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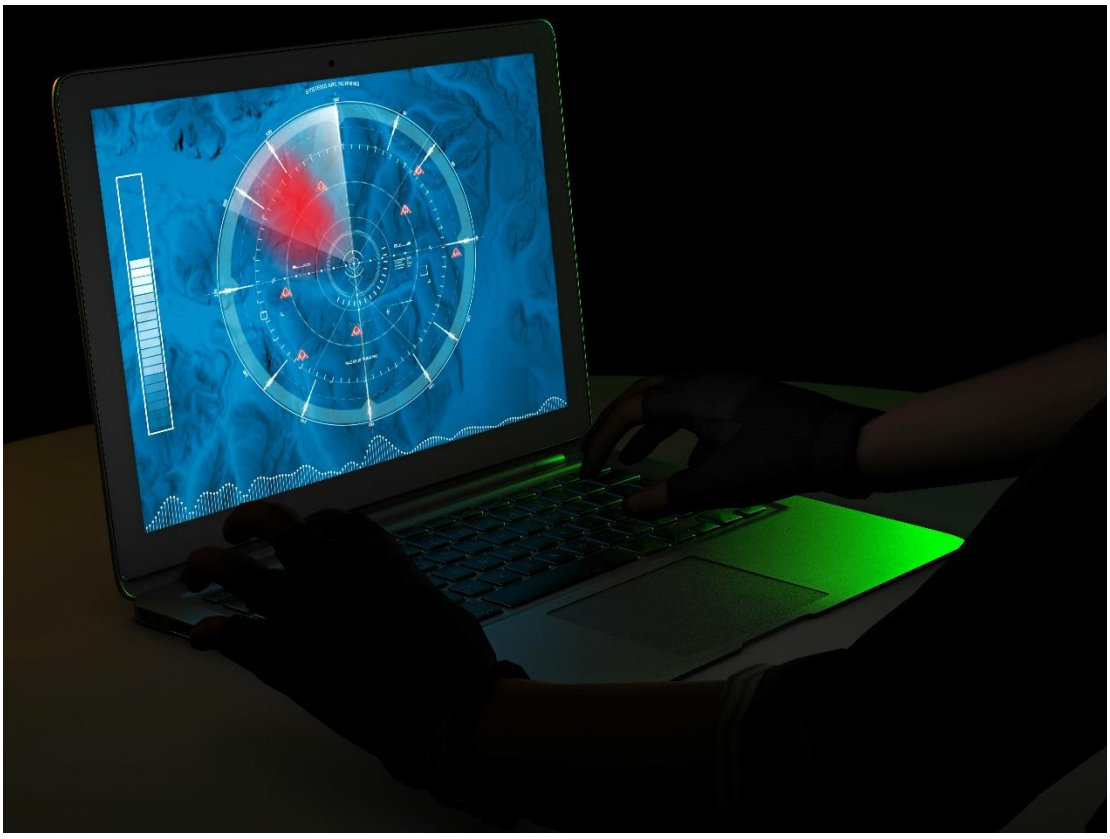
Clinical Researcher

The Authority in Ethical, Responsible Clinical Research

September 2021 (Volume 35, Issue 7)



Soft Skills and Hard Choices on the Clinical Research Radar

Clinical Researcher

Association of Clinical Research Professionals

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EXECUTIVE DIRECTOR'S MESSAGE

The Flexibility to Chart Your Career

Susan P. Landis, Executive Director of ACRP (susan.landis@acrpnet.org)

We've been talking about you, and I hope your ears are burning. You're in demand. With considerable growth projected for the clinical research industry, we need you—and more people like you.

It's a critical part of our service to our members to ensure you understand the breadth and depth of a career path in our industry. You also play a large part in determining where you want to go and how you want to grow. Think of it as the ultimate road trip, with some significant built-in flexibility. Truly, the possibilities are endless.

ACRP is investing in creating a career map for people like you. Check out the blueprint we developed as a start. I would love to hear from you about what we can add or what we may have missed. Underpinning this map are hours and hours of work from ACRP volunteers to document the core competencies for some critical roles—as a start. Thank you for your contributions.

So where do you want to go next? We're hearing from industry leaders that your journey is no longer linear. Indeed, you can go off road and be enriched by exploring peripheral paths—even those that extend beyond core clinical research competencies, such as leadership skills, diversity in clinical research, the use of digital tools in implementing trials and studies, and insights on the complexity of global clinical trials. ACRP is also exploring—we're planning for how we can bring you core *and* extracurricular classes to bolster your fundamental knowledge.

Perhaps it's the right time to get out the map and dream of the next destination in your career. We're committed to being your guide. And, as always, thank you for your contribution to improved health outcomes for all.

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CHAIR'S MESSAGE

Achieving Work/Life Balance Takes Work

Erika Stevens, MA, 2021 Chair of the Association Board of Trustees for ACRP

Does flexibility in work enable balance across one's whole life?

While the idea and application of workplace flexibility has existed since the early 2000s,{1} remote work presents new challenges to the clinical research industry.

Flexible work and alternative work schedules evolved to provide solutions for work/life conflicts. Promoting flexible office hours, summer Fridays off, and hybrid "real" office/home office schedules is touted as supporting employees. Nonetheless, the shift to remote work, while seemingly supportive of flextime, presents an entirely new set of challenges.

Working from one's home/home office erases commute time, changes the dress code, and may reduce associated work expenses. However, remote work demands increased response time, creates screen fatigue, and limits bio-breaks. Juggling virtual meetings and expectations of immediate response may result in lack of personal balance.

The clinical research industry has faced additional challenges to maintain its operations and shift its methods for conducting work during the pandemic. Redefining the operations of work continues and requires adaptability. For example, in the clinical research workforce, we experienced an uptick in decentralized clinical trials and remote data review. While this agility facilitated the continuation of important studies, finding balance in remote work is challenging.

Suggestions for control of your time when working at home: Limit your liquid intake, mute those microphones/headsets, take breaks, and block out the time you need for critical tasks.

I wish you all the best jusqu'a la prochaine fois (until the next time),

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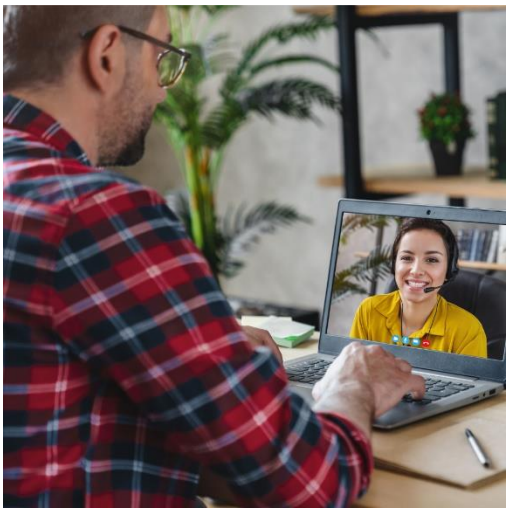
PEER REVIEWED

The Health and Productivity Effects of Remote Work on Clinical Research Associates

Sucheta Sachdeva; Tyler D. Green; Terry L. Oroszi



The COVID-19 pandemic has affected the health and productivity of employees in nearly every industry in the world. If companies were able to stay afloat and survive financial hardship, their leaders often had to make challenging and innovative decisions. Some companies required essential workers to report to work, while others had to furlough or lay off employees. Many companies turned to options for having some or all of their traditionally in-office employees transition to working remotely to remain functional.{1}

Although not uncommon before the pandemic, remote work gained tremendous popularity as a workaround option for many companies that could no longer safely allow employees to work in an office per local regulations. Remote working became a “new normal” practice almost overnight.{1,2}

Despite the recent increased prevalence of remote work, the clinical research industry is no stranger to the concept.{3} Larger companies tend to provide the option of remote work to a number of their employees. There are many positions associated with clinical research that can be completed in a remote fashion. Examples of these positions include, but are not limited to, project managers, data managers, safety managers, line managers, clinical research associates (CRAs), clinical trial assistants, and other similar positions.

Although this review could be applied to a variety of clinical research positions, the primary purpose of this paper is to focus on the health and productivity effects of remote work on CRAs, also known as monitors. A CRA "supervises, monitors, and supports the administration and progress of a clinical trial on behalf of a sponsor."{4}

Although many CRAs typically travel frequently in fulfillment of their job duties, there are also remote-working CRAs that are known by a variety of titles depending on the employer, including in-house CRAs (IHCRAs), site management associates (SMAs), site managers, etc.

The 2020 pandemic placed significant traveling restrictions on many CRAs.{5} To maintain oversight for studies, clinical research sponsors decided to push for remote source document verification methods to be implemented where possible.{6} As sites adjusted to new monitoring plans, CRAs found themselves working from home for extended periods and experiencing the benefits and shortcomings of such a lifestyle.

Numerous terms are used to describe remote work, such as work from home (WFH), virtual work, telework, telecommuting, and e-work.{7} Unfortunately, finding an agreed-on definition for each term is still a challenge.{8} For this paper, remote work is defined as work completed with technology outside the office setting, most commonly in the employee's residence.

General Positive Attributes of Remote Work for Employers

There are several potential cost and productivity advantages to allowing CRAs to work remotely. It can be argued that remote work can save companies on their bottom line,{9} in part because they would not need to lease office space and maintain it for employees.{10} The idea of cost-savings can be further applied to employers of CRAs. Although the employer may cover the cost of internet and home office equipment (e.g., desk, chair, printer, supplies), for remote CRAs, employees are typically expected to cover most, if not, all utilities.

Travel savings are yet another benefit to remote work that would be especially applicable to the CRA position. In the case of traveling CRAs who transition to a fully remote position, the company would save costs on flights, food, per diems, hotel stays, car rentals, transportation, travel time, and any other travel-related expenses.

Another benefit of remote work would be a decrease in employee absenteeism. Employees are less likely to call off work or be late if they work remotely.{11} There would be no need to commute to work and potentially be caught in traffic. Employees would likely work remotely despite minor illnesses or childcare trouble, as they could potentially adjust their environment and workday to accommodate such challenges.{7} IHCRAs/SMAs could take advantage of this flexibility to work later in the day to make up for any time lost during typical business hours. In the end, less company time would be lost, and more work could potentially be completed for the employer.

