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APPLIED CLINICAL TRIALS

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Taking Care of Site Business

LISA HENDERSON
Editor-in-Chief

I'm really excited about this issue of *Applied Clinical Trials*. Tagged as "The Changing Site Landscape," this is our foray to update information presented in September 2018 (see https://bit.ly/34b0vOf) around different site models and bringing clinical trials closer to the point of care. This year, we offer a more in-depth look at representative models that are changing the way investigative sites work. The "traditional, dedicated research site" is morphing to model more efficient, professional, and technologically robust practices and processes that rival those of CROs, while specialty physician groups and large IDNs integrate professional providers that operationalize clinical research within their unique clinical care workflows. Academic centers, long the bastion of both innovation and bureaucracy associated with clinical trial conduct, have instituted change to streamline their business. And at the Veteran's Administration, executives are attacking their own bureaucracies to unify study start-up and make VA clinics a competitive option for sponsored research. What follows are highlights of trends from this issue, as well as trends heard around site practices during the year.

Professionalism. One recognized problem at sites is the varying levels of performance quality and consistency in staff capabilities. There are many ways now available to help clinical research professionals, as well as sites, establish credibility and professionalism. For example, the Alliance for Clinical Research Excellence and Safety (ACRES) recently announced it will begin to accredit investigative sites. The Association of Clinical Research Professionals (ACRP) offers certifications of varying clinical research roles, as does the UK-based International Academy of Clinical Research (IAOCR). ACRP also rolled out its ACRP Core Competency Framework two years ago, initiated so industry could begin to level set the various roles at sites and is discussed as a tool used by many in our main feature (see page 24).

Remote Trials. There is some backlash around the terminology of remote or virtual trials. While many have started calling them decentralized trials, these trials really are around patient centricity and making convenience and location (or inability to get to a site location more specifically) a reality for participants. Clearly, decentralized trials are reserved for the most appropriate of therapeutic areas and populations. More often than not, hybrid trials is the word of the day and means that you offer patients a mix of both on-site and virtual. To that end, sites are incorporating technologies that enable them to be more competitive for the hybrid models.

Remove Recruitment from the Site. I attended a meeting where physician speakers discussed their role as clinical event adjudicators. One view shared was that sponsors or CROs spend about 1% of their time educating the investigative staff on the study protocol, and 99% on patient recruitment. The physicians felt this time allocation should be flipped given the importance of protocol adherence for both data and safety reasons. Given the dire straits of patient enrollment, as well as the diverse ways to reach potential participants, it makes sense to take recruitment out of the core site responsibility, and make it a more strategic process.

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WASHINGTON REPORT

SPONSORS, REGULATORS CAUTIOUS ABOUT RISK-BASED OVERSIGHT OF CLINICAL TRIALS

Despite the high cost and extensive resources involved in monitoring the conduct of and data produced by clinical trials, the research community has been slow to embrace strategies for reducing on-site oversight to reflect risk. Sponsors appear willing to spend more to ensure that results meet regulatory expectations and avoid raising issues that could delay the review and approval of a market application. FDA and other regulators are responding with support for more flexible monitoring of clinical investigators and review of study records in order to limit study monitoring to situations where less oversight raises clear difficulties for investigators, participants, and data integrity.

To this end, FDA has encouraged sponsors to focus on risk in monitoring clinical trials, similar to agency initiatives to modify pharmaceutical plant inspections and pre-approval of product changes to situations likely to compromise product quality and safety. Instead of using on-site monitoring for every clinical site to verify study data and conduct, FDA advises sponsors to limit oversight to the most critical data elements, procedures, and processes, as outlined in guidance issued in 2013 and updated earlier this year. Such situations can be described in risk-based monitoring (RBM) strategies laid out in RBM plans.

Despite these efforts, biopharma companies have been slow to adopt RBM approaches, as seen at a public workshop in July organized by the Margolis Center for Health Policy at Duke University to gain more feedback from stakeholders on the challenges and barriers influencing the adoption of RBM. Jacqueline Corrigan-Curay, director of the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER), opened the meeting by emphasizing the importance of leveraging tools and methods to improve the efficiency and reliability of clinical trials. FDA wants to make risk-based monitoring "a reality for everyone," she said, and is reviewing comments from the recent draft guidance to move forward.

The process begins with risk assessment to help shape the resulting clinical research protocol, explained David Burrow, director of the Office of Scientific Investigations (OSI) in CDER's Office of Compliance. An RBM plan then can be built to support product approval and reduce errors "that matter," he commented. An analysis of 334 OSI clinical investigation summaries over three years reveals relatively few "active recommendations" that raise questions about application quality likely to delay approval. The vast majority of clinical inspections find appropriate compliance with requirements.

Similar efforts by the European Medicines Agency (EMA) support risk-based approaches to clinical trial monitoring to ensure that studies generate reliable information, while protecting study subjects, commented Camelia Mihaescu, of the EMA Committees and Inspections Department. Risk-based approaches, she noted, should reflect trial-specific issues.

Yet, regional differences in monitoring practices, inspection procedures, and acceptance of RBM by regulatory agencies create barriers to wider adoption of RBM, observed Tim Rolfe, director of research-based monitoring at GlaxoSmithKline. Sponsors have concerns about ensuring quality data at multiple study sites that follow a range of research methods, with large, complex trials raising issues that differ with very small studies. He advised FDA to update its inspection guide for clinical sites and to train inspectors in RBM expectations through case examples. Research sites experience "general discomfort" with RBM approaches, according to a study by the Society for Clinical Research Sites, and often feel left out of planning for RBM approaches, which vary notably with each sponsor.

Burrow of OSI was optimistic that recent changes in FDA's Office of Regional Affairs (ORA) to create specialized teams of clinical site inspectors may address some inspection issues. But OSI still finds problems with initial RBM efforts, particularly with record sampling and source-data verification, and limited coordination between sponsors and CROs can be a problem. FDA officials advise sponsors to involve all stakeholders in the RBM process, which should be adaptable and promote human subject protection and data integrity.

— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

8/13/19: Gastroparesis: Clinical Evaluation of Drugs for Treatment

8/7/19: Fabry Disease: Developing Drugs for Treatment

8/2/19: Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment

7/31/19: E8 (R1) General Considerations for Clinical Studies

7/31/19: General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products

7/30/19: Rare Pediatric Disease Priority Review Vouchers

The following committee meetings were scheduled for September:

- Allergenic Products Advisory Committee, ***Sept. 13.*** Discuss the safety and efficacy of Peanut Allergen Powder, indicated to reduce the risk of anaphylaxis after accidental exposure in patients aged 4 to 17 with a confirmed diagnosis of peanut allergy.
- Patient Engagement Advisory Committee, ***Sept. 10.*** Discussed and made recommendations on the topic "Cybersecurity in Medical Devices: Communication That Empowers Patients."

EU REPORT

NO END IN SIGHT TO EUROPEAN DEBATES ABOUT DRUG FIRMS' INFLUENCE ON REGULATORS

Persistent concerns that European drug evaluators are too cozy with pharmaceutical companies are unlikely to be fully allayed by a recent decision from the European Ombudsman that "no further inquiries are justified" into the provision of early scientific advice. The two-year inquiry into possible maladministration at the European Medicines Agency (EMA) has intensified as much as it has resolved long-running controversies over potential conflicts of interest and lack of transparency within the agency.

It was two years ago that the Ombudsman—an official European Union body—decided to follow up on anxieties among many healthcare campaigners and academics about the risk of what they saw as a hazardous overlap: the EMA's roles both in giving early scientific advice to drug developers, and its subsequent engagement in evaluating marketing authorization applications from the very same products it had advised on. "These 'pre-submission activities' may have some positive consequences for public health," said the formal inquiry, but it insisted that it was also "important to avoid even the perception that the eventual opinions of EMA on medicines were influenced by these earlier interactions."

> Questions have been posed for years about whether EMA's recommendations on authorization of a medicine is influenced by the prior interaction its evaluators have with medicine developers.

This summer, after extensive consultations and discussions, the outcome was nothing more than "a number of suggestions for improvement"—and the decision to, in effect, drop the case. The Ombudsman merely urged that "EMA should carefully manage the contacts its evaluators have with medicine developers during the pre-submission phase," and that "EMA should provide greater transparency on its pre-submission activities, with the aim of maintaining public trust in its work." But some of those who have levelled strident and repeated attacks on the agency's operations in the last five years will not be so easily appeased.

Keeping things separate

EU law specifically allows for medicine developers to seek advice from EMA's experts long before they submit a marketing authorization application. It is considered legitimate for companies to seek advice on the relevant procedures, the requirements for demonstrating that medicines are safe and effective, or the design or conduct of clinical trials.

But questions have been posed for years about whether EMA's recommendations on authorization of a medicine is influenced by the prior interaction its evaluators have with medicine developers. The Ombudsman chose to assess how far this may have happened, or even be perceived to happen. And it concluded that not much needs to change.

Plenty of interest, plenty of ambition

Among the numerous representations made to the Ombudsman during the inquiry, national medicine evaluation authorities and the pharmaceutical industry felt the system was broadly sound and protected the public adequately from risk of overlap. But "by way of contrast, many civil society organizations and academics argued that the current practice concerning pre-submission activities needs be improved to enhance the objectivity of how medicines are evaluated," remarked the Ombudsman's decision.

The criticisms focused partly on the risk of bias where the same individuals are involved in providing scientific advice and in subsequently evaluating that same medicine. EMA should widen its pool of experts, and where it was absolutely necessary to have such overlap, EMA should publicly justify it. And there was also frequent criticism of the lack of transparency over the procedures and calls for the scientific advice provided to be open to public scrutiny.

Health Action International (HAI) cited allegations purporting to come from EMA staff that "manufacturers see pre-submission processes as a way to lobby the agency." The European Public Health Alliance warns of "regulatory capture." The International Society of Drug Bulletins says: "EMA's confidential pre-submission "scientific advice" to companies jeopardizes its ability to make independent decisions. Pre-submission activities effectively make EMA a co-developer of the medicine, yet it is subsequently called upon to issue its opinion on whether or not the medicine should be granted marketing authorization."

Critics make complaints about the negative impact of the confidentiality surrounding the process. EPHA warns of the dangers of giving scientific advice "behind closed doors" and of how EMA "black boxes" and "revolving doors" impede transparency. ISDB says "companies that request pre-submission scientific advice could exert control from an early stage over everybody involved in the assessment of marketing authorization applications at both national and European level." According to HAI, "It is impossible to know from the onset the advice a company has requested, and the EMA has subsequently provided, even though this would be relevant information to patients who are considering enrolling in a clinical trial, and to independent clinical trial reviewers." By providing "tailored and confidential advice to one company only," EMA may even be in breach of competition law, it suggests.

EU REPORT

HAI has made clear its concerns that "at the time of assessing an application for marketing authorization, (the relevant committee) members might feel bound by the advice that the very same committee they represent gave in the past to a company/marketing authorization applicant." It says EMA should draw a firm line to prevent overlaps: "A clear separation of roles between advisors and marketing authorization assessors should be established."

And the European Consumer Organization (BEUC) says it wants to know how EMA's pre-submission activities contribute to the development of safe and effective medicines. "A growing number of medicines seem to come to the market for which less robust data is available. How do pre-submission activities contribute to the availability of robust and useful data, while also minimizing the number of unnecessary clinical trials?," the bureau asks.

On the fence

The Ombudsman came down firmly in the middle of this divergence of views. Yes, there is an element of risk in overlap, in acknowledgement of the critics—but, overall, the system offers protection against undue influence, it concluded, in line with most comments from regulators and industry. So there is not a lot that needs to be done. The toughest recommendation the Ombudsman makes is that "to the greatest extent possible, EMA should ensure that there is a separation between those responsible for providing scientific advice to a medicine developer and those subsequently involved in evaluating" it.

The operational result is that EMA's own arguments—essentially that scientific advice is a force for good and should not be tampered with lightly—largely prevailed in the Ombudsman's decision.

