Digital Health Regulatory News for CRO Professionals
Digital Transformation Of Clinical Trials Is Shared Responsibility, CRO Industry Says

Executive Summary
Digitizing data collection and monitoring has taken longer than desired due to various challenges, including resistance to change, unanticipated burdens and trial complexity, officials from ACRO and Medidata say, countering US FDA Commissioner Gottlieb’s criticisms that CRO business practices are holding back change.

The road to digital transformation for clinical trials has been slower than US FDA leaders would like, but overcoming these challenges is a shared responsibility borne by all entities in the research process and not just contract research organizations, representatives from the CRO industry say.

In interviews with the Pink Sheet, Doug Peddicord, executive director of the Association of Clinical Research Organizations (ACRO), and Jackie Kent, senior vice president of product at the digital services provider Medidata Solutions Inc., say numerous factors have slowed the move to digital in the clinical trials space, including resistance to change among various stakeholders, unanticipated burdens, study complexity and regulatory uncertainty.

Peddicord and Kent pushed back against critical remarks about CRO business practices leveled by FDA Commissioner Scott Gottlieb, who suggested the firms are preventing clinical trials from fully leveraging digital tools to collect and audit data in a way that makes studies faster, cheaper, and more efficient.

The CRO industry is committed to moving trials into the digital age and has made significant investments in digitization, said Peddicord, whose group represents both traditional CROs and data solutions companies.

“There’s a commitment to make the transition, to effect the transition to a digital data environment, but progress has been at some points slower than we’d like,” Peddicord said, noting the move to digital has posed challenges for all stakeholders, including biopharma sponsors, CROs, research sites, and regulators like FDA and the European Medicines Agency.

If Gottlieb is frustrated by the pace of digital transformation in the clinical trial enterprise, he is not alone, Peddicord said. “Certainly all the stakeholders, including the regulators, probably have some level of frustration with each other on how it’s gone.”

Similarly, Medidata’s Kent said that CROs and data services providers are not on their own when it comes to bringing clinical trials into the digital age.

“I really believe there is room for improvement for all of us,” Kent said, noting that all entities involved in clinical trials share a common goal of trying to get medicines to patients faster. “This partnership is really important, but it’s an army. It’s taking an army, and I think everyone has room for improvement.”

‘Phenomenal’ Interest In Going Digital
In a Nov. 19 speech, Gottlieb said much of the collection and auditing of clinical trial data still happens manually due to “outdated processes” that “are perpetuated by entrenched players like contract research organizations that profit off the old ways of doing things.” (Also see “Gottlieb Takes Aim At CROs’ ‘Outdated Processes’ In Push For Clinical Trial Digitization “ - Pink Sheet, 26 Nov, 2018.)

He noted, for example, that the move to risk-based monitoring and centralized monitoring has been a slow one despite FDA’s 2013 guidance encouraging such approaches.

Greater adoption of digital technologies could lead to better oversight of trials while also lowering development costs and creating more opportunities for patients to participate in studies, the commissioner asserted.

Center for Drug Evaluation and Research Director Janet Woodcock also has bemoaned the industry and agency’s reliance on legacy processes and “digitized paper” that are slowing drug development. (Also see “Reliance On ‘Digitized Paper’ Is Slowing Drug Development – US FDA’s Woodcock” - Pink Sheet, 14 Nov, 2018.)

In separate interviews, Peddicord and Kent talked about a variety of challenges that CROs and other stakeholders have faced in moving clinical trials into the digital age, as well as some measures that industry players and FDA could take to help move the process along.

The interest level in digitizing trials “is phenomenal,” Kent said. “I don’t believe I’ve been to a sponsor or CRO that is not interested and passionate about digital transformation and how to make clinical trials faster, more efficient, again to serve the patient.”
“But the speed of adoption varies everywhere, and I think it varies due to complexity of studies,” Kent said. “It varies in therapeutic areas. And when you add that all together, I think, where you see maybe that disconnect.”

**Early Challenges Slowed Adoption Of Risk-Based Monitoring**

Unanticipated burdens and the need to educate trial sites have contributed to the slow pace of adoption of risk-based monitoring (RBM), Peddicord said.

