patient community. In this 2015 study, a series of phone surveys were conducted with 42 diabetic patients participating in an ongoing diabetes clinical trial. The results showed a surprisingly high level of patient engagement and satisfaction with their treatment.

Overall, the surveys show positive experience across all dimensions for clinical research participants, with significantly higher levels of satisfaction in many patient-important dimensions, such as access to care, efficiencies in care delivery, and qualities of care received from the research team. Fully 100% of respondents said participating in clinical research reduced the overall cost of their healthcare compared to traditional treatment options; and 95% agreed that adding clinical research improved their overall quality of care. These data points validate what we've long known—that patient volunteers generally have an overwhelmingly positive experience when participating in clinical trials.

Even more intriguing, all participants said that participating in clinical research improved their interest and/or involvement in their overall healthcare. In the free-text response, many respondents said they found that the trial experience motivated them to be more engaged in their care, and prompted them to educate themselves about their disease. They also felt the research team more closely monitored their status, and that the experience inspired them to be more focused on their health.

In an era in which treatment adherence is a significant challenge, these results should excite physicians, other providers, healthcare systems, and payers. Non-adherence is associated with higher rates of hospital admissions, suboptimal health outcomes, increased morbidity and mortality, and increased healthcare costs, according to the U.S. Centers for Disease Control and Prevention.{2}

Looking ahead, further research is needed to quantify the influence of integrated clinical research on adherence, along with patient satisfaction, population health, and cost. However, this and other studies{3,4} suggest that participation in trials can have a positive impact on adherence,

and thus perhaps reduce the negative effect of this trend. Data from patients across several therapeutic categories at several value-based healthcare systems could generate further evidence supporting meaningful integration of clinical research as a care option.

Physicians and Research: A Collaborative Approach

The care delivery model, embedded within a patient volunteer's clinical trial journey, brings tremendous shared value—not just for biopharma companies in collecting data, but in the outcome, experience, and cost to the healthcare consumer.

Despite these benefits, healthcare organizations have often ignored the value of integrating clinical research into the overall continuum of care—and that's a problem. Low clinical trial participation exponentially increases cost of drug development and, more importantly, delays new solutions coming to market to meet unmet medical needs.

This attitude is exacerbated by the lack of collaboration between clinical research teams, physicians, and the broader healthcare organization. Physicians often view clinical research as transactional in nature, and not as an integrated part of a healthcare organization's care options. This often results in trials conducted by investigators unbeknownst to the healthcare institutions employing them.

The impact of this disconnect cannot be overstated. When healthcare organizations fail to integrate clinical research into their portfolio of care options, it creates an environment where physicians may be hesitant to recommend patients to trials for fear of losing track of them. As a result, unless a physician is directly involved in the research, patients who would benefit from participating in a clinical trial typically do not learn about the opportunity.

Today, less than 1% of the U.S. population participates in clinical trials, yet 72% say they would participate if recommended to do so by their doctor.{5} Conversely, large quantities of clinical research study data that could be transformed by healthcare systems into actionable information used to analyze and improve population health are ignored. This reduces the healthcare system's ability to deliver the highest quality of care based on the most current research, and reduces the impact of research spending.

At the same time, the clinical research environment is facing increasingly complex obstacles that could be alleviated through a more collaborative approach to care. Sponsors and clinical research organizations (CROs) are increasingly looking to move clinical trials into settings that have the infrastructure and support of electronic medical records (EMRs) to drive efficiencies in trial delivery while expanding their potential patient pool.

The healthcare landscape is also changing, with a shift from physicians owning their own practices to physicians hired as full-time employees for healthcare systems. By 2020, an estimated 80% of all U.S. physicians will be employed by healthcare systems.{6}

Lastly, patients are becoming actively engaged in their healthcare, and there is increased development of new value-based payment models that emphasize higher quality at lower costs.

Spread the Word

These changes can be leveraged by taking a more collaborative and inclusive approach to clinical research as a care option; but to do that, we need to change the culture around clinical trial participation so that all the stakeholders in the healthcare continuum benefit. That begins with creating a more collaborative culture where researchers, physicians, patients, healthcare systems, and advocates have more opportunities to connect and educate each other.

One driver of change may be the Enhanced Clinical Trials Design Act, which took effect in August 2017 and strives to modernize the clinical trial process and provide more treatments and therapies to improve patients' lives as an integrated part of the care continuum. The Act intends to reduce the barriers for all stakeholders to ensure access to research and the data associated are fully utilized to the advantage of the patient. It encourages conversations between the U.S. Food and Drug Administration, National Institutes of Health, key industry stakeholders, and Americans who participate in clinical trials, and the creation of a framework to facilitate further integration of research in the continuum of care.{7}

Laws alone will not be enough. To bridge the gap between healthcare and clinical research, we need to alter the dialog around what it means to participate in a trial, and engage healthcare providers in the conversations so they feel connected to the care their patients receive.