EMA defense

EMA argued that the provision of scientific advice can minimize the risks of exposing patients to useless or less useful clinical trials, and maximize the value of the data that clinical trials generate; and by avoiding misunderstandings in the assessment process, it can ease administrative burdens and cut can minimize the risks of exposing patients to useless or less useful clinical trials, and maximize the value of the data that clinical trials generate; and by avoiding misunderstandings in the assessment process, it can ease administrative burdens and cut the risk of preventable delays at a later stage.

The agency maintained stoutly throughout that a scrupulous distinction is maintained between the two levels of interaction, so as to give a guarantee of fair dealing and impartiality, Scientific advice is not a pre-evaluation of the data gathered during clinical trials. It is prepared by nominated experts who report to a specific working party, and not by the committee that conducts evaluations of marketing authorization applications. In the rare cases where the same expert contributes to both scientific advice and product evaluation, it is because of scarcity of experts in certain areas of science and medicine, and public health could be impaired by a prohibition of this practice. If EMA identifies possible conflicting interests among any of the experts, it can exclude them from participating in discussions on particular topics. And it is not binding, since it is based by definition on the current state of the art, and may consequently be superseded as understanding advances.

No change, but no relief

The Ombudsman's decision leaves the situation unchanged. EMA will continue to maintain that on balance, the system is good and fair. Critics will continue to say the balance is wrong, and that partiality remains built into the system. And the Ombudsman's views, taking some from column A and some from column B, and offering no more than a heavily-qualified suggestion of maximum caution, fully satisfies neither side. The flurry of soft diplomatic words of welcome from EMA for some elements of the decision cannot disguise the reality that it will continue to proceed as before, despite its commitments to a few equally soft additional gestures toward transparency.

The more trenchant criticisms of the system will, therefore, remain unsatisfied—and, hence, they will continue to feature just as much as before in the public discourse about EMA's independence from industry influence.

The fact that the sharpest criticisms are made by only a relatively small number of contributors to the inquiry does not reduce their significance. Both HAI and EPHA are influential organizations—both of them are represented on EMA's own bodies—and they command a prominent position in European public debates about health and medicines. They and the other organizations that share their views will ensure that the debate will continue to grow over the role of EMA and the influence of the drug industry on regulatory decision-making. And this at a particularly crucial moment for European rulemaking in general, with a new European Parliament and European Commission just about to take up the management of policy for the next five years.

The fact that the sharpest criticisms are made by only a relatively small number of contributors to the inquiry does not reduce their significance. Both HAI and EPHA are influential organizations.

— Peter O'Donnell

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Q&A

WORKFORCE READINESS TECHNOLOGY MINIMIZES RISK IN CLINICAL TRIALS

Clinical trials often encounter operational challenges and sponsors and CROs seek effective site-readiness practices. In this interview, Joel B. Selzer, co-founder and CEO, ArcheMedX, Inc., discusses the impact that healthcare technology has on clinical trials, focusing on the development of the company's workforce readiness platform.

Q: Can you tell us a bit about yourself?

Joel Selzer: I have spent the past 15 years envisioning and delivering innovative technology and data-driven solutions across the life sciences and healthcare industries as an entrepreneur, board member, and advisor. During this time, I have co-founded and led three technology companies, Medical Funding Services, Ozmosis, and currently ArcheMedX. In each venture, we have applied creative approaches to improve the lives of our customers, thousands of clinicians, and most importantly millions of patients.

Q: Can you give us a brief overview of your product?

JS: Ready is an operational intelligence and workforce readiness platform that reduces the risks and costs associated with underperforming clinical trials. The platform enables clinical operations leaders to evaluate and improve the preparedness of project teams and site personnel by analyzing the behavior of each participant as they engage in personalized learning experiences that are designed and delivered within the platform. Ready serves as an early warning detection system to identify risks sooner, ensure resources are more effectively deployed, and enhance staff and site performance.

Q: This product came out of a healthcare and continuing medical education history. What made you choose clinical trials for this service?

JS: We spent the first six years at ArcheMedX powering hundreds of online medical education activities for national medical societies, leading academic medical and research centers, global medical education providers, and major pharmaceutical firms. One of our academic research partners ran into challenges standardizing initiation across a diverse set of study sites and asked if ArcheMedX could help.

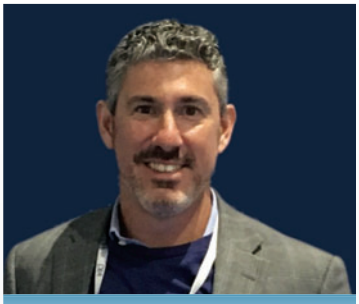
We ultimately enabled them to design and deliver an innovative site readiness program powered by the ArcheMedX platform that accelerated site initiation for a neurology focused trial. That effort opened our eyes to the operational challenges thousands of trials encounter and led us to explore the industry further. In the course of our market research, we conducted informational interviews with dozens of sponsors, CROs, and other trial stakeholders and the critical need to more effectively evaluate and improve the preparedness of staff and sites became increasingly clear.

The result was the development and launch of Ready.

Q: We are seeing more technologies coming from healthcare into clinical trials, which is but one part of the overall healthcare picture. Why do you think that is? What impact will that continue to have in clinical trials?

JS: There are a number of macro trends driving the adoption of technology within clinical trials. For example, rising trial costs, increasing complexity, the continued low success rates of getting to market, and the extreme challenges of recruiting and retaining participants are all multiplied by the continued growth of active clinical studies. This creates a great deal of opportunity for technology-based solutions to make a positive impact.

In particular, clinical trials are accelerating the adoption of digital tools and data-driven strategies. Sponsors and CROs are now using advanced data analytics and deep learning to more effectively design and implement clinical trials that result in more personalized and consumable therapies that benefit patients and providers. From digital therapeutics and advanced protocol simulations to data-driven workforce improvement, the industry can more rapidly and accurately analyze novel sources of data that will inform better decision-making, decrease the costs of clinical trials, and provide the right therapies to the right patients.



Joel Selzer

Q: Investigative site burden is quite often a topic of concern in this industry. Does the implementation of Ready increase a site's burden of tasks?

JS: Many sites today are already struggling to implement a dozen or more trial applications, ever-changing study tools, and increasingly complex protocols. Adding to this burden, they are rushed through training on each system and protocol and often lack the time and interest to properly focus on critical information. By centralizing and personalizing each training experience, Ready makes it easier and more enjoyable for site personnel to engage in critical content over time, increasing their confidence and interest in the study or tool. Ready can also be integrated via web services with nearly any IT system making it simple to create a seamless user experience and securely share data.

Sponsors and CROs are now using advanced data analytics and deep learning to more effectively design and implement clinical trials that result in more personalized and consumable therapies that benefit patients and providers.

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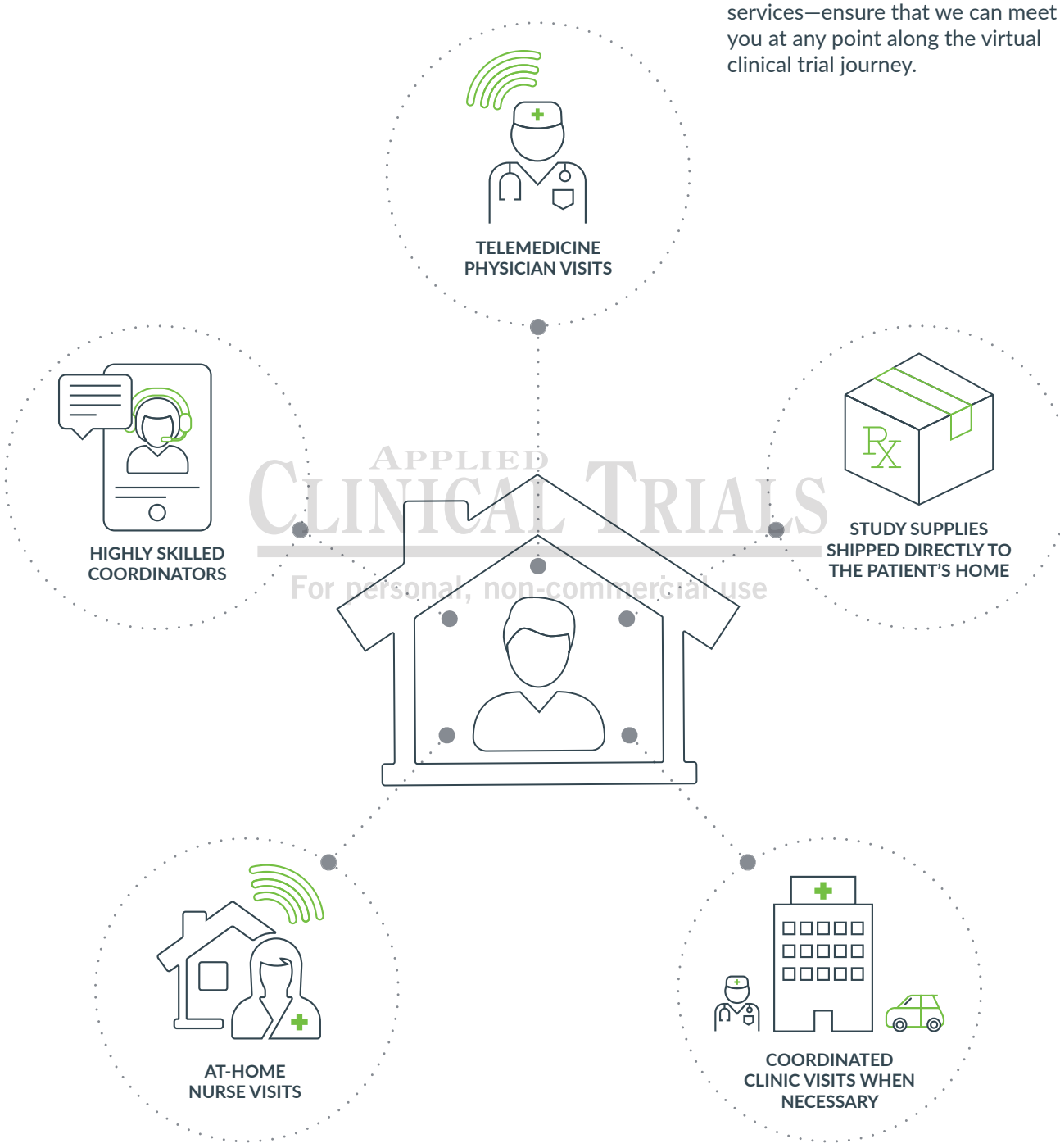

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Q&A

Q: How would you envision Ready changing the way sponsors plan their investigator meetings and subsequent site training?

JS: Ready creates opportunities for sponsors to augment, re-focus, or even replace their investigator meetings, and subsequent site training. By deploying Ready prior to an investigator meeting, the insights it generates can help to focus the meeting on the areas of greatest need and risk. This can result in a more engaging and targeted meeting that accelerates site initiation, better enrollment, and overall compliance.

Ready can be utilized in place of an investigator meeting to significantly reduce meeting costs and provide more measurable data and insights that identify which PIs (principal investigators) are most likely to struggle. The platform can then automatically re-engage any participant to focus on critical aspects of the protocol or other content they may have skipped or struggled with and will continually measure their engagement and response.

Ready can also power a virtual SIV and any subsequent site training, such as protocol amendments and the sharing of recruitment best practices. In each of these use cases, Ready will analyze the unique behavioral data it captures to provide insights that help sponsors focus where additional training, site visits, and/or remote monitoring may be required.

> This unique analysis of behavioral data drives risk mitigation, as well as more effective allocation and deployment of resources that leads to better staff and site performance.

Q: Does Ready impact other oversight practices such as risk-based monitoring (RBM)?

JS: Yes. The operational intelligence and workforce readiness data generated by Ready creates early insight around areas of clinical operation risk and are key pieces of information for any RBM strategy. Since the personalized learning experiences powered by Ready are often delivered during study start-up, the insights the platform provides into the readiness and mindset of participants serve as an early warning detection system that compliments traditional risk-based data and strategies. This unique analysis of behavioral data drives risk mitigation, as well as more effective allocation and deployment of resources that leads to better staff and site performance.

Q: There is also a lot of positive change in the industry to raise the level of education and professional credentials at the site level. How does Ready help sites raise their bar?