Increasing productivity by completing a greater amount of work, in general, is another positive attribute of remote work. Remote employees tend to work with fewer distractions than would be found in the office. Productivity findings could also be applied to clinical research. Typical CRA positions require travel during most weekdays. These former traveling CRAs would replace trip time with more frequent general communication with sites and possibly more frequent official remote monitoring visits, thus transitioning more into the IHCRA/SMA role.

More communication with sites could result in issues being resolved quickly, fewer study issues arising in general, protocol deviations being minimized, safety concerns being reported in a timely fashion, and/or growth of confidence between site staff and CRAs in their work on studies.

In 2013, the U.S. Food and Drug Administration (FDA) released guidance on the subject of centralized (remote) monitoring that encouraged it to be used more frequently than onsite monitoring. Centralized monitoring was especially suggested to reduce costs of clinical trials, improve data quality, identify data trends, and increase efficiency.{12}

The confidence in remote work for CRAs has gained momentum as a forefront option to continue clinical trials during the COVID-19 pandemic. The FDA released further guidance during this pandemic, recommending that sponsors “evaluate alternative methods” to in-person monitoring and giving phone contacts and virtual visits through remote monitoring as examples.{13}

Overview of Benefits and Shortcomings of WFH for CRAs	
Pros	**Cons**
Cost savings for employers and CRAs	Prone to overworking (dependent on individual and employer expectations)
Decrease in employee absenteeism	Health risks from extended sedentary work
Increased productivity	Overwork can lead to burnout
Fewer distractions	Burnout can lead to turnover
Less time spent travelling	
More time spent identifying/resolving site issues	
Increased efficiency	

General Negative Attributes of Remote Work for Employers

Some research disputes the findings on the potential benefits of remote work, citing conflicting information and difficulty measuring the amount of work being completed for specific remote versus in-person roles as obstacles to accurate assessment.{14} Employee accountability is a concern for employers, as it can be challenging to verify that a remote employee is at a workstation and working during business hours. However, the concerns for accountability may be a moot point for CRAs; the traveling CRA position already requires a degree of autonomy to complete most assignments remotely, due to travel to sites for monitoring responsibilities.

Similarly, IHCRAs/SMAs are required to complete remote contacts and visits with their sites. Accountability can easily be verified by contacting the site staff with whom the CRAs complete their visits. Additionally, nearly all CRAs must write reports regarding their visits and provide updates about their sites. Being accountable for their work is engrained into CRAs, as many other team members and the sponsor rely on their updates. Thus, the negative stance of remote work held by some employers may not apply to this position.

Still, depending on the CRA's personality and work/life balance skills, working from home could turn from being a more relaxed option to one where the work appears never to end. If the

CRA has difficulty drawing a clear line between work and personal life, he or she may experience more intense stress due to never being "off" work. These individual coping styles were discussed and helped to postulate a person-centered boundary management theory.{15}

CRAs may feel pressured to work beyond typical business hours to feel "justified" for not traveling. They may think that it is important to be available to site staff and clients at all times, since they appear to be more accessible due to being off the road.

The full responsibility for overwork cannot fall squarely on the employee. Recent meta-analyses for physician and other healthcare employee burnout suggests that organizational interventions would have more effect on the well-being of said employees than ones directed by the employees individually.{16} A prudent clinical research employer would state they support their employees' health and well-being and provide the necessary tools, incentives, and opportunities for remote employees to live healthier lives.

The risks of prolonged sitting can especially be applied to remote CRAs who need to complete source document verification (SDV) with sites during remote monitoring visits that can last many hours. If employers implement changes to decrease sedentary work time for CRAs, it would demonstrate the idea that clinical research employers complete clinical trials and embrace research results to ensure that not just patients of clinical trials, but also their employees, are living healthier lives.

Productivity and Efficiency Tools

Several communication and exercise tools can help remote employees stay healthy and still productively complete their jobs. Many full-time remote employees receive their home office furniture and supplies from the employer. Employers can incentivize a healthy lifestyle for employees by to providing convertible sitting-standing or, preferably, treadmill desks, so employees are encouraged to stand and/or walk while working. Studies have shown potential benefits from combining standing desks with taking active breaks involving movement as the best option for a healthier and less sedentary work lifestyle.{17,18}

For those who make numerous calls, such as IHCRAs, employers can provide high-quality wireless headsets that allow the employee to stand and walk hands-free during meetings and calls. Mild exercise, such as walking, could improve the IHCRA's mood and allow for a refreshing change of pace from sitting through calls. Employers could also proactively provide employees with options for ergonomic computer hardware (mouse, keyboard, etc.) to allow for a more comfortable experience while sitting and typing for long hours. A comfortable and supportive chair could also prevent body aches and sores for employees when forced to sit for many hours due to heavy workload assignments.

These are just a few examples to potentially demonstrate to employees that their employer cares about their well-being and is well aware of the benefits of using such tools to better their health.

Fatigue, Burnout, and Employee Turnover

A study by Helfrich, et al. conducted with primary care providers, nurse care managers, licensed practical nurses, and administrative clerks found that understaffing, turnover, and patient panel overcapacity all largely contributed to burnout within the team, regardless of a specific occupation. The study observed burnout as 30.1% lower for fully staffed teams with no turnover and within the capacity panel of patients.{19} Since these results were the same regardless of profession, they could be applied to the CRA.

Remote employees may feel unheard and exhausted if overworked, which can lead to higher turnover. Burnout can be significantly amplified if the employer does not actively encourage work/life balance, adding to the employee's stress of always being "on the clock." Many organizations impede their employees' time by expecting them to remain in touch with work using remote-based technology, like smartphones, outside business hours.{7}

Moreover, finding replacement employees can take much time, which leads to overburdening of current employees. Overwork due to turnover may especially be evident in the contract research organization setting, where revenue usually depends on new study awards, billable hours worked, and the number of completed monitoring visits.

If CRAs are already working remotely, employers often encourage them to work longer hours and take on more work, especially if their coworkers leave the company. Since the process of finding and replacing employees is costly and time-consuming, delays may lead to never replacing empty positions on certain studies, eventually making it the norm for the covering CRA to become overworked. The vicious cycle may continue to take its toll, leading to CRAs exhibiting symptoms of burnout and further increasing the chances for turnover. One option to break the cycle is to have the employer change tactics for hiring qualified replacements quickly.

Employee Retention

Although the bottom line is important, there is a shared responsibility for companies and employees to implement working limits in consideration of the well-being of employees. The employer should try to be respectful of the employee's time by assigning appropriate workload and ceasing the push for work to be completed outside business hours.

Along with the employer, employees can be trained to manage their time and tasks better so that working past business hours is rarely necessary. Remote employees would also need to work on individual traits to learn to separate work time from off time at home.

One suggestion for remote CRAs is to not forward their work e-mails to their personal phones and to turn off their computers at the end of the business day, effectively "cutting the leash" to the habit of checking work e-mails or walking back to the home office computer to address issues that could wait until the next business day. Having this discipline would be dependent on the individual's dedication to maintaining a pleasant work/life balance.

Conclusion

Although accountability and oversight may initially be a concern, by hiring remote CRAs, employers would enjoy cost savings, fewer employee absentee days, and increases in productivity, among other benefits listed in the table earlier in this article. The CRA, meanwhile, may have several advantages in working remotely, including feeling less distracted, having less stress due to no travelling, increased job satisfaction, and a more manageable work/life balance.

Conversely, if overworked, the remote CRA position would adversely affect mental health, especially if the CRA cannot draw clear boundaries between work and home life.

Overall, both the employer and remote employee are responsible for the success of the business and the health of the remote employee. Although this paper attempts to apply known research regarding remote work to the CRA position, more research needs to be collected and documented, focusing on feedback and data collection regarding remote work from traveling CRAs and remote CRAs directly.

The clinical research industry has had remote working positions for years. Still, it will be interesting to see if employers will have the prescience to amplify the benefits and tackle the challenges involved with the remote CRA position and simultaneously retain employees for the long term.

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PEER REVIEWED

Not Your Mother's Quality Management System: A Next-Generation, End-to-End Automated QMS

Christina Morris; Erika Stevens, MA

Pharmaceutical companies face a number of challenges, including (but not limited to) an evolving regulatory landscape; increased focus on quality metrics by governing agencies; data integrity and governance misalignment; lack of understanding customer needs; difficulty reproducing prior results for inquiries and investigations; multiple noncompliance issues; integration of quality and operations system; and a lack of process visibility (i.e., supply chain management, cycle times, bottlenecks, and shipment across sites).

Quality management system (QMS)-based principles and process automation technology are individually gaining traction on addressing some of these challenges in the pharmaceutical industry, but when combined, they solved people, process, information technology (IT), and operational issues.

Identifying the Customer(s)

QMS is a well-established systematic methodology to mitigate risk, meet compliance regulations, and improve the overall end-to-end operating model.{1} QMS methodology focuses on operational efficiency through the lens of the customer. Identifying the customer in the process or activities at hand is therefore the critical first step to understanding the "why" and "how" of the activities/process.

It is important to note that, while identifying the "customer," the organization must be willing to look internally and/or externally, and will likely find that it has more than one type of customer. Most importantly, identifying and understanding customers and their needs and the required process controls enables a journey that is customer-centric, process focused, and co-produced with the customer. Conducting a needs assessment and determining the desired outcomes will solidify the future automation success.

Understanding the Art of Business Process and IT Strategy

After documenting a customer's requirements and controls, the business/IT strategy should be discussed in conjunction with documenting the end-to-end value chain or process requiring analysis. To begin strategically managing the QMS (people, process, and system/data), the customer is required to rethink its practices in terms of connecting output of one activity to the input of the next activity.

For example, to complete, approve, and execute a clinical trial protocol, clinical operations staff interact with those in regulatory affairs to confirm submission of the protocol in applicable regions; pharmacovigilance staff interact with those in regulatory affairs to confirm relevant protocol safety requirements; clinical operations staff interact with those in biostatistics to confirm the statistical analysis plan; and so on.{2} Further, the activity of drafting and approving a protocol is connected to the larger process of building, conducting, managing, and closing a trial, which is connected to the even larger process of managing a product portfolio, revenue cycle, and so on.