He noted that ACRO surveyed its members several years ago and found that approximately 15% of their clinical trials at that time were using RBM tools for a majority of the project, with a higher percentage having some component of RBM.

“Even two years ago, that was a lower number than we might have anticipated,” Peddicord said. “I think Dr. Gottlieb has suggested that CROs are somehow foot-dragging. I think in fact the case is that there are lots of reasons for the kind of slower uptake than we might have liked.”

There has been reluctance by some biopharma sponsors and clinical sites to move away from 100% source data verification, as well as a lack of clarity from regulators, including FDA and EMA, on how best to implement RBM, Peddicord said.

In addition, the early days of RBM made life more difficult for some research sites, he said.

Sites previously relied on regular monitoring visits and 100% source data verification as a type of quality check for themselves. However, the transition to RBM means fewer in-person visits, more remote monitoring and less monitoring overall, Peddicord said. As a result, ACRO members heard from some research sites that they had to hire people to do the quality assurance work they used to count on with an external monitor.

“There’s a shift that certainly nobody anticipated, that the very thing that was in some ways burdensome, which is regular in-person monitoring ... was also serving a particular function” that kept the research site running, Peddicord said.

In addition, some of the earliest versions of RBM led to practices that sites found burdensome, such as having to fax case report forms, he said. “There’s been some learnings along the way for sure.”

ACRO and the non-profit biopharma consortium TransCelerate BioPharma Inc. have tried to use those learnings as they work to develop best practices for RBM, Peddicord said. ACRO members also have worked with research sites through the Society for Clinical Research Sites, and research professionals through the Association of Clinical Research Professionals, on transitioning to RBM in a way that ultimately reduces burdens for sites rather than increasing them, he said.

In addition, the move to RBM has raised new regulatory challenges for companies, particularly when it comes to concerns about data integrity, auditability and traceability.

“The question of how you really ensure data integrity in a digital environment has taken on some real urgency,” he said “It used to be we could look at pieces of paper and we could ensure that ... the data recorded on the pieces of paper survived … as it moved from one piece of paper to another. That’s a little bit more complicated today, and we’re all making our adjustments.”

“I think all the stakeholders have had some hesitancy” in moving to RBM, “but we’re clearly getting there,” Peddicord said. “My impressions of our members is all of them are devoting enormous resources to the development of RBM tools, they’re devoting enormous resources to the education of ... sites around how best to work with these new tools.”

**Platform Approach To Digitization**

Full digital transformation of clinical trials is inevitable, even if it has taken longer than everyone would like, Peddicord said.

“The market for services and clinical research is going there,” he said. “It’s just the clinical trials environment becoming more and more digital just like every other environment, so we’re going there kind of regardless.”

Kent believes the digital future of clinical trials rests with unified platforms, like Medidata’s, that seamlessly extend from trial design through data collection and analysis. This enables researchers and sponsors to do away with manual processes, such as scanning documents, that result in the “digitized paper” decried by Woodcock.

“As you implement a platform you have that seamless connectivity from the design of your study all the way through the execution of your study and you’re locking your data,” Kent said. “And by applying advanced analytics ... you’re actually analyzing your data, and you’re finding your anomalies and cleaning that data, again all within that unified platform. We have many customers that are in the process of implementing that, which is really that true transformation.”
How Can FDA Help?
While Peddicord and Kent were eager to talk about measures CROs and data solutions companies are taking to push clinical trials into the digital age, they also had some thoughts on additional steps FDA could take to help move this process along.

For one, the agency could do a better job of ensuring that the enthusiasm its leaders have for digitization makes its way down the chain of command, Peddicord said.

FDA’s senior leadership, including Gottlieb and Woodcock, “has clearly encouraged RBM and other digital technologies in major ways for a number of years,” he said. However, from the point of view of biopharma sponsors and CROs, “there has always been some concern that the extent to which that commitment of the FDA’s leadership has not always trickled down to lower levels in the agency and specifically to reviewers.”

Kent said she appreciates FDA leaders’ enthusiasm for adoption of digital technologies, but she wishes the agency would do more on the world stage to encourage buy-in by other regulators.