JS: More than 40,000 clinicians have already improved their knowledge, competence, and confidence with ArcheMedX and this positive change continues to raise the bar at sites across the globe. By deploying Ready, sponsors and CROs can now accelerate this change by more effectively measuring and improving the competence, readiness, and mindset of their staff and sites. Ready can enable the industry to identify skill and knowledge gaps across roles, years of tenure, certification levels, and therapeutic areas and then target workforce improvement efforts on the segments of staff and sites that need it most.

— Staff Report

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eLEARNING:

While risk management efforts in drug development have focused mostly on post-marketing drug safety, the clinical trials process has its own mix of potential risks waiting to derail a company's multimillion-dollar development programs. This webcast focuses on why risk management and assessment are most effective when integrated into clinical trials from the beginning (study start-up phase), rather than as an afterthought.
http://bit.ly/2kghywc

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Medical monitors play an integral role in ensuring patient safety, as trials increase in complexity and as the volume of participant medical data grows. *Medical Monitor Modernist: Driving Productivity Protecting Subjects* is our latest e-book that shows how the medical monitor role is evolving. It also explores how new, intuitive data visualization and analysis software technology is helping medical monitors identify outliers and trends in clinical trial data.
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DATA SHARING

MIXED PATIENT SUPPORT OF DATA-SHARING INITIATIVES

Do patients really want to share their data? The question goes to the heart of the digital health revolution that strategists love to celebrate—and the strategists will be heartened by the results of a new poll by Europe's leading rare disease organization, Eurordis. The vast majority of the 2,000+ rare disease patients responding to an international survey are supportive of data-sharing initiatives to foster research and improve healthcare, and willing to share their data to help research and treatment on diseases other than their own.

But this is no carte blanche. Nearly half the respondents are against their data being shared outside the medical field, and even within the medical field, nearly all of them want something close to full control over the data they share, both over who gets it, and what it is to be used for. They see big risks that their information may otherwise be shared with third parties without their consent, and be used in a context different from the one in which they disclosed it.

It includes recommendations to policymakers, researchers, funders, and patient organizations creating data-sharing initiatives, centered on issues of trust. Governance should be in the hands of people whom patients consider impartial—such as general practitioners—and serious attention should be given to keeping patients informed about progress and outcomes of research for which their data has been used.

The full report is published in the *Orphanet Journal of Rare Diseases* and makes challenging reading. It identifies the "numerous technical and regulatory boundaries that make sharing difficult and for many researchers, clinicians and institutions, still not standard practice." Aside from technical issues, Eurordis also points out that many institutions do not have a culture that promotes new data-sharing initiatives. And researchers remain subject not only to geographic, institutional, or disciplinary boundaries, but often governed by "silo mentalities" that see sharing data as a risk to personal and professional benefits conferred by data ownership. Increasingly prominent attacks on—and sensitivity to—data security compound the difficulties. One of the key recommendations, accordingly, is that policymakers should pursue cultural, technological, and infrastructural changes to make a reality of international data sharing.

Eurordis and its numerous fellow advocates of data sharing had better factor the results of this survey into their planning. Because for all the potential of digital health, without access to the data, not much is ever going to change.

—Peter O'Donnell

NEWS NOTES

NEW COLLABORATION TARGETS PANCREATIC CANCER

Genisphere LLC and University Hospitals Cleveland Medical Center are partnering to study and develop unique strategies to treat pancreatic cancer. According to their agreement, investigators will optimize 3DNA®-based therapeutics designed to target and kill pancreatic tumors. Projects will include delivering a variety of therapeutic cargos, including small molecules and siRNA, formulated with pancreatic tumor-targeting molecules on Genisphere's 3DNA® nanocarrier.

Jordan Winter, MD, chief of the Division of Surgical Oncology at University Hospitals Cleveland Medical Center and director of surgical services at UH Seidman Cancer Center, is the lead researcher on the project. "My lab studies the harsh, nutrient-deprived microenvironment of pancreatic cancer to exploit metabolic vulnerabilities," he said. "By specifically targeting these hypoxic pathways in a multifaceted approach, we can shut down tumor progression. I see our work with Genisphere leading us down a path to the clinic, and commercial development of a lead candidate for the treatment of pancreatic cancer."

Harbour BioMed and PPD team up

Harbour BioMed (HBM), a global clinical-stage biopharmaceutical company, and the CRO PPD have entered into a strategic collaboration to develop HBM's therapeutics in the fields of oncology and immunology.

The selection of PPD as a preferred CRO partner enables HBM, which has operations in the U.S., the European Union, and China, to conduct global clinical studies on its in-research pipeline. HBM's portfolio includes five clinical-stage, in-licensed compounds and drugs generated by its internal discovery efforts, as well as co-discovery/development collaborations with academic institutions and biopharmaceutical companies.

Jazz Pharmaceuticals acquires Cavion

Jazz Pharmaceuticals Inc. announced the acquisition of Cavion Inc. last month through a merger with a Jazz subsidiary. Under the terms of the agreement, the former Cavion shareholders receive an upfront payment of $52.5 million and have the potential to receive additional payments of up to $260 million upon the achievement of certain clinical, regulatory, and commercial milestones.

Cavion, a clinical-stage biotech and now a wholly-owned subsidiary of Jazz, creates therapies aimed at modulating the T-type calcium channel for the treatment of chronic and rare neurological diseases.

Pact focused on mRNA-based drugs

Biopharma company CureVac AG has struck a collaborative research agreement with Yale University for discovery research into mRNA-based pulmonary therapeutic candidates. Under terms of the deal, the Yale University team will perform discovery research on targets related to pulmonary diseases and present therapeutic candidates to CureVac for preclinical and subsequent clinical development. CureVac will provide all funding for the discovery research and retains the option to acquire any rights regarding the candidates.

— Wire reports

11% of sites fail to enrol a single patient*

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*Research from Tufts CSSD Jan 2013

CLINICAL TRIAL INSIGHTS

PROLIFERATION OF RARE DISEASE R&D NECESSITATING NOVEL STRATEGIES

Interest in benchmark data on the scope, performance, and economics of these efforts has grown

Ken Getz

Nearly every week, the Tufts Center for the Study of Drug Development (Tufts CSDD) receives a request for benchmark data on rare disease drug development performance and economics. These benchmarks have been hard to come by, as a large percentage of companies active in this space are privately held. Sponsor companies and contract research organizations (CROs) have been looking for this benchmark data to guide portfolio and development project planning and optimization. Tufts CSDD has compiled some useful benchmarks.

At the present time, rare disease drug development is one of the most active and fastest growing areas in drug R&D. Rare diseases are defined as medical conditions that affect 200,000 or fewer people in the U.S. or fewer than five people per 10,000 population in the European Union. In 2018, approximately one-third (31%) of all products in the global R&D pipeline targeted treatments for rare disease indications. This is up from 15% only 10 years ago. And nearly six-out-of-10 (58%) drug and biologic approvals in 2018 were for rare diseases; up from 26% in 2008.

Biopharmaceutical companies have substantially increased R&D investment in rare diseases, not only to meet unmet medical needs, but also to support development programs at lower relative cost, with fewer competitors, strong demand from patient advocates, and greater opportunities for favorable pricing. This latter expectation in particular appears aspirational given current public perceptions and the political climate.

As more data is gathered characterizing the scope, performance, and economics of rare disease drug development, the opportunity for pharmaceutical and biotechnology companies appears more nuanced.

(MEANS PER CLINICAL TRIAL)	NO. OF SITES	NO. OF PATIENTS	PATIENTS PER SITE
Phase I Rare Diseases	6	31	5
Phase I Non-Rare Diseases	1	20	20
Phase II Rare Diseases	14	107	8
Phase II Non-Rare Diseases	27	268	10
Phase III Rare Diseases	42	524	13
Phase III Non-Rare Diseases	65	3,434	62

Source: Tufts CSDD

Table 1. Comparing the average enrollment for rare and non-rare disease clinical trials during the 2014 to 2018 time period.

Recent Tufts CSDD research suggests that rare disease drug development presents scientific and operational challenges that will necessitate—and perhaps accelerate—the adoption of novel and less traditional clinical development strategies, operating practices, and solutions. Consider a few key findings:

- The average direct cost to conduct a Phase III pivotal trial of an investigational rare disease treatment is approximately half that of investigational treatments for non-rare diseases ($103 million vs. $193 million).
- Although clinical trials for rare disease drugs recruit fewer patients, clinical phase through approval durations for rare disease drug development take, on average, four years longer than those for non-rare diseases due to site and patient recruitment and retention challenges.

What follows are benchmarks that Tufts CSDD—and others—have been compiling. We analyzed data on 4,562 clinical trials for all rare disease medicines in active FDA-regulated clinical trials worldwide between 2014 and 2018. This data was gathered from the www.clinicaltrials.gov website. Data on the economics of rare disease drug development comes from EvaluatePharma. The author thanks Beth Harper (Clinical Performance Partners) for her input and assistance on analyzing rare disease clinical trial recruitment and retention rates.

Clinical trial challenges and their Impact

Sponsor-company investment in R&D for rare diseases has seen substantial growth in global, FDA-regulated Phase I-III clinical trial activity. In total, between 2014 and 2018, there have been more than 4,000 FDA-regulated clinical trials initiated worldwide for rare disease treatments. In 2018 alone, there were 372 new Phase I clinical trial starts; 422 new Phase II clinical trial starts; and 148 new Phase III clinical trial starts.

The vast majority (84%) of active studies on rare diseases are currently in early-stage clinical development. But sustained long-term pharmaceutical company investment in rare diseases is driving up the volume of later-stage clinical trial activity. New clinical trials initiated for Phase II and III clinical trials are increasing at three times the rate as those for Phase I trials (12% vs. 4%).

Pharmaceutical companies and CROs have noted the unprecedented challenges they face in finding clinical research professionals with expertise and experience in specific rare diseases and in identifying and enrolling patients who are managing and living with specific rare diseases. To address these challenges, sponsors and CROs have typically engaged a much larger relative number of clinical investigators in early-stage clinical trials to each enroll a smaller number of patients. To put this into perspective and characterize the magnitude of this challenge during the 2014 – 2018 timeframe (see table above):

CLINICAL TRIAL INSIGHTS

- For Phase I clinical trials of rare diseases, sponsors and CROs engaged, on average, six times the number of investigative sites to recruit one quarter of the number of patients per study, compared with those for non-rare diseases.
- For Phase II and III clinical trials of rare diseases, sponsors and CROs engaged half to 60% of the average total number of investigative sites, respectively, to enroll as few as 15% of the total average number of study volunteers per trial.

The challenges associated with rare disease patient recruitment and retention are even clearer in the substantially higher observed screen and randomization failure rates relative to those rates for non-rare diseases. Eight-out-of-10 (81%) patients screened for clinical trials for rare diseases are not eligible to enroll, compared to 57% screen failure rates for non-rare diseases (all therapeutic areas). More than half (56%) of rare disease study volunteers fail to be randomized, compared to 36% randomization failure rates for non-rare diseases.

But once rare disease patients have enrolled in a clinical trial, they're far less likely to drop out. The premature termination rate—associated with all causes—of rare disease patients randomized for clinical trials is 14%, compared to 21% for those in non-rare disease clinical trials.

Drug development and approval durations

Major difficulties finding and engaging investigative sites and identifying and enrolling study volunteers in rare disease clinical trials adds considerable time and delays recouping development investment. Overall development durations (i.e., IND filing to regulatory decision) for rare disease applications are four years longer than for all other disease segments.

Between 2014 and 2018, clinical durations—overall Phase I-III cycle time—for rare disease investigational drugs took 131 months, on average. This was 68% longer than the average 78 months for all non-rare diseases. Rare disease clinical durations are longer in every therapeutic class observed during the 2014-2018 period: for example, they were 41% longer for all cancer-related diseases; 79% longer for all endocrine diseases; and 64% longer for CNS diseases.

Given unmet medical need, regulatory review durations are four months faster, on average, for rare disease drug applications, compared to review time for non-rare diseases across all therapeutic areas. Submission to approval decisions for rare disease drug applications are 47% faster in CNS diseases; 30% faster in endocrine diseases; and 10% in cancer-related illnesses.

