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How We Get to the Engaged Patient

LISA HENDERSON
Editor-in-Chief

In December 2014, I wrote a blog about clinical trials in 2017 (http://bit.ly/1wSAmk6), where basically I said that clinical trials would change in three years or 2017. Well, 2017 is here and can I honestly say that they have changed significantly? In the blog, I was referring to trials becoming a more integrated part of healthcare, another option made in the continuum of treatment choices offered to patients, as well as their physicians.

That clearly is not going to happen on a large scale anytime soon. However, there are movements in that area. For example, clinical trial matching services that seek to educate physicians about potential trials for their patients (http://bit.ly/2jKqTpo) or Clinical Care as a Research Option (CRCO), which would change the "equation for patients—putting them at the center of clinical trials; therefore, rebalancing the value for them to participate, not just as subjects, but active participants who have access to and understand their own data." (see http://bit.ly/2cZcwzB).

The patient at the center of clinical trials is a theme that came up during a panel convened to discuss the topic of our feature section in this issue, Technology Innovation. In this discussion, the experts first flipped the term patient engagement to the engaged patient, thus reflecting a more active participant in their healthcare choices more accurately. The engaged patient was at the center of many innovations in technology, either directly or indirectly, but ultimately in the final discussions, the engaged patient was one transformational factor in The Clinical Trial of Tomorrow.

In Ken Getz's Clinical Trial Insights this month, he shares retrospective and prospective data that proves the value of patient engagement initiatives in clinical trials. This data, as Getz notes, can be crucial in helping change the internal mindset of senior management, who largely believes that investments in patient engagement initiatives may not have a high ROI.

Patients, subjects, participants....let's be clear, the difference is where and how you get your treatment. But the bottom line is we are all people and at some point in our lives, we are going to be a patient. And at another point in our lives, we may be a subject. Getting to that place of seamless integration of options is not easy. But when you look at The Clinical Trial of Tomorrow, you can visualize how that happens. Take current data sources, make them larger and of higher quality, with standards to share, using analytics and intelligence to apply information to a specific patient or disease, that finds its way to the Healthcare Environment to inform regulations, standards of care, and personalized medicine to the patient, who owns his or her own data, and shares it with privacy and trust for research. Or start with the engaged patient and work the other way, either or any direction works because they are all interrelated.

A huge Thank You to the technology innovation panel members who discussed the topics in detail to arrive at The Clinical Trial of Tomorrow matrix. They get the Engaged Patient, and see the path to the future is paved with more than good intentions.

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PEER REVIEWED

22 A Practical Overview of Patient-Centric Trials

Hélène L. Svahnqvist, Anna Skabeev

A how-to guide for clinical trial managers in implementing patient-centric approaches using today's clinical study model.

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The Clinical Trial of Tomorrow

Highlighting the six broad technology themes poised to transform future R&D

Lisa Henderson

This past year, SCORR Marketing and *Applied Clinical Trials* surveyed our audience on a number of topics around technology—Big Data, innovation, paperless, wearables and mobile health in clinical trials. (a full list of surveys is here: http://bit.ly/2cxrv1W). Instead of creating a new survey for insight into top technology innovations, SCORR analyzed existing data to inform the Technological Innovations Survey Report, which is available here: http://bit.ly/2jbrKTK.

The data showed various levels of acceptance of technologies, depending on the stakeholder (sponsor, CRO, site, service provider) vs. type (paperless, wearables, Big Data, etc.). But across the board, themes around barriers of adoption to new technology or processes emerged. Cost and skepticism about data quality are the leading barriers. Another theme, the fear of change and the reluctance to give up tried-and-true, even if cumbersome, processes or technologies. Next, the ever-present data security concern. Though not always the top concern, security was the most-identified choice resulting from a company's adoption of paperless processes and the second most-identified concern coming from company's use of Big Data.