Similar or like activities are reused/repeated multiple times by different processes in the same and/or different functions. Thus, the assessment is aimed at reviewing the following employee pain points:

- Time spent reworking work products and reports to meet specific compliance and regulatory needs.
- Misalignment of process activities within different functional quality systems documents (QSDs)/standard operating procedures (SOPs).
- Unclear link between interdependent processes and underlining IT system outputs/inputs.
- Training and how it intersects with the process, portfolio management, and commercial concept.
- Multiple technology platforms limiting process efficiency.
- Employee satisfaction and value-added tasks.

Determining the Maturity of the QMS Along the Value Chain to Meet Customer Needs

The concepts of reusability, repeatability, and sustainability are key to every QMS. To determine maturity of the QMS, the current research and development (R&D) value chain requires an assessment. An assessment is conducted on three levels to identify the maturity of process connectivity: 1) review of resources (how they are consumed in the process and systems), 2) review procedures and process (workflow and activities), and 3) review swivel chair activities in IT systems (the systems required and data input/output for the process workflow).

Upon completion of the assessment, the relative maturity of a company's QMS is established, a customer centricity journey is documented, and the process repeatability/reproducibility of key performance indicators (KPIs) is determined. Collectively, the outputs of the assessment identify the highly manual process/activities that would substantially benefit from automation and a future state plan is reviewed and confirmed.

Designing a Fit-for-Purpose QMS

Once the level of maturity, customer's point of view, and pain points are known and the future state agreed upon, designing a fit-for-purpose QMS begins. The basic components of a mature and well-functioning QMS include:

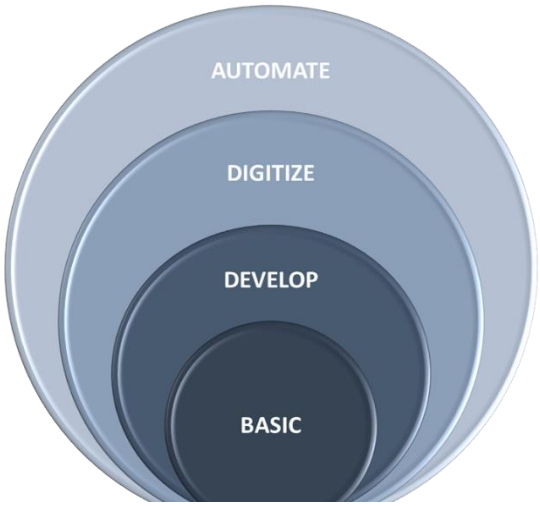
1. People/Movement to a Quality Culture (be obsessed with failure and customer satisfaction and not perfection)
2. Process/End-to-End Business Process Management (connecting the right processes together)
3. Disruptive/Business Process Automation (disruptive technology and an IT framework that drives connectivity and increased production)
4. Risk/Integrated Quality Risk and Control Framework (enabling holistic and offensive risk management)
5. Monitoring/Quality Monitoring and Reporting (enabling real-time reporting and dashboarding)
6. Training/Quality Communication and Training (connecting communication and training to everyday workflow)
7. Business Continuity and Disaster Recovery (responsiveness and preemptive planning to minimize disruptions and/or outages to the research enterprise value chain)

Each of these components is essential to designing a well-connected process and data ecosystem, and must run the entire value chain—across the entire business (front office, back office, and

everything in between). This connects the people through process and data across the entire value chain in a cross-functional manner—from the front office to the back office to the customer.

Figure 1 illustrates QMS maturity. While we could expand on all the basic components of a QMS and how to connect data in the entire value chain, this paper focuses on the rise of disruptive technologies to enable an offensive, agile, compliance-driven, and customer-focused QMS.

Figure 1: QMS Maturity



Automation and Compliance: Next-Generation Clinical Drives Offensive Future-Proofing to Improve Compliance

Compliance is a driving force for all operational procedures and activities. To build a next-generation QMS with disruptive technologies, we first examine the compliance requirements for a digital QMS within clinical trial execution. Understanding the digital compliance requirements enables us to apply the proper technology and become operationally offensive, so we started by asking the better questions:

What standards/compliance requirements are required for an integrated digital QMS in pharmaceutical companies?

To adequately address this question, a review of current requirements and regulatory guidance recommendations commenced. As 21 CFR 11 in the *Code of Federal Regulations* is the precedent for electronic systems and IT system audits, we began with a detailed analysis of the regulation.{3} However, 21 CFR 11 is part of a larger set of compliance standards for product/IT validation. Additionally, reviewing electronic compliance is one part of the overall review process, as there are other International Council for Harmonization/Good Clinical Practice (ICH/GCP) regulations and International Organization for Standardization (ISO) guidelines that are required to implement an integrated digital QMS.

Table 1 provides a sample review of regulations and/or standards that should be considered during the evaluation of an integrated digital QMS. Multiple guidance documents should also be considered and reviewed to confirm current regulatory recommendations.

Table 1: Sample Regulations

	Technical/IT Validation Compliance	**Clinical and/or Manufacturing Compliance**	**Comments**
21 CFR 11	X		Gold standard for clinical IT validation
ICH E6/GCP (applicable CFRs){4}		X	
21 CFR 820{5}	X	X	
ICH Q10{6}		X	Harmonized/Companion with ICH Q8 and Q9
ISO/IEC 9001: 2015{7}		X	Generally harmonized with ISO 13485 and 21 CFR 820
ISO/IEC 13485: 2016{8}	X	X	Generally harmonized with ISO 9001 and 21 CFR 820
ISO/IEC 14971: 2019{9}	X	X	
ISO/IEC 17799: 2013{10}	X		

REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL{11}		X	GDPR (General Data Protection Regulation)
HITECH{12}	X		Health Information Technology for Economic and Clinical Health Act (HITECH Act) Sec. 3001; Office of the National Coordinator for Health Information Technology
Cures Act{13}	X	X	

Note: CFR = *Code of Federal Regulations*; ICH = International Council for Harmonization; GCP = Good Clinical Practice; ISO/IEC = International Organization for Standardization/International Electrotechnical Commission; EU = European Union

Reviewing and conducting an analysis of the regulatory landscape is essential to documenting electronic requirements, user requirements, user experience, and potential user interface issues/risks for a next-generation QMS. Ultimately, the compliance analysis assists in determining (as outlined in the business case below) the disruptive digital process automation tools required to implement a process-based approach to automating the QMS.

How are the standards/compliance requirements expected to change in the next three to five years?

For more than 15 years, regulators provided industry guidance on standards and compliance requirements. Table 2 illustrates a sample of regulatory documents. Based on a review of draft U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance documents, the focus of the major regulatory bodies will continue to be on modernizing clinical trial design, integrating clinical studies data to and from the healthcare delivery model, and addressing the risks of study quality.{14}

It is expected that the regulatory agencies will continue to create inter-agency efficiencies to enable consistent review/approval, provide consistent standards, and focus on issues critical to quality data. Regulatory standards and compliance requirements will change to reflect the need

for better use of automation technology. The ability to move and analyze data in a more efficient/ effective manner will enable a holistic, risk-based approach with near real-time review, reporting, and integration of real-world evidence into clinical trials though the patient journey.

Table 2: Sample Regulations

FDA/ICH Draft Guidance/ Consideration Documents	Investigational Product (Compound/ Molecule)	Medical Device	Manufacturing /Distribution
Institutional Review Board (IRB) Written Procedures – Draft Guidance for Institutions and IRBs 08/2016{15}	X	X	
Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States 04/2015{16}		X	
Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can be Conducted Without an IND 09/2015{17}	X		
Informed Consent Information Sheet 07/2014{18}	X	X	
Humanitarian Device Exemption (HDE): Questions and Answers 03/2014{19}		X	
Charging for Investigational Drugs Under an IND—Q&A 06/2016{20}	X		
Expanded Access to Investigational Drugs for Treatment Use—Q&A 10/2016{21}	X		
Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products 4/2019{22}	X		
Exculpatory Language in Informed Consent 08/2011{23}	X	X	
Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions 11/2013{24}	X	X	

E6(R2) Good Clinical Practice 4/2018{25}	X	X	
E18 Genomic Sampling and Management of Genomic Data 6/2016{26}	X		
E17 General Principles for Planning and Design of Multi-Regional Clinical Trials 7/2018{27}	X		
E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population 4/2018{28}	X	X	
E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimates and Sensitivity Analysis in Clinical Trials 5/2021{29}	X	X	
E2B(R3) Electronic Transmission of Individual Case Safety Reports Implementation Guide—Data Elements and Message Specification; and Appendix to the Implementation Guide—Backwards and Forwards Compatibility 2/2014{30}	X	X	
Q11 Development and Manufacture of Drug Substances—Questions and Answers (regarding the selection and justification of starting materials) 2/2017{31}			X
Submitting Marketing Applications According to the ICH/CTD Format: General Considerations 09/2001{32}	X	X	
M8 Electronic Common Technical Document (eCTD) v4.0 DRAFT Implementation Guide v2.0; and eCTD Implementation Package DRAFT Specification for Submission Formats v2.0 4/2015{33}	X	X	
ICH E8(R1): Revision of General Considerations for Clinical Trials 14 November 2017{34}	X	X	
Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products{35}			X

Case Study on a Next-Generation Quality Management System

Overview

The case study focuses on an integrated and holistic approach for transforming static (written on paper) policies and procedures into process-based automation and document creation, as well as identifying and implementing automation technologies to connect and mature the QMS. The process-centric systems approach enabled identification of process improvement, attention paid to business alignment (reducing the silo work and data), and evaluation of several technologies leading to a less complex and more user-friendly, process-driven, and compliant framework for the end-user.