> Analysts and observers anticipate that sponsor company reliance on data and sophisticated analytics to identify rare disease-focused investigators and eligible patients will intensify.

Responding to a new risk-return profile

The high proportion of rare diseases in R&D and the growing number achieving commercialization will necessitate the adoption of new clinical development models to accelerate timelines and drive greater efficiency. Very small relative markets and long relative development durations challenge the traditional risk-return profile for new drug therapies.

Worldwide, in 2018 an estimated 3,500 small and large molecules targeting rare diseases were active in R&D. This is more than double the level observed 10 years ago. And during the past 25 years, there has been a six-fold increase in the number of orphan designations granted by the FDA—growing from 301 designations in the four-year timeframe between 1994 to 1998 to 1,800 designations in the 2014 to 2018 period. As the volume of designations has increased, so too has the absolute number of approvals: The total number of orphan drug approvals increased from 84 in the 1994 to 1998 timeframe to 316 in the 2014 to 2018 period.

Analysts and observers anticipate that sponsor company reliance on data and sophisticated analytics to identify rare disease-focused investigators and eligible patients will intensify. The adoption of patient-centric approaches is also expected to accelerate. Sponsors and CROs will increasingly look to virtual (direct-to-patient) and hybrid (investigative site with intermittent direct-to-patient) models and convenience-enhancing approaches (e.g., home nursing, telemedicine, wearable and mobile devices, and patient assistance programs) to bring clinical trials to wherever it is easiest and the most efficient for study volunteers to participate. Observers and analysts also expect sponsor and CRO demand for clinical trials embedded within clinical care settings to increase, as will demand for real-world data and evidence to supplement, and even replace, traditional clinical research data.

And at Tufts CSDD, we can expect a growing number of inquiries into baseline and benchmark data on the impact of these approaches on rare disease drug development performance and economics.

— Ken Getz, MBA, is the Director of Sponsored Research at the Tufts CSDD and Chairman of CISCRP, both based in Boston, MA. email: kenneth.getz@tufts.edu

The VA Gets Real on Reform

Sony Salzman

After years of siloed focus—and slow study start-ups—the U.S. Veterans Affairs agency embarks on implementing its multi-year initiative to bolster clinical research

STUDY START-UP

The U.S. Department of Veterans Affairs (VA) has a long history of pioneering clinical research, including first definitive tuberculosis trials in the 1940s, and subsequent studies that led to the first CT scan and implantable pacemaker.

In theory, life science companies should be clamoring to partner with the VA on clinical research. The agency was an early adopter of a unified electronic record system, and its patients are motivated, ethnically diverse former service members—ideal study candidates.

But in recent decades, the VA's research efforts have remained inwardly focused, with the agency's strict rules and protocols making it difficult to partner with the private sector. Today, the VA's study start-up time is 120 days longer than the industry average, according to two independently verified analysis by contract research organizations (CROs), meaning the VA is overlooked in favor of more nimble academic research centers.

Now, however, VA is committed to reform. Rachel Ramoni, DMD, ScD, who joined the VA as chief research and development officer in 2017, has made it her mission to cut study start-up times—much to the delight of advocacy groups like the National Association of Veterans Research and Education Foundation (NAVREF) and the Coalition to Heal Invisible Wounds.

According to Rick Starrs, CEO of NAVREF, VA leadership is committed to change because "they agree with us—that they're missing out on opportunities by being slow."

Reform at the VA will require massive cooperation among the VA's 170 medical centers, 1,000+ affiliated community medical center, and 80 affiliated non-profit organizations.

"There are certain things sponsors want: they want you to be quick, they want you to do a really good job, and they want you to be predictable," says Robin Rusconi, executive director of the Midwest Veterans Biomedical Research Foundation, one of the VA's affiliated nonprofits.

In 2019, NAVREF and the Coalition to Heal Invisible Wounds wrote a letter to Congress that encouraged the VA to cut its start-up time by 100 days. Ramoni signed on to this goal, essentially pairing the VA's existing "Access to Clinical Trials for Veterans (ACT)" initiative with the advocacy groups "100 Days Faster" initiative, pledging to achieve this milestone by 2021.

For the past year, Ramoni and other VA officials have been listening to feedback from would-be pharma industry partners, and one of the most consistent complaints they receive is that it's not clear which department at the VA is responsible for clinical research.

"I know some companies have said, 'well, we just don't know how to begin,'" says Allyson Gage, PhD, chief medical officer of Cohen Veterans Biosciences, a non-profit member of the Coalition to Heal Invisible Wounds. There is no "simple, centralized way of approaching the VA to learn about how to start a clinical trial," she says.

According to Grant Huang, PhD, director of the cooperative studies program within VA's Office of Research and Development (ORD), creating a single point of contact ties in with the VA's other efforts to centralize key pieces of VA clinical research.

Rachel Ramoni

In fact, "centralization" is the core theme of the VA's current efforts to become a more attractive clinical research partner to private industry. Now, Ramoni and her colleagues are focusing their efforts on centralizing three main pieces of the VA's clinical research infrastructure: the institutional review board (IRB) review processes, IT and privacy procedures, and maintaining a single point of contact for industry partners.

"The first year was about planning," says Ramoni. "We're now in year two, which is implementation."

Tackling the IRB problem

The VA's first and most pressing hold-up includes an official VA policy that prohibits working with commercial IRBs—including IRBs that have been vetted by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

"The VA wants to build capacity with [the Office of Research Development] that allows for an enterprise approach," says Roger P. Murry, senior policy, Akin Gump

Strauss Hauer & Feld, the largest lobbying firm in the U.S. "Commercial IRBs are staffed by professionals who do IRBs all day, so let's inject that expertise into the VA."

According to Ramoni, changing the VA's official policy isn't the real barrier to working with commercial IRBs. Rather, it's ensuring that those IRBs meet the level of data security and protection that's required for government health data.

Now, for the first time, the VA is exploring partnerships with commercial IRBs. "We are currently pursuing a memorandum of agreement with two major commercial IRBs to be able to rely on them," says Ramoni, noting the memoranda are not finalized yet, pending review of the VA's information security office.

Another important initiative is to standardize the VA's internal IRB processes through a central IRB. Local VA IRBs meet periodically, so missing a meeting creates major delays.

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Efforts are underway to speed up clinical trial start-up times at U.S. Department of Veterans Affairs clinics across the country.

"It's sort of like missing a prerequisite in college," says Rusconi. "If you miss that first meeting, you have to wait until you can get back into that loop. It can create that slowness and unpredictability in the system."

Currently, the VA has "very, very different IRB reviews as you go across the country, each having vastly different review times," adds Rusconi. "We need to figure out the best way to standardize the timing and the nature of IRB reviews."

According to Huang, the VA is in the midst of transitioning to a more robust, central IRB approach for clinical research.

Streamlined technology review and non-disclosure agreements

From the outside, the VA appears to be a monolith. But internally, each site operates in a decentralized silo, each with its own procedures, policies, and preferences. Now, the VA is working to create a centralized approach for two specific aspects of clinical research: IT review and non-disclosure agreements.

All clinical trials require some form of IT setup, including electronic data capture (EDC) systems. At a typical academic medical center, implementing those systems is a "simple review process," says Gage.

That's not the case at the VA, however, where each site "has its own security officer, and that person might not be up to date on the types of digital data capture available," says Gage, adding that different sites might sign off on different IT systems, creating unpredictability for sponsors.

In an ideal world, the VA would have a centralized information security analysis to allow for more thorough and consistent reviews of clinical trials to come on board. Now, efforts to streamline the IT security review process are underway.

"We've already seen implemented progress through a new team in the office of IT that is helping reduce delays and inconsistencies related to information security reviews," says Murry. The VA has hired about a dozen full-time staff members to develop that expertise. "It's a great example of leadership developing new expertise," adds Murry.

Meanwhile, Huang is spearheading a movement to create a unified non-disclosure agreement. Previously, "for non-disclosure agreements, you would have to go to each medical center," he say. "Now, we have a central authority for non-disclosure agreements."

> The VA is working to create a centralized approach for two specific aspects of clinical research: information technology (IT) review and non-disclosure agreements.

Ultimately, Ramoni believes that bringing industry-backed clinical research to the VA is the right thing to do for the agency as a whole, and for the health of the veterans.

"Clinical trials are a key part of the national healthcare and research landscape," adds Starrs, himself a veteran. "They offer opportunities for patients to get cutting-edge therapies. There's the opportunity with the veteran's system—with nine million veterans patients it in, and a great electronic health record—to be able to partner with industry to do some novel and groundbreaking type things that other systems couldn't or wouldn't do."

Sony Salzman *is a freelance journalist who specializes in health and medical innovation. She can be reached at sonysalz@gmail.com.*

Retention Strategies for Keeping Participants Engaged

A case study of the Parkinson's Progression Markers Initiative

EYE ON PATIENT ADVOCACY

The Michael J. Fox Foundation Recruitment and Retention Team

The Michael J. Fox Foundation for Parkinson's Research (MJFF) aims to speed clinical research by removing obstacles that stand in the way of drug development. In pursuit of this mission, the Foundation gathers insights from a wide range of stakeholders and uses these perspectives to enhance clinical trial processes from start to finish. In *Applied Clinical Trials*' Eye on Patient Advocacy series, we will share best practices and lessons learned from the field of Parkinson's research that can be applied to clinical trials across disease states. In our fourth column in this series, we explore retention strategies used in a landmark longitudinal Parkinson's disease (PD) study.

To complete a study, it is critical to retain study participants. Participant attrition has the potential to interfere with the scientific validity of a study and distort data designed to measure drug efficacy and safety. According to Forte Research:[1]

- Eighty-five percent of clinical trials fail to retain enough participants.
- The average dropout rate across all clinical trials is 30 percent.

Patient retention is an important element of the Parkinson's Progression Markers Initiative (PPMI), a landmark, longitudinal, observational study sponsored by The Michael J. Fox Foundation. PPMI (ppmi-info.org) aims to find reliable and consistent biomarkers for PD progression by studying cohorts of Parkinson's patients (de novo idiopathic PD and PD-manifesting genetic mutation carriers), populations at risk for PD (non-manifesting genetic mutation carriers and subjects at risk due to REM sleep behavior disorder or hyposmia), and controls without PD.

Participants in PPMI commit to long-term participation, providing biospecimens (e.g., blood, urine, spinal fluid), and undergoing multiple neuroimaging, clinical and behavioral procedures, and assessments over a period of at least five years.

The study launched in 2010, and since then, approximately 1,500 individuals have enrolled. PPMI's retention rate has consistently held strong, year after year, at about 86%.

To ensure steady participation and to prevent attrition, PPMI weaves together four key tenets of retention, cultivated and refined since study launch: 1) facilitate participation; 2) communicate study progress; 3) express appreciation; and 4) inform participants of study results.

Facilitate participation through travel concierge services, reimbursement, and remote visits. PPMI study leadership prioritized and simplified long-term participation in large part because individuals carrying specific PD-linked genetic mutations live across a wide geographical area. To facilitate volunteers' continued participation, PPMI cultivated a boutique experience for them and their care partners. Prospective and enrolled PPMI participants are given the option for complimentary roundtrip transportation between their home and appointments at two "super sites" that have the capacity to handle a high volume of study volunteers.

> Participant attrition has the potential to interfere with the scientific validity of a study and distort data designed to measure drug efficacy and safety.

A third-party vendor manages all logistical planning, including participants' accommodations, meals, and travel to and from study visits. This door-to-door service reflects the value PPMI study leadership puts on participation and participants. For participants who choose not to travel to a super site, travel and hotel expenses are reimbursed through Greenphire/ClinCard. PPMI leadership is always looking for ways to reduce participant burden and is currently exploring the possibility of remote (video and enhanced phone) and home visits.