“I am so thrilled with how much they’ve [FDA] moved forward,” Kent said. “If I think about where we were even five years ago, I think the conversations they’re willing to have and the consulting they’re willing to provide that I don’t believe they were willing to do years ago, I mean it’s a two way conversation now.”

However, the great strides FDA has made are tempered by the global nature of clinical trials. “The more they can influence other regulatory bodies across the world with their learnings and their implementations, I think that helps us all,” Kent said.

In addition, Kent thinks a new type of consortium among stakeholders is needed to give trials a bigger digital push.

The TransCelerate consortium, which comprises biopharma R&D firms but has a connection with ACRO, has built a close relationship with FDA and other regulators, she said. However, there are no consortia where all the stakeholders in the clinical trial process – CROs, technology vendors, investigators, and sites – can sit together as peers and talk with the agency, she said.

“I would love to see an organization where we’re all equal that can have the kind of voice, and everybody’s position could be recognized with a regulator like the FDA,” Kent said. Although there are loose connections among such stakeholder groups now, “we don’t really have a group where we’re all equal and we can work together at a more common partnership.”
Gottlieb Takes Aim At CROs’ ‘Outdated Processes’ In Push For Clinical Trial Digitization

Executive Summary
Better use of digital tools to capture – and audit – data can help lower developmental costs, US FDA commissioner says, urging a move away from manual processes ‘perpetuated by entrenched players like contract research organizations that profit off the old ways of doing things.’

US FDA Commissioner Scott Gottlieb is taking aim at contract research organizations, and what he calls their outdated practices, in pushing to bring drug development and regulation fully into the digital age.

In prepared remarks delivered at a Reagan-Udall Foundation meeting on expanded access Nov. 19, Gottlieb talked about opportunities to improve the efficiency and quality of clinical trials by making better use of digital tools to collect better information at a lower cost. These opportunities, he suggested, should come at the expense of CROs’ current business model.

“We don’t use technology well in clinical trials to collect information and use it to do quality checks on the data that’s collected,” Gottlieb said. “We still do a lot of things manually. And in my view, a lot of these outdated processes are perpetuated by entrenched players like contract research organizations that profit off the old ways of doing things.”

“Better use of digital tools for capturing and auditing information can disrupt these old legacy approaches,” he said. “They can provide better oversight, lower development costs, and open up more trial sites, and more providers and patients to opportunities to participate in trials.”

His comments echo recent comments by Center for Drug Evaluation and Research Director Janet Woodcock that efficient drug development is being hindered by a continued reliance on “digitized paper” and the inability to exchange data freely. (See sidebar for story.)

The FDA leaders’ remarks suggest that initiatives aimed at better leveraging digital technologies will be a major focus in the coming year, both externally as it applies to drug sponsors and internally as the Center for Drug Evaluation and Research works to modernize its new drug review process.

“We’re going to be focusing more attention in the coming months on how we can use technology to improve the way trials are conducted, and the way information is gathered and analyzed,” Gottlieb said. “We believe these approaches can expand enrollment opportunities and lower development costs.”

Reducing Clinical Trial Costs
Gottlieb’s remarks on leveraging the digital age for clinical trials and drug reviews, and his criticism of CROs, came during a speech in which he outlined a proposed regulatory framework for software applications intended for use with a specific drug. (Also see “Drug/Software Combos Likely Won’t Require Pre-Market Review By US FDA” - Pink Sheet, 19 Nov, 2018.)

The commissioner’s remarks segued from the opportunities presented by software applications that help patients optimize their use of drugs, to the efficiencies that could flow from better integrating digital tools into clinical research.

“Digital tools present lots of opportunities when it comes to helping patients make better use of new drugs, and better interactions with providers,” he said. “But they also present lots of chances for the FDA to improve our review of new drugs, and the process for how they’re developed.”

In particular, better use of digital technologies could help bring down the high cost of clinical trials, he said.

Costly trials can discourage the development of second- and third-to-market products, which in turn allows first-in-class products to retain monopoly-pricing power after expiration of patents and marketing exclusivity, Gottlieb said.