Process Documentation

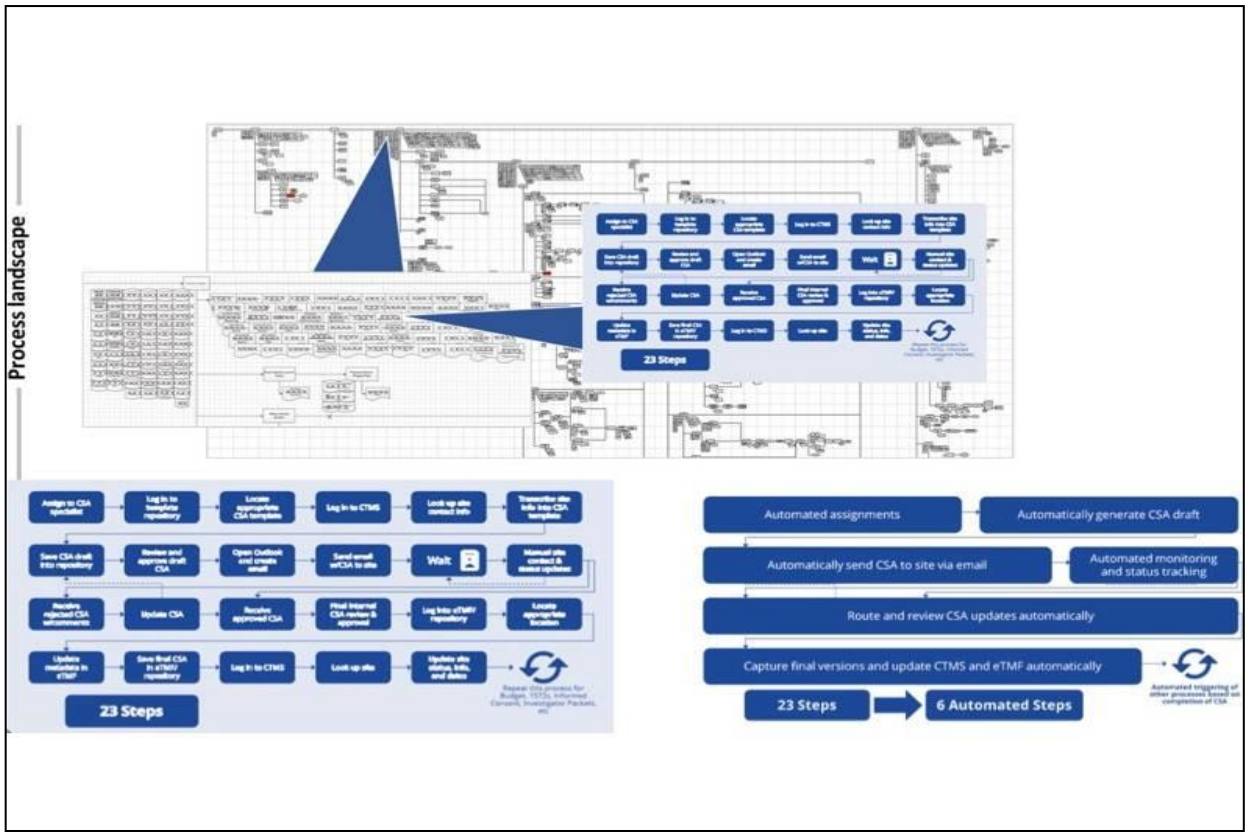
When transforming the document management portion of the QMS, identifying and engaging with related roles, responsibilities, and guidance documents enables a culture of quality to mature. After identifying the quality culture enablers, the current functional processes are evaluated and recorded. This approach will solidify both the top-down and bottom-up change management and increase the sustainability of end-user and stakeholder adoption.

Once process analysis is completed, an inventory of relevant quality documents is mapped within the global and local process. Figures 2 and 3 illustrate the pre-automation and process landscape.

Figure 2: Pre-Automation

Pre-Automation Process Input	Pre-Automation Process Output
• 65 systems • 3,000+ datapoints/fields • 23 manual level 2 process steps with multiple level 3 and 4 activities/tasks below	• 65 document types managed manually (which could product hundreds more, depending on the type of study) • Duplicative data entry up to 68%

Figure 3: Process Landscape (image intended only to illustrate complexity)



Sustainable Content and Life Cycle Transformation

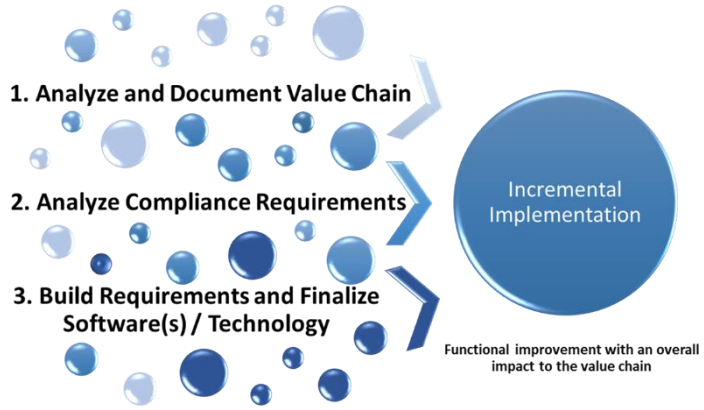
Once the dependencies and other required document(s) for the process were inventoried and mapped, the following steps were taken to transform document management within the QMS:

1. Prepare a new template for a process-oriented and role-focused quality management document
2. Re-write quality management documents with the mature quality principles
3. Review new process with stakeholders and aligned parallel processes
4. Link training requirements to processes and connect with training system
5. Identify and implement automation tools in an agile environment
6. Explore additional technologies to enable better process and content management

Assessing and Deploying Digital Technologies

As the program was built on process, it was essential to assess the process focused on digital technologies. Based on the compliance review, user requirements were drafted and a market scan was conducted to identify applicable tool(s). Identification of a proof-of-concept (POC) process was confirmed and the POC was implemented within the system. A detailed implementation roadmap was created to support continuous and effective cross-functional process automation leveraging data reuse and data critical paths. As illustrated in Figure 4, the process of implementation is incremental.

Figure 4: Incremental Implementation



Results

The intent and scope of the business-led project resulted in an integrated, process-centric QMS document landscape. The business directives included achievement of a system that was simple, user-friendly, process-centric, and compliant. As a result of developing and delivering on the project, the return on investment (ROI) was intended to be more qualitative than quantitative. Post-automation processes are illustrated in Figure 5.

Figure 5: Post-Automation

Post-Automation Process Input	Post-Automation Process Output
• 33 systems • ~ 1,500 datapoints/fields • 23 level 2 steps	• System produced 27 essential document types and stored documents in appropriate storage via automation • Reduction of data entry by 48% • 6 automated level 1 processes • Realtime dashboards

Ongoing feedback indicated that the new process-centric document landscape was significantly easier to use. The end-user could more readily navigate the processes and find the associated documents and/or operating procedures to execute, saving them administrative time and adding real value to their task.

Additionally, compliance qualitative measures were met, as the new QMS documents and change controls passed inspection. Upon meeting the qualitative measures, the team conducted an analysis to identify qualitative ROI. Figure 6 highlights the level of impact gained through process automation. The benefits of this case study were realized over a period of 18 months and are as follows:

- The impact was greatest at the local country level, where the reduction of document maintenance was greater than 50%.
- In some cases, and in some functions, more than 80% greater efficiencies in document management were gained.
- The value and impact to the business and the end-user are substantial for both global and local levels of the organization.
- The application of QMS automation enables the same business impact, regardless of customer along the value chain.
- Further, it is expected that the increase in ROI will continue (possibly double) once automation is fully deployed.

Figure 6: Impact Level

Global Level Impact		Local Country Level Impact		Enabling Growth Impact	
33%	25% +	50% +	49%	30% +	25% +
Reduction in QMS policies and procedures document management	Reduction in new policy or procedure approval	Reduction in local policy and procedures management	Fewer local policies and procedures	Acceleration of change programs due to analysis of value chain	Acceleration in integrations and integration activities

Conclusion

Table 3 illustrates the value created through QMS implementation. We can create critical process paths that align with critical data paths. Once these two paths converge, data are further "connected" to overall value chain processes, including front- and back-end operation activities. These principles were leveraged to merged best-in-class QMS principles with an automation platform to drive process-centric value and business efficiencies, enabling a higher level of customer satisfaction and increased risk management. The results optimized business operations and increased data throughput (reuse not reentry), removing the mundane non-value-added tasks and focusing on the pain points in the process, all the while creating a path that allows pharmaceutical companies to meet quality and compliance standards.

Table 3: QMS Implementation Overview

Initial Client Process Assessment	QMS Implementation Goals	Value Created
Process documentation written to reflect topics instead of processes	✓ Document current R&D process and re-design QMS in a process-oriented and user-focused method ✓ Showcase process sequence for end-user	✓ Streamlined landscape of quality management documents with structured end-to-end processes, clearly defined roles, and consistency among all documents with regard to inputs, outputs, roles, and prior and subsequent processes

End-users created workaround for conducting activities as finding documents was time-consuming and topic-focused	✓ Meet or exceed compliance standards ✓ Identify and manages risks ✓ Better asset/portfolio management	✓ Increase of end-user acceptance of the documents as guidance and support ✓ Strengthened confidence in completeness and regulatory compliance of the QMS
Lack of clarity on which process documents or sections apply to a specific role	✓ Connect process to other functions and enterprise activities and processes	✓ Alignment of processes, regulations, monitoring measures, risks, and training
Training plans did not support compliance within the process (input and output, reference to relevant prior or subsequent tasks, overall enterprise value chain training, process to enterprise requirements)	✓ Identify technology solutions to connect disparate legacy systems to processes and training ✓ Identify and manage training risks ✓ Better asset/portfolio management	✓ Enables training compliance ✓ Enables the end-user to better manage training requirements

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SITES & SPONSORS

The Qualities to Evaluate in Your Site Evaluation Representatives

Elizabeth Weeks-Rowe, LVN, CCRA

With site evaluation visits, that adage about how "presentation is everything" rings true and applies to far more than the confirmation of the capabilities of a site's facilities and equipment. It even extends beyond the training and experience of the investigational staff. An integral element of site evaluation is the fundamental first impression (or communication flow) between the site and sponsor, the cornerstone from which that important relationship flourishes.

How a site presents its capabilities to a prospective study sponsor means everything; how enthusiasm is demonstrated, how information is communicated, and how abilities and logistics are translated will most definitely influence site selection decisions. Considering that the key to a successful site evaluation is how the site is showcased to demonstrate experience, equipment, and patient access, choosing the appropriate site representatives to carry out the presentation is paramount to facilitate this process.

The site representatives must be knowledgeable, to be sure, but also should have the right balance of clinical savvy and winning personality to make the best impression. Anyone with sufficient understanding of the investigational site can answer the essential questions regarding site infrastructure/policy/process, site personnel/experience, and site equipment/ facilities, but the idea, well-rounded researcher charged with shepherding site evaluation visits can also frame the narrative with enthusiasm and finesse to strengthen the site's image.