Communicate study progress through newsletters, update calls, and a centralized webpage. Reminding participants of the bigger picture is a meaningful way to engage them in the collective success of a study. According to a 2017 report by The Center for Information and Study on Clinical Research Participation,[2] the number one reason individuals choose to participate in clinical research is to help advance science or the treatment of a disease or condition. Given this initial motivation, updates on study progress and contributions to the field will facilitate continued engagement. In PPMI, study progress is communicated in several ways:

- PPMI newsletters provide high-level updates on the study (e.g., study enrollment progress, how the data and samples collected are being used for research) as well as interviews or profiles of study participants and/or study staff.
- PPMI update calls, which are scheduled throughout the year, feature presentations and Q&A sessions with study researchers and study team members.
- A PPMI participant webpage allows centralized access to digital versions of the participant newsletters and recordings of study update calls.
- PPMI blog provides regular news about the study, including recent findings that have emerged from the data.

Express appreciation through a thank-you booklet. Letters from members of the Parkinson's community, researchers, MJFF staff, statisticians, and study coordinators were published in a print and digital booklet to thank and honor volunteers for their participation. Collecting the personal reflections of the many individuals involved in or impacted by PPMI is a meaningful way to empower participants and remind them of the larger cause they are tied to.

Inform participants of study results through newsletters, update calls, and a webpage. The majority of study volunteers (90%) want to receive results from the clinical trial in which they participated.[3] Because there is ongoing analysis of PPMI data and continued follow up of participants, study results are shared on a rolling basis. Using familiar channels to communicate study progress is a great way to close the loop with study participants.

Putting it all together: Host an event

PPMI staff and study leadership also show their commitment to the study's success, and their appreciation for participants, by hosting annual study update luncheons and dinners that incorporate all the tenets of retention. Having an in-person get together gives participants the chance to meet other volunteers and share experiences of living with PD and taking part in PPMI. During these events, local site staff present study progress and provide relevant results from ongoing data analysis. Michael J. Fox Foundation staff also attend and, together, all study stakeholders thank participants for their time and commitment.

Using familiar channels to communicate study progress is a great way to close the loop with study participants.

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

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Creating Medicines 'Appropriate for All'

Bristol-Myers Squibb's cardiovascular development leader discusses the importance of diversifying clinical trials for better patient outcomes

By Christen Harm

EXECUTIVE PROFILE

Charlotte Jones-Burton, MD, today executive director and the cardiovascular development team lead, innovative medicines, at Bristol-Myers Squibb, grew up in a small rural town in Arkansas. Her family was one of many in the community of 18,000 living beneath the poverty line—and one of many impacted by serious disease, in particular diabetes, heart disease, and kidney disease. Through it all, however, Jones-Burton's mother taught her to dream big and think big. Jones-Burton became a physician, graduating from the University of Maryland (UMD) School of Medicine with an MD in Medicine, and later earning a Master of Science in Epidemiology and Preventive Medicine.

Following school, while serving as an assistant professor at UMD Medical Center, Jones-Burton was awarded a competitive training grant from the National Institutes of Health that provided her the opportunity to explore clinical research. During this time, she was drawn to the pharmaceutical industry, and in particular, the rigorous clinical research taking place to develop medicines for patients worldwide.

Presently, Jones-Burton leads Bristol-Myers Squibb's cardiovascular development team, where she's overseeing the launch of numerous clinical trials for cardiovascular disease (CVD). As the leader of a team that's working from discovery to commercialization, Jones-Burton thinks critically about the discovery process, making sure the strategy that's been outlined is efficiently and accurately executed, in order to deliver effective results to patients.

According to Jones-Burton, the best part of being involved in clinical trials, professionally, is that she can continue exercising that drive to think big, ask questions, and find answers. "That's essentially what we do with clinical trials—we identify areas where there is an unmet medical need, we ask questions, and we seek to then answer those questions through a clinical trial," she says.

Cardiovascular R&D

According to the World Health Organization (WHO), CVD is the number one cause of death globally. In 2016, an estimated 17.9 million people died from CVD, accounting for 31% of all deaths worldwide. Given these numbers, BMS focuses on developing novel medicines for CVD patients in need, especially those in underrepresented communities. Jones-Burton currently oversees BMS's clinical program for Eliquis (an anticoagulant treatment to prevent stroke in people with atrial fibrillation), which will soon include a pediatric clinical trial. "I'm most excited about the opportunity to work on the pediatric program, because there is no direct oral anticoagulant that has been approved for children who are at risk for venous thromboembolism, or who have venous thromboembolism," Jones-Burton says.

Jones-Burton is also leading a collaboration BMS has with Janssen, around another antithrombotic treatment, a factor XIa inhibitor that is currently in Phase II clinical trials and will be tested across four different indications in studies that will happen almost simultaneously. The goal of the program is to improve standard of care by reducing the risk of thromboembolic events, without increasing the risk of bleeding in patients who have cardiovascular thromboembolic diseases such as stroke or coronary heart disease

Challenges around cardiovascular trials

Jones-Burton argues that a false optimism exists around CVD. "There is this belief that cardiovascular disease is no longer a public health problem, when, in fact, it remains the number one killer of people worldwide." She says the biggest issue around CVD trials is the notion that conditions in this area are addressed adequately by current treatments and are no longer of significant concern, which limits funding for research.

"I think it's important to recognize that there is still an unmet medical need within cardiovascular research," she stresses.

Another issue plaguing CVD clinical research, according to Jones-Burton, is a lack of innovation where unlike in oncology, for example, trials tend to be much larger and less flexible and adaptable to design changes or new approaches. She says to better realize the promise of future CVD drug development, the industry needs to think through innovative ways to restructure CVD trials. Jones-

Burton points to increasing diversity in trials as one possible solution, where results can potentially be generalized to all patients. For CVD, doing so may help accelerate the traditionally longer time frames it takes to advance medicines in this space and bring them to the patients that need them in a quicker, more efficient manner. As the industry continues to grapple with these problems, Jones-Burton says, "as long as we continue to not just speak about how we can improve, but take actions and remain committed, we'll find ourselves in a much better space."

However, as an optimist and a problem solver, Jones-Burton believes that while issues might still plague the CVD disease space, change is being made on a macro level, which is translating to the pharmaceutical industry as well. "We're becoming even more hyper-focused on the patient," she says. "This vigilant examination of patients will, in turn, drive a lot of the innovation and speed at which the industry moves."

Jones-Burton points to the advances that have been made in technology and big data as an example of this promising future. "We're in this era where we have so much data at our fingertips that we can finally begin to start problem solving what's in front of us," she says. Jones-Burton believes that as long as the industry continues to focus and hone in on making strides in CVD, headway will continue to be made for patients in need.

Trial design and diversity

As populations globalize, the ability to diversify clinical trials is becoming increasingly crucial in influencing patient outcomes. This is especially important for communities with economic and medical needs, who most often, are the populations Jones-Burton's research is aiming to better help.

According to the Centers for Disease Control and Prevention, nearly half of African Americans have some form of heart disease (48% women, 44% men); the most common conditions that increase the risk of CVD in these groups include diabetes, high blood pressure, and obesity.

To that end, the physician and researcher in Jones-Burton believes that the industry, and its workforce, should prioritize diversity in all aspects of R&D, from trial design to execution. This prioritization of diversity will present "a complete understanding of how patients of all kinds respond to investigational therapies," and, thus, potentially having a wider impact on patients and, ultimately, communities.

Jones-Burton points out that when looking at the magnitude of patients that have CVD, it is crucial that the industry is more inclusive of women and diverse groups. This, she contends, "will help us create medicines that will be appropriate and applicable for all." Jones-Burton believes that if the industry diversifies its workforce, trials will include better insights to inform the science and the business, creating improved patient outcomes.

For Jones-Burton, diversifying new voices in clinical trial design and implementation is all about "leading the development of innovative medicines to help all people," regardless of community. To achieve this, she says, the industry must seek a diverse workforce, as well as recruit diverse patient populations to enroll in clinical trials. "It begins early in the process, ensuring that we have a diverse group of basic scientists, biologists, and chemists who are doing the discovery, as well as clinical researchers and key opinion leaders informing the research."

Charlotte Jones-Burton, executive director, cardiovascular development team lead, innovative medicines, Bristol-Myers Squibb, oversees the launch of numerous trials for CVD.

In her role, Jones-Burton says she practices ensuring diversity on a daily basis. "Diversity on my teams is very important," she says. Jones-Burton is strategic in how she puts these teams together, wanting to meld differing and varied geographic, gender, age, racial, and ethnic perspectives. "That comes with an awesome responsibility, because when you have diverse people, you have to ensure that you have an environment of inclusion where they feel that they are included and have the ability to grow in their careers," she says.

Jones-Burton also says that this diversification comes even before somebody knows they want to pursue a career in the life sciences, or even, if they're just thinking about a career in the industry. Jones-Burton leads an initiative at BMS that allows young students of color, from late middle school to early high school, to spend a day shadowing employees in order to envision what a career in the life sciences might look like.

Mentorship and outreach

One area that Jones-Burton feels is an important piece of this diversification mandate is mentorship. "Strategic networks and relationships matter, and it really helps me help other people," she says. Jones-Burton spends time mentoring women and men of all racial and ethnic backgrounds across the globe.

In 2015, Jones-Burton co-founded Women of Color in Pharma (WOCIP), a nonprofit organization that promotes the development and advancement of women of color in the life sciences. With the motto, "Get Inspired. Be Inspired," the group's vision is to transform the industry with women of color—in particular black and Latina women. WOCIP is an outlet to showcase women of color who are excelling in the industry, but also a way of "empowering women to understand what their value is, so they can articulate it, as well as building core competencies for leaders within the industry," says Jones-Burton, who has helped grow the organization to include a worldwide network with chapters launching in the U.S. and EU.

In turn, WOICP has helped Jones-Burton grow as well. She remarks that she "has evolved as a leader, showing up at Bristol-Myers Squibb on a daily basis, understanding what my value is, and being willing to have the courage to offer the insights that I bring to the table as an authentic leader."

The Changing Landscape for Clinical Trial Sites

Cindy H. Dubin

Exploring how clinical research sites are redefining their business models to be more flexible, collaborative, and customized.

SITES

As the complexity of medical science continues to accelerate, so does the complexity of clinical trial research. In his State of the Industry presentation at the annual Association of Clinical Research Professionals (ACRP) meeting earlier this year, Ken Getz, director of sponsored research at the Tufts Center for the Study of Drug Development (CSDD) and chairman of CISCRP, hit attendees with some hard facts about how complex protocols are impacting clinical trial outcomes. Among them:

- There has been an 86% increase in total data endpoints per clinical research trial over the past 10 years.
- Nearly 40% of trials begin under enrolled and 11% of sites fail to enroll a single patient, resulting in those sites operating in the red.
- The cost to develop a successful drug has increased from $802 million in 2003 to $2.6 billion today, yet, the average ROI has continued to decline, hovering around 3%.
- The average time it takes to bring a drug through clinical trials has decreased, but the rate of success has gone down by almost half, to 12%.[1]

Couple all of this with varied site performance, increasing staff workloads, limited access to data analytics, and difficulty finding patients, and the result is a clinical site landscape on the cusp of change. This transformation is most evident in how clinical research sites define their business models to be more flexible, collaborative, customized, and efficient.

Is 100% reliance on a preferred partner sustainable?

One common business model is for a sponsor to work with a preferred provider. In this model, there is an established relationship/rapport between companies. The advantage is working with a known team, known quality, and expected performance.

"The preferred partnership model provides visibility in the pipeline and may bring forth technology assets and dedicated internal people and resources," says Jennifer Byrne, CEO of Javara, an integrated research organization (IRO) based in Winston-Salem, NC. "But where these relationships often fall short is that they are not centered on a deep understanding of the provider/partner's infrastructure. While I have seen that preferred relationships can yield improvement, it's my strong belief that preferred providers have much greater potential to bring about a long-term and transformational partnership vs. a short-term, transactional collaboration."

Joan Chambers, former vice president of marketing and strategy for ClinX affiliated companies, which provides clinical and outsourced business services, agrees. "Preferred providers hold the promise of delivering high levels of performance and efficiencies, but this type of relationship can sometimes come at a high cost," she says.

Additionally, there is concern with high turnover within these organizations that results in disruption and impacts the investigative site staff, and potentially the study. Having preferred providers is important, however, Chambers says having a blend of other providers to work with is equally important. Building multiple relationships with stakeholders in different capacities can prove more beneficial than being 100% reliant on a specific company. As an alternative, sponsors are forming partnerships with clinical networks that can offer access to multiple

companies, accelerated research, faster patient recruitment, and more viable patients.