TECHNOLOGY INNOVATION

Impacts, influencers, and game changers

While the above report focuses on current attitudes around technology innovation, *Applied Clinical Trials* assembled an expert group late last year to choose the top technology innovations affecting our industry—despite industry hesitation. The forward-looking panel included: Brian J. Chadwick, President, Bring Life Sciences Consulting, Inc.; David Evans, Managing Director, Accenture, LLP; Ken Getz, Director, Sponsored Research Programs, Tufts CSDD and Chairman, CISCRP; Wayne Kubick, CTO, HL7; Craig Lipset, Head of Clinical Innovation, Pfizer; and Alan Louie, Research Director, Life Sciences, IDC Health Insights.

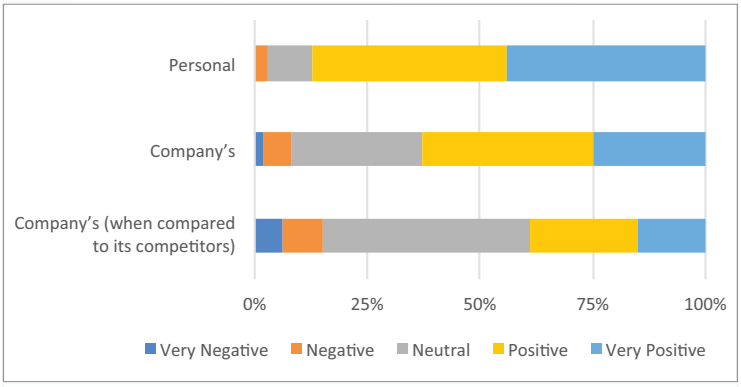
What started as an attempt to winnow down a long list of technology innovations (nominated by our Editorial Advisory Board) to impact clinical research this year, became a robust discussion about technologies affecting research now, and those poised to ignite the "Clinical Trial of Tomorrow." Rather than choose the top technologies, six broader themes emerged that encompassed many of the innovations.

This final mind map or matrix (see facing page) was conceived because of the inter-relatedness of those themes. For most of the discussion, the "Engaged Patient" was the transformational game-changer—the one area that overarched all others, at the center of a hub-and-spoke model. However, ultimately, while a seismic shift in the way healthcare, clinical trials and clinical care is conducted, the Engaged Patient was placed within the bigger picture clinical trial of tomorrow. Many of the six topics and their listed sub-topics are inter-related, however, so as not to clutter and confuse, we decided to leave the dotted line relationships out.

What follows is the discussion of what constitutes the Clinical Trial of Tomorrow.

"My default is we are in the business of developing medicines, and anything is an enabler to that. Therefore, I shouldn't be entirely dependent on any one technology," said Lipset, shepherd of the sponsor viewpoint. This set the frame for the discussion. What are sponsors considering for clinical trial technology that will impact today, tomorrow, or trials starting now but not ending until five years from now? The technologies chosen are used in many industries—how they are applied or will be applied in clinical trials is how the committee ended up grouping the categories. Said Evans, "There are foundational technologies, but how will we use them to solve patient problems?"

Attitudes on Innovative Processes/Technological Advances in Trials



Source: SCORR Marketing and *Applied Clinical Trials* Survey Report, February 2017.

The Clinical Trial of Tomorrow

Source: *Applied Clinical Trials* Technology Innovation Panel, January 2017. Designed by Wayne Kubick.

From the vantage of an industry tech analyst, Louie said, "If you look at it from a tech-first perspective, IoT and wearables, while having a significant adoption on the consumer side—but still waiting to cross the chasm—hasn't found its killer app in the life sciences. At some point down the road, there's going to be a great new app that everyone is going to want to incorporate into a lot of major trials because it delivers something useful and valuable, which it's not doing yet." A valid point, you don't know what you don't know.

But what we do know is that while current wearables and devices may never pass the sniff-test for trials (or could get passed by with that killer app), their brethren in the Cognitive Computing/AI world—such as the artificial pancreas, which uses a "learned" glucometer and insulin pump that "make" the dosing decisions for patients based on their blood sugar levels—are just around the corner. Chadwick says AI will be big and is influencing current thinking in future clinical trials. Presently, "intelligent" devices are going through the 510k process, so their consideration is not far off. In another example, the FDA is exploring its RAPID system using NLP to identify potential public health outbreaks.