The following sections define the qualities I see as contributing to strong site evaluation representatives.

Know Thy Site

Investigational site models are as diverse as the personnel they employ. The dedicated research site, the academic health center/large health institution, and the physician practice with a research department; each have unique infrastructure, policies, and personnel for supporting the research within said model. Site familiarity—truly knowing the investigational site—is integral to present an effective site picture.

It is a verbal and visual process, with dialogue between sponsor and site personnel to confirm policies, processes, and personnel (verbal) being followed by the physical tour to confirm facilities and equipment (visual). Though site representatives may have a wealth of knowledge about their facility, they won't risk missing or incorrect information. They will banish ego from the process and seek answers to the unconventional queries that may also come up, such as: confirming all institutional research standard operating procedures with quality assurance, obtaining the expiration dates of Good Clinical Practice training certificates for immediate research staff, and defining the breadth of principal investigator (PI) research experience (i.e., number of years as a PI, number of studies conducted, and therapeutic areas).

If the study has specific equipment criteria to support endpoints, a site representative will confirm the parameters with each respective department (e.g., make/model of freezers for the investigational product, imaging specs for computed tomography equipment, respiratory therapists for pulmonary function testing). The smallest details demonstrate conscientious consideration which speaks volumes about the site's efforts to obtain and sustain studies.

Know Thy Self

Site representatives hosting evaluation visits should have a plethora of qualities to assure positive institutional representation. However, they are not expected to know everything and should solicit experienced colleagues to supplement any deficiencies. They are not expected to be a television host with a gleaming smile and perfect poise and articulation. They should strive to demonstrate the "3 Ps and a C" that embody an appropriate site representative: courtesy, professionalism, positivity, and preparedness.

Courtesy and Professionalism

The site representative is the proverbial host and should ensure a friendly, comfortable atmosphere during the visit. Conversation should extend beyond strictly clinical topics; small talk before the official "talk" can go a long way to breaching barriers and encouraging open dialogue. People appreciate it when someone takes an interest in them beyond their profession; they are much more than the task they perform.

Remember the value of soft skills such as maintaining eye contact, not interrupting conversations, and saying please and thank you—these should never be assumed unnecessary or underestimated. The site representative should remind each attendee, a day or two before the visit, of their start time and duration of participation to ensure there are no schedule conflicts or barriers to attendance.

Positivity

Site representatives should positively represent their institution throughout the site evaluation visit process. This is best accomplished with knowledge of institutional research accomplishments and transparency of capabilities during the study discussion (knowing what can be done, and proffering solutions when equipment or logistics don't align with study requirements).

For example, if the study has pharmacokinetic lab draws that require a refrigerated centrifuge, but the site lacks this type of centrifuge, the answer should not stop with the missing equipment. Instead, the dialogue should be continued with the site representative asking if he or she can build rental of the centrifuge into the study budget, or alternatives for acquiring equipment. If the study requires a complicated study drug reconstitution process, an experienced pharmacist should attend the evaluation to discuss his or her experience with similar investigational drug infusions.

Finally, site personnel should demonstrate enthusiasm for study participation. This quality will positively impact the process.

Preparation

When the sponsor representative schedules the evaluation visit, the site representative should confirm meeting times with all personnel involved and provide an agenda in the event multiple departments and ancillary locations are involved. They should ensure all participants have the protocol synopsis and slide presentation for review prior to the meeting. They should have a copy of the feasibility survey at hand to offer enrollment statistics for studies conducted in the same therapeutic area. They should complete all required paperwork by the time of the visit to ensure and efficient and organized process.

Know Thy Colleagues

For smaller research sites, often one key individual is more than capable of conducting the site evaluation visit. However, at larger institutions, all departments potentially participating in the study will require representation during evaluation to accurately convey the full site picture of capabilities. The site representative should understand how each department representative will interact with the sponsor representative during the evaluation visit; essential personnel must be vetted and coached, if necessary. Each person has the potential to make an impression that will influence site selection decisions. From the pharmacist to the PI, everyone must have a clear understanding of the time requirements, conversational parameters, and appropriate behavior and discussion topics.

I once completed a site evaluation visit at a large academic health center. The research nurse was pleasant, knowledgeable, and enthusiastic about site participation. All departmental personnel participating provided comprehensive information about capabilities without issue. However, when the time came for the pharmacy tour and investigational product discussion, the evaluation visit took a decidedly negative turn.

The pharmacist was stern and tried rushing the process. She commented on the pharmacy's large workload and sparse storage space. She seemed to purposefully discourage interest and made us both feel uncomfortable. After the pharmacy tour, the research nurse apologized and assured me the pharmacy could accommodate the study requirements. Though I did ultimately recommend the site for the study, the pharmacist's negative attitude created uncertainty in the overall ability of the site to conduct the study.

Conclusion

A site representative who embodies the enthusiasm, information, and professionalism to best showcase the investigational site will help take the institution from assessment to selection status.

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A NEW E-R-A IN CLINICAL PROJECT MANAGEMENT

Sending Out an SOS for Soft Skills

Zoran M. Pavlovic, MD

Periods of crisis, extreme uncertainty, and severe threats to corporations experienced due to globalization, several economic recessions in the last two decades, and most recently the COVID-19 pandemic negatively impacted the conduct of clinical trials worldwide. They also led to reconsiderations of current clinical trial project management best practices and called for new models, capabilities, and innovative techniques to meet the challenges of clinical research activities in the upcoming "next normal." The vital aim of "A New E-R-A in Clinical Project Management" *is to facilitate these processes by discussing key factors that will transform mindsets and skillsets of clinical project managers, project teams, and organizations by efficiently promoting, developing, and boosting their Excellence (E), Resilience (R), and Agility (A) capacities, so they can continue to support patient-centric clinical development of innovative treatments efficiently.*

According to surveys of employers worldwide, soft skills are in high demand, and companies usually struggle to recruit people with high levels of these capabilities.{1} The reason is simple—these skills are highly predictive of success in the labor market.{2–4}

The concept of soft skills originated way back in 1918 when, during the regular meeting of the Joint Committee of the National Engineering Studies, many engineers were interrogated about the skills and abilities they considered vital in ascertaining success in the building engineering profession. The term itself was coined in 1972 and became widespread after 1990, though the topic has been addressed with many synonyms: life skills, transversal skills, transferable skills, future work skills, skills for social progress, critical competencies for lifelong earnings, and others.{5}

According to Robles,{6} soft skills represent a combination of interpersonal (people) skills and personal (career) attributes, as shown in the equation he made: *Soft Skills = Interpersonal (People) Skills + Personal (Career) Attributes*. For instance, interpersonal (people) skills are the foundation of successful customer service because they foster a happy attitude, effective communication, courteous engagement, and remain composed in stressful situations.{7}

On the other hand, personal characteristics typically include personality, likeability, time management, and organizational skills,{8} while career attributes pertain to communication, teamwork, and leadership skills.{9} A recent review article on soft skills gave a more granular description categorizing them as inter-, intrapersonal skills, and their combination (see Table 1).{10}

Table 1: Types and Forms of Soft Skills

Types of Soft Skills	**Forms of Soft Skills**
Intrapersonal Skills	Commitment Leadership Self-motivation Positive work attitude Creative problem solving Strategic thinking Willingness to learn Time management
Interpersonal Skills	Communication Persuasion Negotiation Teamwork Conflict management
Combination of Intrapersonal and Interpersonal Skills	Commitment Leadership Honesty Responsibility Adaptability Tolerance Problem solving Decision making

The most comprehensive list of soft skills is given by Simplicable, which distinguishes around 87 of these skills.{11}

Importance of Soft Skills in the New Normal Economy

A recent report from The Skills Network in the U.K. identified the top 10 soft skills currently sought by employers, based on the number of times they are requested in job postings.{12} Strong communication skills are the number one soft skill required by employers. However, the demand for management skills has also generated headlines. With the spread of the COVID-19 pandemic, organizations are willing to invest more in their managers' coaching to lead, facilitate, and motivate their colleagues, particularly with people feeling the additional pressures while working remotely. Soft skills like enthusiasm, planning, and detail orientation were also highly ranked, indicating the need for today's workforce to plan and execute work efficiently.

Further, the Organization for Economic Cooperation and Development recently reported that the COVID-19 pandemic increased employer demand for a specific type of "classical" transversal skills like "communication skills." According to their findings, it's crucial to be able to communicate effectively, especially when people are under pressure to give and receive precise instructions, or when they need to use new tools to communicate without the opportunity of having face-face interactions. The same applies for being able to work in teams (teamwork).{13} On the other hand, a recent United Nations Industrial Development Organization-European Training Foundation survey showed that creative thinking, analytical skills, and multitasking potential are also highly valued by businesses.{14}

State of Soft Skills Training

Unfortunately, too little attention is given to soft skills improvement by many senior executives. All too often, organizational leaders may view the concept of training for soft skills as requiring a simple seminar to motivate employees, but such activities provide minimal value to the firm that pays for the training in terms of any learnings being applied on the job or other business-related benefits.{15}

Therefore, the most pragmatic ways to approach measuring financial and other tangible benefits tied to soft skills training are to start the process by identifying the type of training that will provide the highest possible payback. Once the topic is specified, a return on investment (ROI) evaluation using appropriate metrics should be implemented following the training completion

(usually at the first, third, and sixth months). An excellent example of this practice was described recently by authors from Harvard University, Boston University, and University of Michigan's Ross School of Business who evaluated the effectiveness of soft skills training in Indian workers. After training a randomly selected group of women laborers on a variety of soft skills, such as problem solving and self awareness, the study measured the impact of training on metrics such as productivity and retention. The results showed an astonishing 256% ROI.{16}

Another great example comes from Google, which in 2013 reviewed 15 years of hiring, firing, and promotion data. This project led to the surprising discovery that hard skills ranked lowest among the top seven qualities of Google's top employees.{17} Among the top characteristics of a successful Google employee found in the study were:

- Being a good coach
- Communicating and listening well
- Possessing insights into others (including their different values and points of view)
- Having empathy toward and being supportive of one's colleagues
- Being a good critical thinker and problem solver
- Being able to make connections across complex ideas
- STEM (science, technology, engineering, math) skills expertise

Although acquiring or improving your soft skill armamentarium requires continuous professional coaching and everyday practice, certain tips from organizations that may be considered stakeholders in the pursuit can facilitate a quick start down the path toward soft skills excellence. Here are some suggestions from Indeed, a global recruitment agency{18}:

- Be open to feedback.
- Communicate often with your colleagues and managers.
- Emphasize teamwork.
- Build positive relationships.
- Step outside your comfort zone.
- Get ready to learn.
- Adapt to workplace changes.
- Observe others.
- Work through conflict.
- Take on a leadership role.
- Arrive at work on time.