His prepared remarks referenced a “soon to be published FDA study,” which found that nearly half of the novel drugs approved from 1991-2000 had a competitor within two years. In contrast, for drugs approved from 2001-2010, it took five more years to achieve the same level of competition as those approved in the prior decade, he said.

Gottlieb similarly cited the agency’s findings on second-to-market competition when he testified before the House Energy and Commerce Subcommittee on Health in July. (Also see “US FDA’s Gottlieb Touts ‘Seamless’ Clinical Trials, Worries About Second-To-Market Products “ - Pink Sheet, 25 Jul, 2018.)

Novel trial designs incorporating digital tools and real-
world evidence can help make trials more efficient, while also better reflecting diversity of the intended patient population and making trials more accessible to patients, Gottlieb’s prepared remarks state. This is especially true for trials of second-to-market drugs, which can be difficult to enroll due to the existence of available therapy.

“Technology can also make it easier to disrupt the old way of conducting clinical trials, and disrupt some of the entrenched structures that make site selection, site auditing, and data collection more paper-based, and more outdated than it ought to be, and more costly than it should be,” he said.

Favoring Risk-Based Monitoring
In particular, digital technology could alleviate some of the current burdens of study monitoring, Gottlieb asserted.

“Traditional on-site monitoring of each clinical site to evaluate study conduct and perform source data verification is highly resource intensive and accounts for up to a third of the total clinical trial cost,” he said. “But, traditional on-site monitoring doesn’t guarantee data quality. Findings must still be evaluated to determine their true impact, and whether additional actions are needed.”

He pointed to a 2013 agency guidance that recommends sponsors use a risk-based approach to monitor clinical trials rather than requiring 100% source data verification. (Also see “Clinical Trial Monitoring Not Ready To Go Completely Off-Site, FDA Says” - Pink Sheet, 19 Aug, 2013.)

“Risk-based monitoring focuses sponsor oversight on risks to the most critical data elements and processes necessary to achieve the objectives of clinical investigations. This is another way that the use of digital technologies can make the development process more efficient, less costly, while improving our levels of oversight,” Gottlieb said.

Risk-based monitoring also can help break the “lock” that CROs have on clinical study monitoring, Gottlieb said. “This is a lock on research that can serve to drive up costs while making it hard for community sites to participate in clinical trials.”

FDA’s guidance encourages the use of centralized monitoring as a component of risk-based monitoring, conducted in conjunction with targeted on-site monitoring. However, the agency has learned that risk-based approaches to monitoring, including centralized monitoring techniques, have not been fully implemented, Gottlieb said.

He cited stakeholder concerns that if 100% source data verification is not used, there will be a greater risk that an issue identified by FDA could lead to an adverse regulatory action. “And stakeholders may have uncertainty about the best technological solutions for carrying out centralized monitoring, including challenges with integrating these systems into their operational workflows.”

“We recognize that these are important questions and concerns that we need to be address. And we’ll look at ways to address these challenges more in 2019. We want to better understand the extent to which risk-based monitoring has been implemented, the ongoing barriers to full execution, and how the FDA can continue to advance implementation of risk-based monitoring – especially with centralized monitoring.”

Capitalizing On Cloud-Based Tools
Building technical and organizational capacity for risk-based and centralized monitoring can help FDA, industry and other stakeholders prepare for the conduct of decentralized and hybrid clinical trials, Gottlieb asserted. This could involve trials where procedures are conducted in a home setting, or routine data collection is facilitated through electronic health records, wearable devices or smartphones.

“This is how technology can help disrupt entrenched models for doing things in a way that expands opportunities and creates new efficiencies,” Gottlieb said.

“Clinical trials will continue to incorporate more of these technologies, allowing researchers to reduce the time it takes [to] generate reliable insights from the clinic to better inform efficient product development,” he said. “FDA reviewers will also harness more of these tools to improve how we collect information more efficiently, and analyze it more reliably, to take more timely, targeted action to mitigate serious health risks.”

FDA will soon announce how it plans to allow sponsors to make better use of cloud-based analytical tools in the clinical trial and clinical review process, Gottlieb said. “These new steps we’re working on will help advance the use of digital technologies as a tool for improving the capture and evaluation of data as part of the review process.”