Even simple conversations with patients about the value of clinical research can change the way they think about participation. In a recent survey conducted by Greater Gift, we asked participants that attended a Hero's Journey Art™ Project event held in Winston-Salem, N.C., if they would be willing to participate in a clinical trial. The project combined science and art to convey the importance of clinical trial participation and raise awareness of clinical research. Before the event, 25% of respondents said they were "probably not willing" or "not willing" to participate in a clinical trial and 40% said they were "somewhat willing." After the event, the number not willing to participate dropped to 12%, and those who were somewhat willing rose to 60%.{8} Collectively, the data show increased willingness to participate following the event experience.

All of us, as healthcare consumers, need to be informed on these opportunities. That's where healthcare industry organizations come in.

Breaking Down Walls

Healthcare organizations need to break down the barriers between clinical research and conventional treatment, and to create opportunities for physicians and their care teams to learn about and even participate in these care options. When physicians feel confident that a trial will benefit their patients, and that they can stay engaged in their care, they may be more willing to suggest clinical research within the menu of options.

Such integration can be accelerated using rapidly evolving healthcare technologies and other approaches that get at the core of infusing clinical research with everyday care:

- Predictive analytics can identify gaps in care and help guide pathways toward clinical research to fill those voids.
- Outcomes research can help chronic disease management and preventive health by leveraging continuous engagement in the community.
- Precision medicine technologies can help extract patient and clinical intelligence to guide personalized treatment via clinical research.
- Telemedicine addresses the issue of patient access and can help to fill gaps in patient care and engagement.

With the necessary healthcare and research interfaced platform, implementing a clinical research program can create the infrastructure needed to better manage care coordination—thus resulting in reduced cost of care and improved treatment decision making.

New technologies and partnerships have the potential to help build integrated networks and to support value-based healthcare delivery, offering potential for innovative organizations to drive change. Such partnerships may also enhance the trust placed in clinical research by both healthcare providers{9} and the public.{5}

Further, we need to create platforms to broadcast the data, and to share individual success stories highlighting how clinical research has changed the lives of patient volunteers who participate.

Often the media only focus on negative stories about clinical research, but the industry is full of extraordinary examples of lives transformed by clinical trial participation. Consider Emily Whitehead, who had a resistant form pediatric lymphoblastic leukemia and was out of treatment options when she joined a ground-breaking CAR-T cell therapy trial in 2012. Within three weeks of participating, she was in remission and has been cancer free ever since.{10} Similarly, after Carl Walker, a hemophilia patient who at one time required thrice-weekly blood infusions, participated in a gene therapy trial in 2011, he no longer needed any infusions—either preventative or as a result of an injury.{11}

For every life-saving example, there are hundreds of other stories of research volunteers who had positive clinical research experiences, felt valued by the staff, and, because of that engagement, were more invested in their care and maintained better adherence to their treatment regimen. We need to celebrate all of these stories, and to spread the message of what it means to participate and what clinical trials entail. We can encourage our social circles to consider participating and we can speak to our healthcare providers about potential opportunities.

Finally, the biopharma industry must do its share. For biopharma, a collaborative and integrated approach to clinical research touches on four areas of importance to the industry:

- **Population health improvement**: A common goal for all healthcare stakeholders.
- **Patient advocates for research**: With positive experiences, patient volunteers become advocates for clinical research, leading to greater acceptance and participation. Patient advocacy organizations also serve as a vitally important and influential resource, given the deeply entrenched and trusted relationships they have with their constituencies.
- **Trial effectiveness**: With the right engagement and strongly managed processes, trials become more effective.
- **Trial efficiency and cost management**: A collaborative approach to clinical trials can greatly improve the efficiency and speed of a trial while reducing costs.

Conclusion

All of the approaches touched upon in this article lead to improved patient experiences, based on high levels of engagement by all stakeholders, including physicians and organizations. Optimized support for patient volunteers and physicians and other healthcare providers, coupled with high-quality, standardized processes, allows the right physician to connect the right patient to the right trial. This improved patient volunteer matching reduces the frequency of screen failures, improves retention rates, and enables positive healthcare experiences.

Collaboration amongst all stakeholders—patient volunteers, healthcare providers, healthcare systems, drug developers, and policy makers—must be increased to better communicate the value of integrating clinical research into the overall continuum of care, and to further enhance public trust in, and patient engagement with, clinical research.