The next generation of preferred providers

The bespoke model

Offering sponsors a group of provider sites in a single network could be the next generation of preferred provider. According to Mark Lacy, CEO of hyperCORE International, the clinical research industry is fraught with inefficiencies due to a disconnected and fragmented system between sponsors/CROs and research sites. hyperCORE is looking to change that by offering a centralized network. Formed in April of this year, hyperCORE is a network of clinical research sites and network companies that provide Phase I-IV clinical trial services at more than 80 sites worldwide. Each member operates as an independent company but integrates common functions to streamline business and clinical operations by sharing best practices.

"Years ago, the pharma industry didn't look upon networks very kindly because they were loosely set up," says Lacy. "Now, pharma companies and CROs are more interested in going to more organized networks."

hyperCORE's bespoke model allows a customer to contract with one or multiple companies within the network. "One contract saves time and money, but that doesn't mean everyone necessarily wants that kind of partnership," says Lacy. "So, our model allows clients to customize a model that is best for them. We really offer the best of both worlds: a one-stop-shop with many areas of expertise."

"Getting a group of site networks working together to provide a one-stop-shop is an interesting idea," says Jim Kremidas, executive director of ACRP. "From a business model perspective, the value of a site network is more than the value of each individual site. Achieving standardized processes and business activities would create operational efficiencies and better quality data."

Member companies are adept at examining protocols at the point of development to determine what is practical and what is not. As protocols become more difficult, the goal, says Lacy, is to write protocols with fewer endpoints that will require approval. "And that means we can accelerate research, get a drug to market faster, and save money for our clients."

Companies in the hyperCORE network go through an initial vetting process and are then assessed annually in an effort to maintain quality. "Companies will be kicked out if their quality falters," says Lacy. "Metrics are the biggest indication as to whether they are collecting good data and enrolling high quality patients."

The IRO model

High quality data and faster patient recruitment are also at the heart of the Javara's IRO model. It's a patient-centric approach that ensures clinical trials are readily accessible as part of the care delivered by health organizations and academic medical systems, while improving the clinical trials experience for all stakeholders.

"Our IRO model is expanding the value proposition of clinical research and brings forth a more efficient and reliable model for pharma and CROs that, together with our health system partners, delivers on patient accrual and data quality," says Byrne. "At the same time, we are intentional about improving outcomes for patients."

The IRO uses data analytics to align clinical trials with the patient population within a healthcare organization to better serve the needs of those patients. While larger populations are a target, Javara and the healthcare organization also pursue any therapeutic/disease category that fits unmet medical needs for smaller populations. By aligning clinical trials—matching patient to trial—with the unmet patient needs, clinical trials can help to decrease costs to healthcare organizations, enhance health outcomes for patients, and increase engagement of patients in their own healthcare management. The IRO embeds so-called clinical trial navigators (CTNs) within the day-to-day workflow of a healthcare organization to work alongside providers and patients (both in-person and remotely) to increase participation in clinical trials.

"Our greatest value proposition to the healthcare system is that we are bringing the best of the best trials to patients," says Byrne. "Sometimes we are talking about millions of patients; understanding their unmet medical needs, and looking across the drug development pipeline to match the patients to companies researching cutting-edge treatments."

"Sponsors want to get closer to patients and create more high performing sites," says Kremidas. "Integrating clinical care—working with healthcare institutions—and offering clinical research as a therapy option will bring access to more patients."

In the year since its launch, Javara has forged partnerships to offer that access. One is a research relationship with Wake Forest Baptist Medical Center to provide integrated research models within specific sectors of the complex health system, which includes an academic medical center, a health network, community-based physicians, a medical school, and five community hospitals. Additionally, a relationship between Javara and a practice management organization in the Houston metro area has Javara building a research infrastructure in the region to match thousands of potential clinical trial patients to hundreds of providers within one electronic health record (EHR).

Bringing the right patient to the right trial with the right provider at the right time is the North Star, says Byrne. Slightly more than two million patients participate in clinical trials. While this may seem like more than enough patient volunteers to meet the needs of existing clinical studies, an estimated 58 million patient volunteers are actually needed. "I believe that low trial participation is a public health issue," says Byrne. "Working with healthcare partners highly committed to clinical trial access for their patient population is success for us."

According to Kremidas, one of the biggest bottlenecks, even with good performing sites, is access to patients. "The hyperCORE and Javara models will offer better access to patients, a more streamlined operational business model, and improved efficiency and effectiveness," he says. "This will produce better quality data and help trials be done more quickly. That, in turn, leads to new therapies for patients, which is the ultimate goal."

Turning physician clinics into trial sites

Helping healthcare practices bring therapies to patients is the goal at Elligo Health Research. This healthcare-enabling research organization provides technology, infrastructure, processes, and study coordinators to specialty physician practices. In turn, physicians can offer clinical trials to patients. "The patients are participating in clinical trials with their trusted physician at a location they are used to visiting," explains John Potthoff, PhD, CEO of Elligo.

Elligo creates partnerships with its physician clients, such as Austin Area Obstetrics, Gynecology and Fertility, which was interested in offering an oral alternative to surgery for treating endometriosis. The physicians had tried to conduct clinical studies, but found it challenging to balance their regular patients with the added commitment of leading a study at a standalone research center. Additionally, patients were reluctant to travel consistently to an unfamiliar location.

Ultimately, Austin Area Obstetrics, Gynecology and Fertility chose to work with Elligo to conduct a Phase II double-blind trial of the oral endometriosis treatment. Elligo study managers joined the full-time physician staff and handled all aspects of clinical trial management. And, using the clinic's EHRs, the Elligo staff identified patients that would benefit from participating in the endometriosis trial.

"We embed into their practices so it's a seamless integration," says Potthoff. "We follow their processes and procedures and adapt our infrastructure to the way they practice medicine. We do a custom implementation that allows us to work alongside and enable them to provide clinical research as a treatment option for their patients."

Eight months after trial commencement, Austin Area Obstetrics, Gynecology and Fertility became the highest screening and enrolling site on this study in the U.S., says Potthoff. Coming off the success of the endometriosis study, the practice added three trials in its office.

For it and other clinics with whom Elligo partners, Potthoff says the benefit of Elligo is giving its partners more access to resources than any one individual practice may have to do a clinical trial. Elligo brings the research into the clinic, including staffing, technology, basic infrastructure, and supplies, without the physicians needing to invest their own clinic's dollars into the research program. Potthoff says that is typically the number one deterrent against physicians conducting their own research within their clinics.

"Many don't have the capital or bandwidth to put together the infrastructure to participate in clinical trials," he says. "Partnering with Elligo allows them to be focused on healthcare and clinical delivery of services to patients. It's a low-risk opportunity for them."

A framework for staff and workflow process standardization

The pharma industry does recognize that the performance quality of sites varies dramatically. Kremidas believes the root cause of this variance is a lack of consistency in how staff—including principal investigators (PIs) and study coordinators—at investigator sites are screened, hired, trained, and validated for their competency.

"This is a major problem in the industry right now," he says. "Many of these people are dropped into their positions and are expected to learn on the job. Site performance comes down to people and if the wrong people are in the job, the site will not perform well." Kremidas says it's critical that the industry comes together and determines what it wants in terms of staffing, hiring qualifications, training, career development, and validation that site staff is indeed performing well.

In an effort to establish consensus on these topics, ACRP created a multi-stakeholder Workforce Innovation Steering Committee (WISC), which includes sponsors, CROs, site networks, academic sites, regulatory folks, and technology vendors. Together, they developed a Core Competency Framework (based on the work of the Multi-Regional Clinical Trials Joint Task Force out of Harvard and Bringham Women's Hospital) that defines every role at investigator sites. The committee has also created hiring guidelines for study coordinators that provide a framework for defining various competency levels for those executing protocols.

Both Javara and most of hyperCORE's members are using the ACRP Core Competency Framework. "We utilize the core competencies as part of our performance evaluation process and incorporated some of the key areas of job responsibility related to the clinical trial navigator job description, which we use when assessing and interviewing potential new CTNs," says Susan Donahue, director of operations for Javara. "The benefits to Javara is a workforce that is being molded and trained with uniformity and aligns with industry-wide competencies and proficiencies." She adds that the ACRP Core Competency Framework provides a foundation, but Javara has created a highly bespoke training experience specific to its team that focuses on customer service training to elevate the patient, healthcare provider (investigator), and pharma/CRO client experience.

Like site networks, academic research institutions have evolved. This has placed demands on the academic clinical research workforce, as people are being asked to take on increasingly diverse and sophisticated tasks. As new responsibilities emerged, existing jobs needed to be redefined. This resulted in a work environment that was frustrating, unfair, and inefficient in the eyes of workers and leadership.[2] In response, some academic research sites turned to ACRP's Core Competency Framework to standardize workflow processes, how they staff clinical research studies, and how they define staff roles.

One of these institutions is Duke University School of Medicine. Four years ago, Duke set out to modernize its clinical research landscape. Denise Snyder, associate dean for clinical research in the Duke School of Medicine, says Duke used to have 80 job classifications, and job titles were selected based on salary. "I knew we needed uniformity," she says. "We couldn't define accountability and responsibility without consistent job classifications."

Duke's Workforce Engagement and Resilience group utilized the work of the Joint Task Force for Clinical Trial Competency (JTFCTC) to create a framework for clinical research jobs at Duke. The competencies are used as the foundation to help managers select titles for new positions, and provide professional development and career advancement opportunities. Duke ultimately reduced its job classifications from 80 to 12 based on competencies. Employees have consistent job classifications and responsibilities, as well as a clear path to advancement. The university is projected to save millions in

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"The clinical research profession has been standardized across the institution," says Snyder. "This reduces organizational turbulence and creates opportunities for staff to grow their careers in a transparent, competency-based system."

With its clinical research team's competencies now established, Snyder says the next step is to help the workforce think about clinical research workflow from beginning to end. This requires identifying the touch points that may slow things down and working closely with its IT partners to streamline the workflow. An OnCore clinical research (trial) management system tracks data and helps establish the workflow.

"It is important for academic research sites to strategize, plan, and implement standardized workflows for clinical research programs if they are interested in continuing to conduct and manage clinical research programs or to even enter into clinical research," says Chambers.

Vanderbilt also recognizes the importance of workflow standardization to support project managers, research nurses, and research coordinators. Teams use custom software to automate the workflow, internally audit processes, provide suggestions to leadership based on findings, and identify a central point person accountable for all aspects of study setup and ongoing regulatory oversight. Additionally, new software installations support detailed time tracking and effort reporting, dynamic project management, and the ability to design mobile applications, dashboards, and work queues.

"These new technologies have empowered us to operate more efficiently and gain business insights that would not be possible through an off-the-shelf, standard clinical trial management system," says Bree Burks, senior director, Vanderbilt Coordinating Center, Vanderbilt Institute for Clinical and Translational Research.

Standardizing processes has led to an extended career ladder for Vanderbilt's more experienced research staff. Burks explains that this ladder begins by serving in more of a supportive role where entry level staff are tasked with work from lead research coordinators and nurses based on their current level of knowledge and abilities. When ready, support staff then serve as the independent coordinator for clinical research studies. "We have further identified tiers of studies based on complexity of the work," she says. "Studies are considered basic if they do not require our coordinators to interface with a patient's clinical care team, are considered routine if the study requires the coordinator to partner with the clinical team in order to drive clinical care in a way that is not critical to the patient's treatment plan, and are considered complex if the study requirements are a critical part of the patient's care plan."

Once research coordinators have independently managed a complex study, they have the option to transition into one of five different career tracks: CRNs; business intelligence and informatics; personnel management; auditing, compliance and education; and investigator-initiated trials. "These career tracks allow us to offer more advancement for our staff, and have increased job satisfaction as employees can spend more time focusing on their individual passions and strengths," says Burks.

Data Analytics Empowers Site Selection

"With the accelerated growth in clinical trials activity and stricter laws imposed by the FDA, the data available is getting better," says Ron Ronauro, founder of Incite Advisors. "With better data submitted, it makes sense that people will want to analyze the data and view it comparatively."