Meanwhile, Glassdoor, another job search and review platform, gives priority to these two ideas for improving your soft skills{19}:

- Get a coach.
- Practice with a friend.

Moreover, here is my four-step "Why Do You Create" approach, which I use to coach leaders, managers, and employees on how to most efficiently (quickly and effectively) acquire and improve their desirable soft skills:

WHY

- First, I ask my client about his or her primary motivation to improve/acquire a particular soft skill.

DO

- Then we jointly develop their daily curriculum, and I teach them how to keep a soft skills diary and monitor their daily progress.

YOU

- Then I assess my client's personality traits, personal strengths, and ways of learning new things.

CREATE

- Finally, we formulate the creative homework assignments that he or she can practice on the job and outside the office (at home, during leisure time, etc.).

Conclusion

I want to conclude my first column installment for *Clinical Researcher* with a piece of straightforward, practical advice to all employers, leaders, managers, human resource partners, and talent acquisition and management professionals: Take care of your employees as you would take care of your diamonds. Their primary value multiplies a hundred- or even a thousand-fold when they are regularly "polished." So, begin investing in soft skills training to prevent high turnover, low performance, low morale, and low engagement among your staff so that your company may not only survive but thrive in today's VUCA (volatility, uncertainty, complexity, ambiguity)–filled economy.

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TRIALS & TECHNOLOGY

A Race Against Time: How COVID-19 Changed Drug Development

Gadi Saarony, MBA/MIM

March 18, 2020 marked the day the U.S. Food and Drug Administration (FDA) brought clinical research to a near stop, sending the life science industry into an existential crisis. Almost immediately, clinical trial organizers found themselves in a fight for survival, contending with pandemic-related challenges in data collection, availability of site staff, scarcity of personal protective equipment, and, perhaps more importantly, dwindling participation and engagement of patients in clinical trial processes.

Despite these challenges, clinical trials and their practitioners have since persevered. They are not only experiencing a fundamental transformation, but an all-out renaissance.

In many ways, the pandemic has forced business leaders to completely rethink the ways in which they conduct clinical trials on a global scale—bridging legacy gaps that have long existed within the industry. Now, as a result of game-changing innovations in telemedicine, decentralized monitoring, and wearables, clinical trials are experiencing a resurgence in both engagement and interest—with 68% of U.S. adults with at least one medical condition saying they are now more likely to consider participating in a trial than they were before the pandemic.

With the above in mind, here are a few key insights about how the COVID-19 has catalyzed a digital renaissance within the clinical trial space.

Smarter Trials

Ask anyone in clinical trials, and they're likely to say the same thing: trust is integral to the process. Because any data you collect are ultimately included as part of your regulatory submission, healthcare companies want to ensure—with the highest degree of certainty—that their therapeutics are manufactured, administered, and monitored correctly, every step of the way. However, due to safety concerns stemming from the COVID-19 pandemic, many in the industry were forced to put their trust in a digital world, albeit while asking how they can uphold confidence in processes they can't be present to oversee.

In gaining this confidence, many life sciences company leaders needed to lean on existing technology in order to seamlessly adapt clinical trials processes to the new normal. Thankfully, equipped with the latest in telehealth, eConsent, and wearable technologies, clinical trial directors quickly realized that they could track and monitor patients in real time—using trusted devices—all from the comfort of their own homes. Not only did this make clinical trials easier, it made them smarter, connecting site training and patient engagement tools with existing regulatory compliance solutions and clinical site technologies that, consequently, improved data accuracy and quality.

With an estimated 85% of all Americans currently owning a smart phone, the ability to meet with, and record, trial participants remotely has since created a much smarter and more flexible approach to clinical trials, consequently giving healthcare companies access to a fuller picture of therapeutic efficacy.

Faster Trials

While it's difficult to label anything having to do with COVID-19 as a "positive," one of the few blessings of the pandemic has been a heightened interest in clinical trials. Historically, clinical trials have taken anywhere from two to six years to complete. Now, with the COVID-19 vaccine rollout showcasing the incredible speed and efficacy of clinical trials at scale, life sciences companies have since realized that they can leverage decentralized technology to encourage optimal trial candidates to participate. In doing so, not only can they make data collection processes faster, they can also speed up data collection, analysis, and submission processes.

Consider the implications for future studies. Equipped with the very breakthroughs that "kept the lights on" during an otherwise dark period in research and development, scientists have since been able to speed up the process by which data are recorded, analyzed, and reported—leveraging past data to make informed decisions on everything from protocol optimization to site selection to patient engagement. In fact, some experts estimate that machine learning and other artificial intelligence technologies can potentially speed up clinical trial processes by 300%.

Sites that can leverage clinical research solutions are well prepared to bring this level of scale and access to the industry. By combining new cutting-edge tools with heightened interest in the process, trial organizers may finally be able to streamline costly and time-intensive processes that have long inhibited scientific advancement—all while providing trial access from the comfort of a patient's own home.

Safer Trials

Of course, it's worth noting that the COVID-19 pandemic has played an incredibly important role in ensuring the safety of the clinical trials process as well. Imagine, for a moment, that you're a scientist studying a promising therapeutic at the beginning of the COVID-19 pandemic. You're in survival mode, working tirelessly to keep your trial alive while participants are scared. Yes, you're worried about agility and efficiency, but safety is really of the utmost importance—ensuring that the potentially life-saving treatments you're creating are actually helping, and not hurting, those who need them.

Thankfully, clinical trials directors have since been able to breathe a sigh of relief. Not only have remote technologies proven effective at ensuring trial safety, they have also been shown to be tremendously helpful at spotting red flags, monitoring side effects, and triaging symptoms before they become severe. Simply with a touch of a button, a patient's smart phone has now become an outlet to ask questions and/or report problems, allowing scientists to focus on patient centricity, education, and enablement in a more direct and more transparent way.

Whereas before patients would have to wait for in-person visits to receive assistance, now they can reach out at all hours of the day—a game-changing advancement that has forever revolutionized the patient-provider relationship and allowed for around-the-clock access to valuable information.

Final Thoughts

As the threat of the COVID-19 pandemic recedes and we are beginning to return to normal, there will be hundreds of stories published about how industries have risen to the occasion in the face of adversity. None, however, will be as consequential as the tales told about clinical trials. At a time when many industries were paralyzed by indecision, the life science industry remained unwavering in its commitment to improving global health while leveraging pioneering digital advancements to keep its most promising assets alive. The result? A digital revitalization of legacy processes that proves that the best in clinical trials is surely yet to come.

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SCIENCE & SOCIETY

Making Quality Management a Reality

Al O. Pacino; Matthew Chandler

The use of digital health technologies continues to be a viable solution for clinical research advancement. Many research leaders have considered adopting the use of quality management services in clinical research trials. Quality management systems (QMS) are at the forefront of incentivizing and implementing professional data handling. Administrators of clinical education and course learning should be open to exploring digital QMS options when it comes to the maintenance of student/staff records. Site leaders who need to be more aware of the specific capabilities, performance levels, and functionalities of their staff and facilities can turn to QMS for insights on the delivery of research training, connectivity, and security. Site managers and research staff can improve compliance, ensure protection of data, and scale up training standards that address the health outcomes of populations.

Modernizing Preparedness Leads to Compliance

Right now, digital-based training is applied and optimized in the search and design of innovative drugs, life-saving vaccines, and medical test devices. Additionally, care is being redesigned to address how patients are managed, diagnosed, and monitored for disease progression. As technological solutions advance scientific discovery, several sites are becoming more aware of the benefits of modern solutions for departments such as Human Resources and Quality Assurance.

Paper-based systems are becoming obsolete, as they are unable to maintain up-to-date information and struggle to realize total compliance. Hesitation appears to be steadily decreasing when it comes to the adoption of electronic-based QMS. When implementing or continuing the use of a QMS, it is important that all appropriate staff members are familiar with its capabilities. For this reason, a site should consider using an outlined protocol for the implementation of a QMS. The creation of a specific protocol for the system would also be beneficial, especially if an audit is performed at the site.

To demonstrate commitment to building site staff capacity, a multidisciplinary, digital management system can increase distribution, verification, and completion of required training. Having a learning management system (LMS) can be beneficial, but operationally, sites are required to comply in other areas aside from the training of staff members. QMS are now capable of offering a variety of other services that administrators should be aware of.

Internal evaluation is necessary since many systems on the market offer a variety of features which assist in the internal regulation of training, e-commerce, cross-department communication, and privacy standards. Systems that prioritize collaboration between educational institutions and research development for organizations can provide better access to continuing medical education (CME). Collaborative systems have resulted in the development of tools which update researchers about major diseases, indications, and therapies.

The delivery of systems that aid in compliance and implementation will generate more opportunities for everyone. The ability to adhere to new educational requirements, privacy laws, and efficiency standards creates more confidence between clinical research and healthcare institutions. Over time, both staff members and management benefit from efficiently managing end-to-end protected digital processes that leave no patient behind.

Leave No System Behind

Interoperability is one of the most important features for an effective QMS. This is the ability for products or systems to work with one another via a compatible interface. Newer quality management systems can be integrated into more siloed or single-purpose systems; for example, through application programming interface (API) connections.

A common question among managers and staff is whether connecting an LMS system with a more interoperable one is possible. Ideal QMS should be able to communicate with existing, more siloed systems. Copyright holders of certifications and broader education programs exist all over the globe. Therefore, it is becoming necessary for internal management systems to have education distribution abilities and global accessibility required for clinical research professionals. Sites need to consider QMS that can aggregate internationally to accredited and accurately translated clinical research courses.

To maintain business and operational success, management systems should have international reach and connectivity. Sites should also evaluate if their preferred QMS allows for increased ease of acquiring studies by having business networking functions and monitoring the study from start-up to completion.