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ICH IN FOCUS

Computer System Validation—A Risk-Based System Lifecycle Approach

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In the April 2018 installment of this column ("ICH E6(R2) and Data Integrity: Four Key Principles"), computer system validation (CSV) was briefly discussed as one of the key principles of data integrity. It was emphasized that a one-size-fits-all approach to CSV is not aligned with regulatory expectations; validation should be risk-based, taking into consideration "the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results."{1} The column also pointed out that the system should not be considered in isolation of the relevant business process—rather, the entire business process and data flow should be considered in the risk assessment.{2}

ICH E6(R2) Section 1.65 describes Validation of Computerized Systems as "a process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system."{1} This timeframe from design until decommissioning is known as the "system lifecycle." All systems have a lifecycle—a beginning, a middle, and an end.

This column will provide a discussion of the key concepts and industry best practices associated with the risk-based system lifecycle approach to CSV.

Planning Activities

The system lifecycle begins with the planning phase. A formal, planned approach to CSV ensures that quality is built into the system. Two types of plans are generally documented in a CSV effort: a Validation Plan and a Test Plan.

A *Validation Plan* is written at the start of the *validation* project to define the overall approach to the validation effort. The Validation Plan documents how the validation will be executed, along with the timelines, key deliverables, and key members of the validation team.

A *Test Plan* defines the overall approach to the testing effort and the general types of testing that will be performed.

Both types should be risk-based plans, taking into consideration the regulatory impact of the system as well as system novelty and complexity. They should also leverage supplier documentation, where available, to avoid unnecessary duplication.{3}

When applying a risk-based approach, the planning documents can vary significantly. For applications which follow a common process, such as Excel spreadsheets, the validation and test plans can be defined as a procedure outlining the validation requirements and documentation necessary to validate a specific spreadsheet. For more complex systems, such as one for electronic data capture (EDC), the planning activities will need to be defined specifically for each system.

User Requirements and Functional and Design Specifications

User Requirements define what the system must do to meet the intended business function. Requirements should be gathered from the users (i.e., representatives of the business process) and they should be written in such a way that they can be objectively tested.

Functional and Design Specifications define what the system will do to meet the requirements and how the system will function at a technical level. These specifications should also be written to enable objective testing to be performed.

Similar to the planning activities, the User Requirements and the Functional and Design Specifications should be risk-based and leverage any supplier documentation. The system is then built based on the Requirements and Specifications.

Again, using the spreadsheet and EDC examples, the details contained in the requirements specification will vary greatly based on the intended use and complexity of the system. The

requirements of the spreadsheet can vary greatly based on the complexity, functionality, and calculations incorporated into, as well as criticality of the results generated from, the spreadsheet.

The EDC system's complexity and intended use would also drive the level of detail included in that system's specification documents. The emphasis is on defining and designing the system to meet its intended use.

Testing

During testing, one or more system components are tested under controlled conditions and results are observed and recorded. Test scripts are developed, formally documented, and executed to demonstrate that the system has been installed and is operating and performing satisfactorily. These test scripts are based on the User Requirements and the Functional and Design Specifications for the system.{3}

To ensure that there is a clear link between the test scripts and the Requirements and Specifications, a *Traceability Matrix* should be generated. The rigor of the traceability activities should also be based on a risk assessment.

Testing is required for an effective performance of a software application or product. It is important to note that testing is not equal to validation. Validation is more than testing, although testing is a fundamental piece of the validation process.

There are four levels of testing for software: unit (or code) testing; integration/module testing; system testing; and customer acceptance testing, generally known as user acceptance testing or performance qualification.

Unit testing is performed by the software developer as part of the software development process. It is a level of software testing where individual units/components of software are tested. It is important that testing be performed during the development of a system in order to potentially eliminate errors early in the process.

Integration/module testing is one of the most critical aspects of the software development process, as it involves individual elements of software code (and hardware, where applicable)

being combined and tested until the entire system has been integrated. Errors found at the integration testing phase are less expensive to correct than errors found at a later stage of testing.{4}

System testing is a level of software testing where complete and integrated software is tested. The purpose of this test is to evaluate the system's compliance with the specified requirements.

User acceptance testing is then performed by the users as the last phase of the software testing process. During such testing, actual users test the software to make sure it can handle required tasks in real-world scenarios, according to the requirements and the business process and associated procedures.

There are instances where not all levels of testing are performed. The type and complexity of the testing executed is based on the use and criticality of the system. For a simple spreadsheet, the testing may be limited to user acceptance testing.