That is the service Trial Insights, a digital reporting tool developed by Incite Advisors, provides. The purpose is to simplify data produced through clinical trial, biomarker, and medical diagnostic studies into an intuitive and user-friendly dashboard. Publicly available data is curated nightly from information hubs and customized to fit a researcher or research organization's specific project needs.

"We found a number of database solutions providing clinical trial intelligence, however, they tend to be strongest for the big blockbuster indications and less focused on niche, rare diseases," says Ranauro.

Every night, data is downloaded and scrubbed from seven public domain sources of clinical trial and related information: ClinicalTrials.gov, PubMed, PubChem, Therapeutic Target Database, CMS Open Payments, FDA Bioresearch Monitoring Information Service, and World Cities. At the end of the data processing, summary dashboards are computed, specifically focused on sponsors, drugs, investigators, medical devices, and diagnostics. Users register via the Scientist.com marketplace, where they describe their area of interest. Trial Insights packages a weekly email digest for the requested landscape and provides the user a link to access data.

One of these users is Alira Health, an integrated consulting firm with expertise in advanced wound care that relies on Trial Insights to analyze site performance and new clinical trial trends in the industry based on medical device, pharma, and cell tissue products. "The Trial Insights metrics for each site allows us to pinpoint which key opinion leaders are active in specific treatment modalities," says Mitchell Sanders, chief scientific officer, Alira.

In some cases, sponsors may be required to provide documentation to support their decision to recruit certain sites for a particular drug trial. This documentation can be managed by the sponsor to support audits and justify their site selection criteria, because the software maintains the history of investigators' and, therefore, sites' clinical trial activities and a transcript of their publication activity. Ranauro says the information found on the Trial Insights platform can guide decision-making across the pharmaceutical, biotechnology, and CRO industries, as clinical trial data is a primary information source for competitive intelligence, research planning, and clinical study planning.

Kremidas says that Duke and Vanderbilt are among a handful of academic institutions that are leading the charge in workflow process standardization. "We are trying to help them get the word out about how effective this is so other academic research centers can do the same."

Hybrid studies bring sites into the virtual world

Technology company VirTrial, which focuses on facilitating a hybrid approach to clinical trials by combining in-person and remote visits, is partnering with members of ACRP and the Society for Clinical Research Sites to spread the word about the value of telemedicine—and help VirTrial carve out a niche in clinical research.

"We are collaborating to offer all of their members free training on the VirTrial platform as well as training on telemedicine etiquette," says Amanda Rangel, vice president of business development, VirTrial. "Participating sites will become certified as a virtual trial-capable site and can market themselves as such. Similarly, participating clinicians and site staff can complete the training and become individually certified as virtual-trial capable. Our hope is that we can introduce this slow-paced industry to telemedicine as their first step into the virtual world and eventually get them to add more complex technologies such as wearables."

Rangel acknowledges sponsors have some hesitations adopting telemedicine because there is no standard protocol that would allow patients this flexible option and there is no quantifiable return on investment. "It's a risk-adverse industry," she says. "And when you ask the industry to spend money upfront on patient-centric solutions, they want to know their savings on the back end. We can show well-vetted estimations, but can't show them proven data yet."

What she can show them is how the VirTrial platform works. Rangel explains that VirTrial purchased a platform from virtual care company Synzi, which is used currently at 1,700 hospitals, and customized it for clinical research (Full disclosure: VirTrial CEO Mark Hanley sat on the Synzi board and was already familiar with the platform). The platform has a secure environment for sharing videos, bidirectional text messaging, and emails between sites and patients, whereby patients can ask questions and study teams can send automated reminders to patients to take their study medication. The platform can be used on any device, including patients' personal devices. Best suited for Phase III and IV studies and rare diseases, the goal is to reduce the number of times a patient has to visit a clinic. In fact, VirTrial's vision is to replace about 25-40% of standard clinical trial visits with virtual visits to create hybrid studies.

"Our vision is not to replace sites," says Rangel. "We don't want 100% virtual trials because we know the intrinsic value of having patients develop a relationship with a study coordinator. VirTrial is a tool that helps sites remain sustainable and competitive in this new virtual world."

Clinical research is a competitive business

Staying competitive is crucial in the virtual and real worlds. "Historically, the site enterprise has been a cottage industry, like healthcare in general," says Kremidas. "Today, improved efficiencies are required to manage the site business in an effort to offer a full spectrum of offerings."

Burks agrees: "Recent changes within the healthcare market have forced academic medical centers to manage their clinical research portfolio like a self-sustaining business. Although discovery has been a long-time part of our mission, only recently have we had to identify the true cost of discovery and proactively plan for and manage it independently."

She adds that tighter budgets gave way to consolidation and centralization, with the challenge of continuing to foster unique clinical expertise where necessary. "Not everything is a 'widget' that can be easily managed centrally across our medical centers to increase efficiency and drive down costs," says Burks. "However, many administrative functions (such as financial planning and management, regulatory support, data abstraction, and informatics support) can be effectively standardized."

Currently, Vanderbilt offers an array of options for its clinical research investigators. The Vanderbilt Coordinating Center provides support to investigators for all levels of clinical and translational projects. Its fee-for-service model means investigators only pay for the resources required to support their study. "This provides flexibility in that investigators do not have to pay for full-time staff to support a new study unless full-time effort is required," says Burks. "This flexible model also allows well-funded investigators the opportunity to build up and manage their own coordinator (or team of research coordinators) that can provide dedicated support for their specialized area."

Overall, Burks believes that the changes made at Vanderbilt have allowed the academic research institution to remain competitive with smaller, private clinical research sites. "This enables patients to be treated in a clinical trial with the support and active involvement of their physician and multidisciplinary healthcare team," she says. "Although we previously struggled with providing competitive turnaround times and consistency in communication and staff, we are dedicated to the mission of research and innovation. We recognize we have a unique ability to leverage our rare expertise in an effort to continue to provide our patients with unmatched treatment options."

Snyder also believes there is always more work to be done. "We've come a long way, but we have a long way to go," she says. "For instance, we still need to think about site quality. We have the right people, the right systems, and better processes but we have to continue to chip away at all these things to improve the quality of the research coming out of Duke's School of Medicine. We want to attract sponsors. It takes a cultural shift to accomplish quality research. And if we deliver more quality, not quantity, then we will change care because clinical research changes care."

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***Cindy H. Dubin**, Contributor, Applied Clinical Trials*

Improving Information Exchange in Clinical Trials

Jason Methia

Executives from across the clinical research enterprise converge to discuss the steps—and technology—needed to strengthen industrywide data sharing.

DATA SHARING

Seamless information exchange remains a challenge in clinical trials. Trial times are getting longer, product development costs are rising, and getting treatments to patients is harder.

Former FDA Commissioner Scott Gottlieb emphasized the importance of life sciences and clinical research companies modernizing clinical studies by focusing on greater collaboration and data sharing.

The industry is also making this issue a priority, according to the *Veeva 2019 Unified Clinical Operations Survey*, which surveyed nearly 500 clinical operations professionals from around the globe. Industrywide, clinical leaders report the need to improve information exchange among study partners to reduce manual processes (71%), improve collaboration (66%), and increase visibility and oversight (64%) during trials. As more organizations focus on streamlining clinical processes and systems, stakeholders will be better aligned throughout the trial lifecycle to speed drug development.

Veeva recently brought together industry experts from across academia, sites, CROs, and sponsors (see list on facing page) to discuss opportunities to improve information exchange in clinical trials, the potential for technology to advance collaboration, and practical steps to impact positive change.

Q: While the industry recognizes the need to improve clinical trial execution, experts point to a range of common challenges, including the inability to share information easily across stakeholders. What is preventing the seamless exchange of clinical trial information among stakeholders?

Doug Schantz: The lack of interoperability among data sources is one major challenge. Acquiring, combining, and analyzing the different types of clinical trial data all sourced from an innumerable number of vendors also present a huge challenge. With as many as 15 different vendors in a given study, analyzing and aggregating multiple data sources is never easy. Lack of standards means data is structured differently among dozens, if not hundreds of vendors.

Ken Getz: One of the biggest challenges is the fragmentation that exists within and between companies. The drug development enterprise has long operated in silos with limited coordination and integration among internal functions. This is exacerbated by the rising numbers of external service and solutions providers involved. This fragmentation manifests itself in the disparate and incompatible applications that disaggregate how data is gathered and managed.

Bree Burks: I believe that the biggest issue is that the groups with the operating capital and the technical capabilities to address this challenge are not involved with the day-to-day work of clinical trials and, so, do not prioritize the need for better information sharing.

I'm just starting to see healthcare facilities, insurance companies, and technology providers with the necessary assets start listening and working to help solve these issues. The involvement of these larger companies is required to drive change. The technology company must work directly with sponsors to create a connection that automates and retrieves data in the same way among all its stakeholders.

Jeff Kingsley: Too many parties are in the stack. In other industries, there is more direct communication with the customer. In our industry, an immense distance exists between the site and the sponsor. There's the biotech company, the CRO, separate companies for invoicing and labs, and so on. The distance between the site and the sponsor is hampering industry growth by slowing the ability to communicate information and then successfully implement innovation.

Initially, the rationale for bringing in new vendors to the mix was to improve research and efficiency, but

there's no longer a direct line of communication between sponsor and site. This lack of communication creates barriers which are worsened by disparate, disconnected technologies.

Hunter Walker: I think the biggest hindrance is the lack of data exchange standards. Looking at the medical and electronic health record (EHR) world that is part of healthcare today, a lot of these companies developed big systems that have essentially created silos among stakeholders. After entering data into the system, the user has no easy means for data export, migration, or exchange. This dramatically impacts the communications between the site and CRO, as the CRO typically manages the EDC system and the site has its own EMR (electronic medical record)/EHR.

Q: What positive outcomes could be achieved by addressing these challenges?

Schantz: When you can gather and share data more easily, you win back time and money because you don't need as much overhead internally to monitor and process data. Speed and cost savings would be the biggest impact when addressing data-sharing challenges. Companies could reinvest the savings to develop more innovative medicines. Right now, many can't afford to develop their entire pipeline of new drugs because clinical trials are so expensive.

> The distance between the site and the sponsor is hampering industry growth by slowing the ability to communicate information and then successfully implement innovation.

Getz: More open, coordinated, and integrated development holds numerous compelling promises: 1) faster access to more robust and comprehensive data and information supporting faster and more efficient decision-making; 2) accelerated insight into patient response to investigational therapies and into patterns of efficacy and safety that inform continuous learning; 3) better and more rapid identification of eligible patients and relevant professionals; 4) more convenient and flexible models that bring clinical trials to patients wherever and whenever they can most easily participate. Ultimately, these compelling benefits shorten development cycle times and lower development operating costs.

Burks: One positive result would be the ability to conduct more studies with fewer resources. There's some fear across academic medical centers that the industry will take studies away from us. About 40% of our effort concentrates on data abstraction and data entry, and technology removes much of that burden. By eliminating this work, sponsors can use those resources to support additional studies and better understand the data science capabilities of places like Vanderbilt.

Kingsley: If we solved this information exchange issue, all parties would have a closer relationship and be able to work together more flexibly. This is so important for a successful clinical trial because we are in a complex working environment where it's very easy to make seemingly inconsequential mistakes that cause big problems down the road—something as simple as a wrong date on an invoice.

Discussion Participants

Doug Schantz, *executive director, development operations* at AstraZeneca. Schantz is head of U.S. site management and monitoring for Phase I-III programs. He oversees nearly 300 people globally responsible for site selection, contracting, study start-up, eTMF and CTMS maintenance, site monitoring, and project leadership.

Ken Getz, MBA, *director of sponsored programs and associate research professor* at Tufts Center for the Study of Drug Development. Getz directs grant-funded research studies looking at pharmaceutical and biotechnology company R&D management practices; and clinical research landscape trends (e.g., outsourcing, investigative sites, study volunteerism, technology adoption).

Bree Burks, RN, MSN, CCRP, *senior director* at Vanderbilt Institute for Clinical and Translational Research (VICTR). The VICTR is an integrated clinical and translational research infrastructure that has raised the quality and scientific rigor of the research conducted at Vanderbilt and Meharry Medical College.