Digital Priorities for Site Sustainability

When it comes to a site's selection of a QMS, there are many factors to consider. Like the smartphones we use every day, we have come to expect certain features to be present. Some of the modern capabilities offered by QMS platforms are tools that enable privacy for individuals. As new laws regarding the digital handling of personal identifiable information go into effect across the globe, these tools are an essential feature for any QMS platform.

In accordance with the roll out of new privacy laws, professionals are being asked to own their personal identifiable information (PII). Allowing third parties to verify the authenticity of the information and sharing that information with global organizations for business and compliance purposes is becoming normalized. Innovation resolves the challenges that sites and sponsors face in legally collecting PII required to minimize redundancies, fraud, improve human subject protection, patient safety, and data variance in clinical trials.

Having a single location for receiving updates and managing the adherence to privacy regulations can be cumbersome, especially for sites using paper-based QMS. The good news is, robust systems offering personalized and digital account services now exist. These systems provide opt-in access for any stakeholder, including physicians, nurses, first responders, clinical researchers, and many others. Universal personal electronic accounts have the potential to

revolutionize the dissemination of clinical research personnel information and expand access by providing users with a primary source and single location for parking their credentials and other important PII, as now required by international law.

A robust QMS should also have reminder features and internal protocol/module creation. It is imperative for department administration and research staff to stay aware of the status of professional documentation, records, or CME certification, so they do not become outdated. Innovative developments have allowed researchers to be notified and to individually complete the updating of professional information while managers are more easily able to track such changes.

Sites are now able to comfortably oversee professional documents, set expiration alerts, add third-party verifications, and collaborate with organizations or businesses. Departments such as Human Resources can directly benefit from modern management systems that give them the tools to create site-specific protocols and education modules. Instead of filing and sifting through binders of internal protocols, sites can more easily locate and distribute protocol training for staff readiness by using quick search features. E-learning libraries are also being modernized to include courses pertaining to patient privacy protection, regulatory compliance, and communication standards. Perpetual access to the most recent information is best achieved through the non-siloed, electronic QMS.

Conclusion

Since the COVID-19 pandemic began, business leaders have transitioned their staff to remote work and have seen prolonged success. Efforts have demonstrated that electronic communication and dissemination of process information is possible and can be expanded upon. As emerging technology enhances medical care and clinical research, stakeholders at sponsors, academic medical centers, contract research organizations, hospitals, and independent study sites can prepare executive personnel to integrate even more applications.

Use of telemedicine, artificial intelligence, and digital therapeutic tools are informing medical policies and public health actions. A new approach of setting up robust digital/e-learning

libraries as a catalyst for capacity training and education can contribute to shaping the future of research. CME, which includes globally standardized competencies, is key to site feasibility.

It takes time to attain the highest competencies and qualifications for all levels of research professionals. The journey to medical excellence runs through the transferal of lifesaving skills and sound medical decisions to subjects. Countries throughout the globe benefit from incentivized educators and organizations that develop tools which track learning and manage capacity for various personnel. New connective platforms can establish the infrastructure needed for new site opportunities. Education and training can be modified into dozens of languages to provide a standard of care for all patients.

Assessing and implementing the right QMS in combination with high education standards will produce quality practice. Reliance on siloed and outdated systems is holding back site progress. We should not fear change, but rather, learn how new ideas and technology can improve life for all of us.

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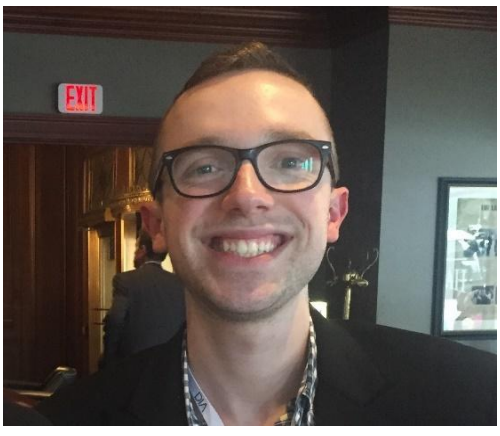

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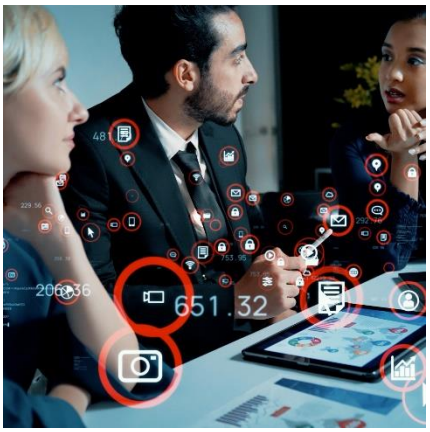
PRESCRIPTIONS FOR BUSINESS

Streamlining Adoption of Digital Technology in Clinical Trials Through Use of Open-Source Algorithms

Geoffrey Gill, MS



Clinical trials have become both increasingly expensive and less reliable as the focus of therapy development has shifted to managing chronic illnesses. Wearables and other digital technologies have the potential to transform clinical trials by allowing investigators to transition from using occasional—often subjective—measures of health, such as patient-reported outcomes, to continuous, objective measures, such as the patient's level of activity or quality of sleep as measured by a wearable device. These metrics have the potential to be highly targeted and precise.

For example, stride velocity 95th centile measured at the ankle with a wearable device was recently accepted as a secondary endpoint for ambulant Duchenne muscular dystrophy patients by the European Medicines Agency.{1} Recognizing the potential of digital endpoints, the Clinical Trials Transformation Initiative (CTTI) released a series of recommendations, including a detailed flowchart showing how to develop endpoints, in June 2017.{2} These recommendations provide a clear path to developing digital endpoints.

The Quest for Qualification and Validation

Despite the potential benefit of digital endpoints and clear guidance on how to qualify them, getting even one endpoint accepted by regulators still requires significant work. The challenge comes from the fact that there are literally thousands of potential digital endpoints and more than 100 types of digital sensors, each with its own algorithms and outputs. Even different versions of the same device will often have different algorithms that generate different results.

There is also a need to validate endpoints on the patient population of interest, as validation on one patient group might not necessarily mean an endpoint will provide accurate outputs for another patient group. Therefore, it is very unlikely that a study team will find a prepackaged solution with a validated endpoint and sensor combination for a pathology of interest. In practice, this means that clinical trials study teams are faced with the choice of going through the entire validation process for their particular patient, sensor, and endpoint combination; capturing just an exploratory endpoint; or abandoning the effort altogether. Further, unless the sensor they use provides the raw data and the algorithm is available, teams will be tied to that particular sensor if they choose the exploratory endpoint alternative and want to use it in later trials.

Fortunately, using open-source algorithms can dramatically streamline this process. By using the V3 validation framework published by members of the Digital Medicine Society,{3} the validation process can be broken into three logically distinct steps:

1. **Verification** – verifying that the sensor provides the right data.
2. **Analytical Validation** – proving the algorithm converts the sensor data into a physical phenomenon, like steps, accurately.
3. **Clinical Validation** – ensuring the physical phenomenon is a relevant clinical measure.

The first step, verification, depends only on the sensor. It should be performed by the manufacturer and should only need to be done once. Assuming verified data, both analytical and clinical validation depend on the algorithm. By using open-source algorithms, researchers can effectively share algorithm validation—no matter what sensor was used to generate the data—if the sensor went through the verification step.

The power of this approach can be demonstrated using atopic dermatitis (eczema) as an example. There are many potential endpoints of interest with this condition that could be measured using wearable sensors,{4} including:

- Scratching events per hour
- Number of scratching events
- Scratching duration per hour
- Total sleep time
- Wake after sleep onset
- Sleep efficiency

There are already open-source algorithms that address these endpoints. For example, Pfizer has developed software called Scratch.PY that calculates all these endpoints for nocturnal scratching, based on data from a wrist-worn accelerometer.{5} Pfizer has performed significant validation studies on this algorithm, and it is free for anyone to use. Researchers that employ Scratch.PY can build on this significant validation effort. Furthermore, if they publish their research, that strengthens the foundation for future researchers looking to validate endpoints for their studies.

A great example of how a validation foundation can be built steadily over time is provided by an open-source package called GGIR, which generates a wide variety of activity and sleep endpoints from wrist-worn accelerometer data. More than 300 peer-reviewed papers have used GGIR, including more than 90 published in just the past year.{6} Hundreds of thousands of participants have been studied in a wide variety of therapeutic areas. Table 1 summarizes a small selection of the studies performed using GGIR to process the data.{7} No single organization could match this level and rate of research.

Table 1:

STUDIES PERFORMED USING GGIR DATA PROCESSING.

Therapeutic area	Patient Cohort	Number of Patients (n)
Cardiovascular	Heart surgery patients [44]	80
	Stroke [15]	41
	Cardiovascular Disease [16]	23,742
	Coronary Artery Disease [17]	58
Central Nervous System	Muscular Dystrophy [18]	128
	Dementia [19]	26
Musculoskeletal	Idiopathic inflammatory myopathy [20]	55
	Muscular Dystrophy [18]	128
	Sarcopenia [21]	131
Mental Health	Depression [22]	359
	Bipolar Disorder [23]	46
	Post-Partum Depression [24]	21
Diabetes	Gestational Diabetes [25]	697
	Type II Diabetes Mellitus [26]	635
	Type II Diabetes [27]	246
Rehabilitation and recovery	Pulmonary rehab patients [28]	79
	Bariatric surgery patients [29]	22
Pulmonary	Cystic Fibrosis [30]	9
	Idiopathic Pulmonary Fibrosis [31]	35
Aging	Older adults [32]	1,451
	Post-menopausal women [33]	1,316
Lifestyle	Sedentary adults [34]	191
	Obesity [35]	1,986
	Smoking [36]	3,063
	General population [37]	85,388
Children	Obese / overweight [38]	208
	Adolescents [39]	2,526
	Children [40]	2,636
Pregnant Women	Pregnant women [41]	2,317
	Pregnant and overweight [42]	257

What's more, all this validation material is available for any sensor that provides accurate accelerometry data. The GGIR research has used many different types of wrist-based accelerometers. By using open-source code, researchers are no longer tied to a single device and can leverage validation and user studies from a wide group of researchers.