As the complexity of the spreadsheet increased, so too would the level of required testing. If the spreadsheet was actually a workbook (a collection of spreadsheets within a single file) leveraging data from multiple spreadsheets, the need for unit/integration testing would increase. For an EDC system, the need for all levels of testing would be more likely due to the typical complexity and configuration of such systems.

Change Management

Once the testing is complete and the system has been released into production, the validation effort is not over; the system needs to be maintained in a validated state throughout its lifecycle through decommissioning or transition to a new system.

Unfortunately, sometimes a "bug" in the system is discovered. This would require a software patch to be installed. Or perhaps a new user or functional requirement is necessary to be implemented, which could require a system upgrade.

All of these updates should be performed under *Change Management*, in order to maintain the validated state of the system and ensure all changes are tracked and documented. This would

include infrastructure, software changes, layered software, database changes, and changes to network and workstations. Any changes to the validated computerized system should be reviewed and authorized by user representatives, and the changes should be tested based on the risk assessment.

Managing the change is essential, no matter what type of system it is. What will vary are the change management activities and rigor associated with the given change, based on the impact of that change. For a simple spreadsheet, implementing the change might be as simple as updating the spreadsheet and re-executing the validation process. For more complex systems such as an EDC, implementing the change will include updates to documentation and execution of appropriate testing to ensure the change works as intended, and that the change did not cause an unintended impact to other functionality within the system.

Conclusion

Computer system validation is an essential process for ensuring, as well as documenting, that a computerized system does what it is designed to do—consistently and reproducibly. It is not measured by the number or size of documents or deliverables that are produced, but is most effective and efficient when properly planned and executed using a risk-based approach that focuses on human subject protection and reliability of trial results. It should also take into account system novelty and complexity and leverage supplier documentation, where available, to avoid unnecessary duplication.

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ON THE JOB

Overcoming Software Challenges at Clinical Trial Investigator Sites

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Once a clinical trial has reached the point of patient recruitment, the prime source of data generation and collection becomes the network of investigator sites engaged in the trial. Whether the sites are based at medical clinics, hospitals, or academic medical centers, or are independent trial management sites, together they contribute vital trial data which are otherwise unavailable.

Running an investigator site is an exercise in administration involving registering for clinical trials that are a good match, completing feasibility studies, following the tenets of good clinical practice, overseeing staff training and development tasks, keeping up to date on clinical regulatory requirements and data privacy requirements—all before a single patient has been added to a trial and before a single data point has been created.

Technology can be seen as an additional burden. Often presented as a set of tools and methods to make work more efficient, the experience of dealing with multiple trial sponsors and contract research organizations (CROs) means sites normally have to operate with a baffling array of systems, many of which don’t provide tight integration with in-house systems. With incompatible systems and multiple processes remaining manual, double capture, delays, and inconsistencies become commonplace.

Any processes with handoffs and manual interfaces are generally points where data tracking and information access are poorest. This creates challenges further down the line for insight gathering and analysis.

It Gets Worse

Where teams need to communicate, e-mail seems to be the default. This works because, well, who doesn't have e-mail? Yet, with all the ease of use and wide distribution, e-mail can be its own burden. With long conversation threads covering multiple topics, it's hard to see what is being asked and what is being answered.

Even when dealing with a single sponsor (or third-party distribution partner/CRO), multiple systems may be in use. Separate systems have been developed over many years for ordering new supplies, reporting Time Out of Environment and temperature excursions, managing investigational product returns and destruction requests, reporting adverse clinical events, and more—all with inconsistent interfaces, different username/password requirements, and different standard operating procedures. All place a burden on investigator sites—particularly those smaller sites with fewer specialist staff to deal with technical issues.

In the near future, sites will also have data sources that sit with the patient, in the form of apps that request regular input, smart devices such as smartphones, and custom medical wearables—all generating data and likely all incompatible with one another.

What's the Solution?

With so many sponsors and CROs active at the same time—not to mention the rapidly increasing pace of clinical research—it's unlikely that any single system will be available to sites for managing all these data anytime soon. That doesn't mean that sites have to accept the status quo.

Multiple sources are here to stay, and smart software solutions can be created for allowing additional feeds, new partners, and more functionalities to be incorporated with less stress to administration procedures. By designing for open interconnections, more operations can be accomplished in one system. Allowing site systems to connect and automatically reformat and transfer data means manual steps can be removed, operations can speed up, and more flexibility can be offered for the future.

Managing multiple incompatible software systems is a challenge, but there is hope with new software models. Designing software to manage complexity and plan for flexibility is achievable, mainly by abstracting connections from the core of the software. By adopting an architecture that anticipates multiple incompatible data connections, the core software can continue to develop and grow, whilst managing many data sources, including sources not yet known.