Jeff Kingsley, DO, MBA, CPI, FACRP, *founder and CEO* at IACT Health, a research management organization with 18 wholly-owned and integrated clinical research offices throughout the Southeast U.S. The family of companies conducts Phase I-IV research in nearly every medical specialty; inpatient and outpatient; and pharmaceutical, biotechnology, and medical device.

Hunter Walker, *chief technology officer* at Atlantic Research Group. Walker is responsible for all clinical data management, safety, and data integration and analytics systems. His team manages and deploys all cloud-based applications powering all enterprise operations.

Site turnover is another issue that could be alleviated by improved collaboration. Metrics from Tufts indicate that the churn rate is getting worse. Principal investigators may be more likely to stay if the day-to-day burdens like double data entry were eliminated; then we would have more experienced investigators able to manage more trials.

Walker: Coming from the mid-sized CRO perspective, we would like it if our clinical research associates (CRAs) didn't have to travel so often to sites to verify data by reconciling the TMF (trial master file) with the site's trial binder. Less travel would benefit both the CRO and industry; eventually, the CRA role and the data manager role would merge. The net result would be more trials with greater efficiency.

Less travel also means that CRAs could focus more on relationship-building and training with the sites, which could lead to better protocol compliance. In a time when drug development is focused on precision medicine, trials will entail collecting even greater volumes of data to ensure FDA compliance. Less travel would increase efficiency to support the future of more complex trials.

Q: What concerns are holding some stakeholders back from adopting new technology to support collaboration?

Schantz: The technology is starting to come around but the big question is who should be making the investment? It depends. Right now, it's not clear who should be paying for site-facing technology that resides at the site. That's an issue under exploration.

> We need to approach data sharing as strategic and not transactional by taking a deeper look into programs that require site involvement and patient recruitment.

Where there is the opportunity for site-facing technology, expecting the sites to have one standard is no fairer than expecting the sponsors to have one standard. This discussion should start with site-facing technology opportunities such as eTMF and maybe even beyond. Or, even with pre-processors for EHRs to allow them to load into the EDC system. Sponsors and sites must start a dialogue around this issue. If a site has certain standards, it doesn't necessarily mean that they're compatible with sponsor standards.

Schantz: Many argue that technology exists to support a vision for open, integrated innovation. However, high-level operating fragmentation, absence of clear regulatory direction, high risk aversion, challenges of juggling legacy and new development activity, and the dysfunctional ways that companies adopt innovation contribute to the huge barriers that hold back various stakeholders.

Burks: One concern for academia is how we tend to look internally to solve this problem. Instead of working in isolation and looking for solutions that address just our needs, we must find opportunities to leverage established technology and channels. We have to stop being narrow-minded with creating solutions just for our academic medical center instead of thinking about the bigger problem.

For example, instead of determining how to just automate our own data exchange, we should look to the sponsor or CRO that already has a relationship with a technology company that can integrate processes across sites. Instead of taking on the burden, we can focus on how to improve patient engagement and how to locate patients. These align with our core competencies much more than technology automation or information exchange across stakeholders.

Kingsley: Sponsors are multi-billion-dollar behemoths with quite a bit of bureaucracy. When deciding their budgets and budgetary approval rules regarding what they will pay and what is negotiable without escalation, they design it for the average research site. The average research site, on the other hand, doesn't even question technology, as they are not investing in it. Any investment in technology with a sponsor is outside of the budget paradigm and rules of site engagement. The issue must be escalated, causing timeline delays which hurt both parties. So, we're always balancing our budget negotiations with the acknowledgment that time matters so that the sponsor can start collecting data.

I believe that sponsors should compensate sites for investing in technology. We've invested in e-source, e-reg, and artificial intelligence but have not found any sponsors willing to compensate us for anything. I explain to sponsors that investing in these technologies doesn't significantly benefit me—it benefits them much more. The typical response is that technology is just the cost of doing business.

Walker: There is confusion in the industry about who should make the investment in technology. I believe that funding should come from sponsors, as they are on the top of the pyramid and stand to gain the most. However, I do think that CROs must be willing participants and make some contribution as they predominantly interface with the sites. CROs should encourage sponsors to look at how they can better support sites as well as be willing to support technology adoption internally.

Sites should remain focused on patient care, but they need new tools to better conduct research. In the last 20 years, the industry shifted the burden of data entry onto the sites. Originally, CROs manually created case report forms on paper with data entry personnel entering information into the data management system. When EDC systems arrived, sites entered the data directly, which eliminated the middle step but has also increased the burden on sites. Therefore, it is fitting for pharma to make the largest investment in technology to improve data input and exchange. Easier data entry for sites means trials can be conducted faster.

Q: Looking three to five years in the future, how would the dynamic between sites, sponsors, and CROs change if information exchange were more simplified, streamlined, and even automated?

Schantz: Seamless information exchange would greatly enhance the ability to transmit more unstructured patient data along with structured data to get a more accurate and complete view of the patient and their response to a medication.

I don't see interactions with CROs changing dramatically, but dynamics between sites and sponsors will change. The interoperability and ability to transmit data will reduce burdens on sites to speed trials and improve visibility for sponsors. It creates opportunities for increased data sharing, interoperability, and automation to support more strategic relationships between sites, sponsors, and CROs. We need to approach data sharing as strategic and not transactional by

taking a deeper look into programs that require site involvement and patient recruitment.

Streamlined information exchange would also make it easier for sites to support new trials. The decreased information overload and administrative burden would lower the cost of entry to participate in clinical trials.

Burks: I anticipate new types of support services to bridge the gap between large, private CROs, and people doing the work. New companies describing themselves as "integrated research organizations" (IROs) are partnering with academic medical centers to really know their systems, issues, and what's going on in the pharma and CRO world. As data is automated and embedded into more informatics and systems, I foresee IROs serving as a bridge between sites and even the healthcare system.

IROs feed a pipeline of studies, identifying technology systems and even research coordinators that can get the work done so that the academic medical centers and the health systems can focus their staff on being experts in the therapeutic area and take a more patient-centered approach. This model can help institutions like Vanderbilt provide exceptional clinical care through discovery and innovation.

Kingsley: The ideal result of improved information exchange would be transparency. With transparency, I could communicate, for instance, more directly with the medical monitor and make third parties aware of important notes or conversations without repeating everything.

The positive outcome is faster, more efficient trials, with a better relationship among different parties now siloed from each other in their processes. We would have fewer emails, less one-to-one communication, and a pool of centralized information from which everyone could learn. Conservatively, we probably spend two hours daily responding to redundant emails. Eliminating them would be a huge time saver. In addition, transparent data sharing would support greater confidence among partners and improved decision-making.

Walker: I think there is fear that sponsors wouldn't need CROs as much. However, I believe CROs would adapt and move toward forging better relationships with sites. Much of outsourcing today is just transactional. Sites see patients and enter data while we ensure the site enters it cleanly. By improving information exchange and empowering sites with better technology to do that more efficiently, they can conduct better research. With CRO training, sites could begin to take the time to actually look at collected data, which doesn't happen very often now.

Q: How would these changes trickle down to the patient and impact the patient experience?

Schantz: Ultimately, improved collaboration means getting new medicines to patients more quickly. Lowering entry barriers to conduct clinical trials would open the door for more patient participation as well as more sites. With medical staff less burdened with routine tasks like data entry, they will also have more time to focus on patient care. Study coordinators can spend less time inputting information and engage with patients in a more memorable and intimate way that improves study results.

Getz: All benefit under the aspirational model of open, integrated innovation. Notably, open innovation is necessary to achieve a higher level of patient engagement desired by both the public and patient communities, especially with the growing focus on rare disease therapies.

The professional community, too, will covet faster access to more robust and comprehensive data and information that supports faster and more efficient decision-making; accelerates insight into patient response to investigational therapies and patterns of efficacy and safety that inform continuous learning; rapid identification of eligible patients and relevant professionals; and convenient and flexible models that bring clinical trials to patients in locations most convenient to them.

By improving the way information is handled, we can make it easier for these rural sites to participate profitably, giving patients access to more clinical trials.

Burks: This technology should allow us to put patients in control. We've seen this paradigm with Uber and Lyft as well as in the banking space, where technology puts the customer in control, with new options and awareness. I do think that patients will gain this kind of control of their own healthcare and have more options, a new term called "clinical research as a care option."

Technology also will connect patients directly to sponsors, who may not need as many middlemen collecting data. Doc AI is an example of an artificial intelligence company that enables patients to join medical studies and input data. They already have around 40,000 users. These types of resources give patients control of their own healthcare record that they can submit directly to the sponsor.

Kingsley: Our coordinators spend 70% of their time at a computer responding to redundant emails and queries rather than with the patients. Freeing coordinators from mundane administrative work would increase patient interaction and retention.

Walker: More patients could participate in clinical trials, especially in rural settings where populations are underserved from a clinical trial participation standpoint. By improving the way information is handled, we can make it easier for these rural sites to participate profitably, giving patients access to more clinical trials.

Jason Methia *is Vice President, Site Strategy, Veeva Systems*

How Organizations Can Put Sites First When Implementing New Trial Technology

Organizations that continue to disregard the technological needs of one of the industry's core audiences run the risk of having their trials ignored.

KK Rumrill
SVP, Trial Management Services, IQVIA

More than 10 years ago, the digital revolution came to the clinical trials industry and ushered in a host of new technologies for clinical trial sites worldwide. While a few technologies were lauded, many sites found themselves overwhelmed by the sheer number of new solutions and frustrated as sponsors promoted so many of them that they ultimately made trials harder to run.

In the years since, the industry has responded to site concerns by updating older technologies to be more intuitive and introducing new tools designed with sites in mind. This has helped some sites become less wary of new technology. However, there's still much work to be done. There are many steps organizations can take to implement a site-first approach that ensures their tools aren't missing the mark.

One of the most important steps is to include site personnel throughout development of software or systems. This should be done regardless of whether the organization is implementing new technologies or updating existing tools. Sponsors and CROs often have sites they've cultivated good relationships with through repeated studies. These sites are important because they are often more willing to offer feedback, speak about existing problems (and ways to solve them), and test new features prior to launch.

Organizations should also consider using existing site relationships to create small task forces or advisory groups to provide feedback, offer suggestions, and test software or processes before they are rolled out externally. When site personnel are not available, consider codeveloping with another third party, such as a trial sponsor or CRO.

System features or updates that reduce site workload or eliminate repetitive actions are also big-ticket items when it comes to keeping sites happy. Features such as visit calculators, contact directories, and easily searchable document exchanges in the site portal streamline operations and enhance efficiencies. Cross-trial features that allow sites to apply credits or actions taken in one trial toward another reduce redundancies. For example, sites that complete and attest to taking good clinical practice training for one trial now have that credit applied across every trial that requires the same training. Technology can also streamline administrative functions and allow tasks to be assigned to specific roles. Communication with sites during setup is critical, because organizations may not immediately recognize every task that leads to repeated actions and inefficiencies.

Integration is another feature the industry hears about frequently. Sites often report that they must use multiple systems with individual log-ons to manage trials, which slows trial execution and adds to site burden. Organizations should do everything in their power to ensure functions can be performed seamlessly within one integrated system. A single sign-on to a portal that contains all the tools necessary to run the trial is much more efficient than having multiple-point solutions that don't talk to each other.

Technical support is also key. Organizations typically provide this for clients and should do so for trial sites as well. A communication plan with escalation guidelines combined with a searchable contact directory and a document to address frequently asked questions improves the likelihood of site satisfaction, even when technical or process issues arise. Site personnel often prefer to speak to a person in their time zone who speaks their language to resolve an issue.

Many organizations communicate with site personnel on an irregular or as-needed basis. Instead, they should consider creating standard communication practices and establish a cadence for sending updates, feedback, and more. An example of this would be compiling and sending all information regarding upcoming data locks on the first Monday of every week or month. Site personnel who know to expect an email every Monday will be conditioned over time to look for and read the message.

Creating a site-first culture is arguably a necessity as the industry continues to chart the next 10 years of the technological revolution.

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