The work that has been done to date is just a start for GGIR to achieve approval as a validated endpoint for a clinical trial.{6} However, once approval has been granted, any organization can potentially use that approval as evidence for its own trial—even if it uses a different device. Furthermore, the availability of a large amount of evidence from different therapeutic areas should make extending the validation to those applications significantly easier. Finally, consolidating around a de facto standard like GGIR will start to provide a consistent measurement to be integrated into medical practice.

The Consistency Conundrum

One cannot overstate how important consistent measurements across devices are to using digital medicine to help treat patients. It would be impossible for doctors to treat patients if every blood pressure monitor or thermometer relied on its own metrics for measuring these symptoms. Doctors need to establish consistent normal ranges and thresholds to know how to treat their patients.

Of course, it is relatively easy for different manufacturers to make their blood pressure monitors and thermometers comply to the standards without common algorithms, because they only measure one or two metrics taken at a single time. That is essentially the same as the verification step for digital sensors. Achieving consistency in digital measures without using a common algorithm, on the other hand, is far more difficult.

A major value of digital measurements is that they can monitor continuously over a long period of time to measure subtle changes in health in the real world. This facility is vital to accurately measure the progression of chronic diseases, which affect more than 50% of the U.S. population and represent more than 86% of the country's healthcare costs.{8} However, this means that rather than measuring a single value at a point in time, huge amounts of data must be aggregated, consolidated, evaluated, and summarized.

Without common algorithms, achieving consistent results is effectively impossible. By embedding these algorithms in open-source software, it is possible to ensure consistent results from the start.

The Challenges

Although the benefits of using open-source algorithms appear quite clear, not all stakeholders in the industry support them. Some companies believe that they will be able to get their proprietary algorithms adopted and achieve monopoly profits as a result.

This approach faces immense barriers, not only because of the huge effort required to validate algorithms and the need for consistency across devices, but also because customers, regulatory bodies, and healthcare providers all want levels of transparency which are not generally available with proprietary algorithms. While some companies may succeed at keeping their algorithms to themselves, the majority of applications being developed by various firms will likely adopt common algorithms, if not open source.

Moving Forward

Clinical trial sponsors and regulators are starting to play a major role in this movement toward adopting open-source algorithms. Many of the leading pharmaceutical companies and other industry organizations are participating in the Open Wearables Initiative (www.OWEAR.org), which promotes and facilitates the use of open-source algorithms for clinical endpoints. OWEAR is also working on CTTI's Novel Endpoints Project. In Europe, Mobilise-D is a major collaborative program involving industry, academia, and government to develop open-source algorithms for gait measurement.

More can be done. Sponsors and regulators should strongly encourage the use of open-source algorithms. Sponsors should share validation material and pre-competitive data more broadly. Regulators should encourage and facilitate this sharing as much as possible. Through collaboration, we can accelerate the adoption of these vital tools significantly and help patients live healthier lives.

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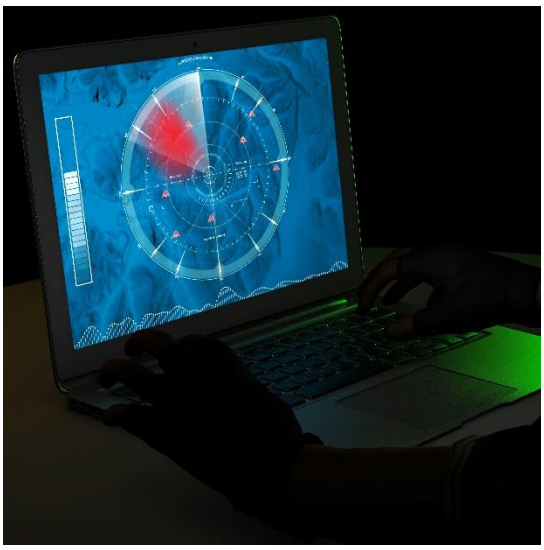
OVER THE TRANSOM

Is There Anybody Out There?

Gary W. Cramer



If memory serves me correctly, it was sometime in March 2020 that I was dragged, kicking and screaming, from my cubicle in the ACRP headquarters along the Potomac River in Alexandria, Va., and forced to work at home during the early days of the pandemic. Well…not really, but I was one of the last of the staffers to make the transition, because I had, up until then, never been a fan of the work-at-home concept. In fact, I had long been the type to avoid even the most generous offers of flexible, hybrid home/office schedules and kept schlepping into headquarters except in situations when I absolutely had to work from home for reasons that were beyond my control and, thankfully, temporary.

As fate would have it, the next several months of logging into work from my apartment and having no face-to-face contact with my office colleagues was good practice for the fact that I needed to get used to being a full-time, remote worker anyway. That wasn't because the restrictions on going back to the office dragged out so long, but because I had planned to move out of state in mid-2020 long before COVID-19 was even a tiny speck way out on the edge of the medical community's radar screen. Achieving a change of scenery without a change in employment had been on my mind since late 2018, and I had given myself plenty of time to prepare for the logistics of it, if not for the mental readjustments that would be required.

Now nearly 15 months into working from home in a lovely part of Pennsylvania—still never having set foot back in my old cubicle or even gotten within striking distance of Alexandria—I

am mostly reconciled to the idea that this very well may be how I will spend the rest of my full-time career. A big adjustment after 30-something years of commuting to work? Sure. A kick in the pants to sharpen up certain "soft skills" that are necessary to thrive in this altered environment? Absolutely.

One solace is that I know I am far from alone in this new normal thingy so many of us are still feeling our way through. With that in mind, I thought we'd take a step back from being so research-centric in our explorations of news from the outside world in this issue's column, and enjoy a more general look at what other sources of knowledge (no endorsements implied) are saying about new perspectives on soft skills and work/life balance for the times in which we find ourselves.

Women Report Greater Stress and Better Coping Strategies Related to Work

The latest edition of LinkedIn's Workforce Confidence survey takes an in-depth look at America's stress levels among 4,958 LinkedIn members, finding that 74% of women say they are very or somewhat stressed for work-related reasons, compared to just 61% of employed male respondents. However, women also are more inclined to do something about these burdens. When asked how they view seven possible stress-fighting strategies, women in the workforce showed greater interest in each path than their male counterparts. The strategies include taking (or planning to take) time off, taking breaks during the day, ending work at reasonable hours, not checking in on work after hours, turning down extra responsibilities, being open with colleagues about stress, and using employers' mental health benefits.

Don't Avoid Avoidance Strategies When in Search of Work/Life/School Balance

As if achieving a work/life balance wasn't hard enough, researchers say many of us are juggling a third factor: school. That creates conflicts, say Bonnie Cheng, a PhD candidate at the University of Toronto's Rotman School of Management, and Julie McCarthy, an associate professor at the Rotman School and the University of Toronto Scarborough, often resulting in dissatisfaction in the area that caused that conflict. For example, skipping a family function to stay late at work can lead to less satisfaction with work. However, avoidance techniques can help, the researchers' recent study shows.

Using a group of undergraduate students who also worked outside school and had family responsibilities, the researchers surveyed them at two different points in time to gauge how much conflict students were experiencing from their competing responsibilities, the different coping mechanisms they used to deal with them, and how much satisfaction they derived from their activities. The study found that students who used avoidance strategies, such as not dwelling on their problems, were better able to manage conflict across work, family, and school, and experienced more satisfaction.

"Our intuitive notion of avoidance is that it's counter-productive, that it's running away from your problems," says Cheng. However, she says, there are different kinds of avoidance. "We found that while wishing for your problems to magically disappear is counterproductive, the process of taking your mind off the problems at hand actually helped people manage multiple role responsibilities and increased their satisfaction." The trick, she stresses, is not allowing avoidance to slip into escapism. The finding is equally applicable to any situation where people are juggling multiple role responsibilities, including volunteering and coaching.

Soft Skills Don't Help Job Seekers with Disabilities in Early Interviews

A new study by Rutgers University researchers finds that job candidates with disabilities are more likely to make a positive first impression on prospective employers when they promote technical skills rather than soft skills, such as their ability to lead others. The findings, published in the *International Journal of Conflict Management*, contrast this with the results for candidates without disabilities who were positively evaluated when they highlighted either hard or soft skills during initial job interviews.

"Job interviews are challenging for everyone, but particularly so for people with disabilities who have always had difficulties presenting themselves favorably to gain employment," said Rutgers Business School professor and study coauthor Mason Ameri. "[They] encounter an implicit bias that they will not be as productive as their non-disabled peers. Knowing how to navigate the conversation with potential employers is critical for leveling the playing field."

In three studies, 1,711 participants watched videos of candidates—either visibly seated in a wheelchair or not—using influence tactics to answer an opening question during an interview for

a project manager position. Participants were asked to rate their perceptions of the job candidate's employability and appropriate level of salary, as well as how trustworthy they appeared. For candidates without disabilities, discussion of hard skills or soft skills led to more favorable perceptions. While the expression of hard skills similarly improved the employability rating of the candidate with the disability, discussion of soft skills did not.

New Tool Does Well in Evaluating Doctor's Bedside Manner

The best way to improve a doctor's bedside manner may lie in a new tool that evaluates and helps medical residents improve their communication and other soft skills to become better doctors, according to a new study led by Women's College Hospital's Dr. Tim Dwyer. The study, published in the *Canadian Journal of Surgery*, is the first to look at the medical residents' collaboration, communication, and other soft skills, or what are known as CanMEDS competencies, in orthopedic surgical training.

"While we do a great job at evaluating the medical skills of residents, we don't have a good tool to objectively test their soft skills such as teamwork and how to communicate bad news to a patient, which is just as important in their careers as surgeons," said Dwyer, an orthopedic surgeon and lead author of the study. "Our new examination tool is very effective in objectively testing multiple soft skills in one examination session in an orthopedic residency program."

The study, involving 25 orthopedic residents with various years of training, examined how medical residents handled cases of suspected domestic violence, their ability to manage the operating room, how they applied evidence-based medicine, and how they communicated with patients' disgruntled family members regarding delays in surgery. It tested six soft skills: communicator, collaborator, manager, health advocate, scholar, and professional.

"For decades, medical residents' soft skills were examined on paper," said Dwyer. "Our study shows that this tool offers a better, more objective exam alternative, and it has a potential to spread beyond orthopedic surgery to other specialties."

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