Getting Abstract

Abstraction really is the way to go; and it can be thought of both in a micro and macro sense. In a micro sense, within a single software application, one may use abstraction to separate different elements and allow changes to small parts of the application to be carried out without impacting the whole.

At a macro level, one may abstract tasks to different tools. Myriad reporting and presentation tools are available on the market, such as Tableau and PowerBI (to name two), which connect to many different data sources. Adding a new data source? No problem—make a small adjustment to the dashboard tool and everything ticks on as normal. Removing a data source? Same thing.

Generally, using off-the-shelf tools and applications for common tasks, dashboards, reports, and alerts, for example, is a great idea. It reduces the custom code that needs to be managed and the number of systems that users need to log into each day, just for starters.

For smaller sites where the in-house information technology (IT) provision may be minimal (or non-existent), anything that reduces IT burden is a good thing! Designing operations around an abstract model allows smaller site operators to do a lot of their own configuration and use external specialists for discrete projects. This keeps costs down and yields flexibility as the site manages what the site wants to manage and outsources the burden of more complicated tools.

Most critically, because of abstraction, sites are not at the mercy of a single provider to look after a software behemoth. Abstraction fosters an environment in which small tools and applications targeting simple tasks cooperate with one another to ease the site IT burden.

Conclusion

With better analytics and more of the clinical operations and data management requirements covered by fewer systems, the training burden is reduced and information is free to flow faster and more accurately—keeping both sponsors and CROs happy.

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DATA-TECH CONNECT

The Essential Task of Keeping Technology Clean

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As our clinical research work environments become dependent on technology, we need to be mindful of the cleanliness of these devices. Technology facilitates research workflows with devices such as laptops, smartphones, tablets, desktop computers, and others that help us collect data from our patients. However, while this equipment may seem benign, it is important that we know the healthcare risks associated with use of these devices for both patients and staff.

One of the reasons that people participate in clinical trials is that there is no other option. Life-threatening disease states can leave patients in immune-compromised conditions while they are undergoing experimental treatments. The elderly who participate in clinical research may also have more susceptibility to infection due to immunosenescence.

Considering how these and other patient populations enter our facilities assuming that adequate cleaning of our equipment has taken place, we certainly need to live up to that expectation for their sakes. Research sites need to know not only the proper way to clean this equipment, but how often it should be done.

Healthcare-Associated Infections from Technology

Research has shown for years that technology devices are likely sources of healthcare-associated infections (HAIs).{1} Contaminated hands seem to be the root cause, which in turn touch keyboards and the associated mouse. A study testing 100 keyboards in 29 clinical areas of a

teaching hospital found that 95 were positive for the microorganisms *Streptococcus, Clostridium perfringens, Enterococcus, Staphylococcus aureus,* fungi, and gram negative organisms.{2}

Another study, published in the *Annals of Clinical Microbiology and Antimicrobials,* screened the hands and mobile devices of 200 healthcare workers who worked in the intensive care unit and operating room. The results showed that 94.5% of phones demonstrated evidence of bacterial contamination, including gram negative strains on 31.3% of mobile phones and *S. aureus* strains on 52%. Perhaps the most alarming finding of this study was that 89.5% of participants never cleaned their mobile phone.{3}

The incidence of contamination is not limited to inpatient areas. A comparative study found that 61.5% of computers in hospital outpatient clinics were contaminated.{4} This supports the notion that ambulatory facilities can be just as susceptible.

Recommendations for Cleanliness

The best way to keep technology surfaces clean is to use them with clean hands. Either wash with soap and water prior to use, or keep an alcohol-based hand sanitizer product at the ready. If you use gloves to conduct clinical research procedures, avoid touching technology devices with your gloved hands and remember to clean your hands after taking the gloves off but before touching any tech. If you are using shared computers in situations during which you cannot guarantee the cleanliness habits of others, consider washing your hands after using the computer.

Professional standards can be used as a guide for the cleanliness of our technology. However, the absence of meaningful infection prevention protocols for information technology devices should be given the same consideration as other medical devices.{1} A non-touch screen monitor should be cleaned per the manufacturer's instruction when visibly soiled.

Conclusion

Contamination prevention is the ideal approach to take with technology, but it's one that comes with safe practices. Organizations may consider policies and procedures that address this aspect of research environments. Clinical research sites can be hectic, but the constant reminder that

clean hands are safe hands as we work with human subjects and technology is essential. This safe practice will protect patients and researchers, alike.

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