Getting to Cognitive Computing/AI is not an easy thing. Evans explained: "In machine learning, it has to have a gold standard of large volume and high quality endpoints to learn or determine decisions. You still have to build the Big Database using high-quality data in order for the machine to interpret what the unknown is so that it can learn." Therein lies the inter-relatedness to "Intelligent Enterprise" and Big Data. Without large volumes of high-quality data in a consistent format, the pattern recognition, decision support, and signal detection is not achievable.

Evans believes that data can also come from the Connected Computing sector. "As the connected universe expands, you have to have large volumes of high quality data to go to Big Data, to inform analytics," he said. "But currently, we have a lot of data, but not the quality," Kubick agreed that Big Data may not be transformational in 2017, but the connected computing impact is now.

Patients: The center of interrelations

Getz said, "In some ways, the patient piece becomes an overarching principle that applies to all of these areas we are discussing. Connected computing creates a more convenient patient engagement, a more interactive patient engagement." He continued, echoing Lipset's point about technology's effect on drug development. "At the very center, is the notion that all of these technologies ultimately serve the goal of assuring the drug development enterprise that its relationship with the patient is optimized. It becomes the most relevant, most informed, most convenient for our study volunteers, and most efficiently run that ultimately delivers the best therapies."

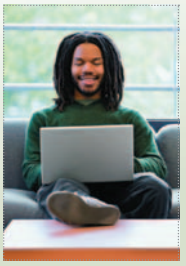
Kubick said, "While I don't think blockchain is going to be ready for primetime in our industry for several years, one of the compelling cases is having much more and control, and better control, over security and privacy in the hands of the patient. It is what's critical to making patients more willing to share and exchange their data for research purposes."

#1 ENGAGED PATIENT

WHAT IT IS: Flip patient engagement to the engaged patient to more accurately represent the transformation taking place through them with technology. For the engaged patient, characteristics include interactive, more involved and more informed decision-making, convenience, improved comprehension, greater disclosure, and building trust, wrapped up with patients providing their own data.

WHY IT WAS CHOSEN: With almost all the technologies chosen, they ultimately served the goal of assuring the drug development enterprise that its relationship with the patient or patient community is optimized.

IMPACT: Transformational



#2 HEALTHCARE ENVIRONMENT

WHAT IT IS: The larger environment that affects directly or indirectly technology, innovation, clinical care and clinical trial decisions.

WHY IT WAS CHOSEN: Each is a control that moves the technology needle, which without some kind of compliance involved, the market may not have adopted it. For example, regulators around the world are now demanding compliance with data transparency in clinical trials.

IMPACT: Current, influencer

#3 COGNITIVE COMPUTING/AI

WHAT IT IS: Artificial intelligence, natural language processing, learning healthcare, machine learning, intelligent devices—anything that pulls the data in the right way and applies it where it's needed automatically, i.e., real-time data access and analysis.

WHY IT WAS CHOSEN: Cognitive Computing/AI was chosen for its downstream influence. While currently being used, it will not significantly impact clinical trials this year. But its applications deserve attention for the clinical trials of 2018 and beyond.

IMPACT: Influencer

#4 CONNECTED COMPUTING

WHAT IT IS: All the Internet of things, wearables, connections, smartphones, sensors, etc.,—those in use now and will be for the next few years—that offer real-time data everywhere.

WHY IT WAS CHOSEN: Connected computing creates a more convenient and interactive patient engagement experience. There are tangible opportunities in this category for clinical trials, but are limited by current challenges, mostly around regulatory-grade devices, validation and data quality.

IMPACT: Current

Kubick continued. "It basically means to secure their trust, so they feel confident that the data will be used for the right things." Lipset said permissions that are baked into a chain of control closer to the patient is a great potential enabler for empowering tools for patients.

In addition to the trust-building that blockchain could offer, data privacy and clinical trial data disclosure—two additional choices on the original list—are also an exercise that help build patient trust. But here, the impetus for privacy and disclosure are regulatory authorities.

Evans said, "The regulators are a control. You can't have any technology enabled to the patient without, first, having regulatory scrutiny. Even Google or Apple engage with FDA on a regular basis on how to innovate into that area and how they fit into the regulatory framework."

And while some may see the FDA or other regulatory authorities as a hindrance to innovation or a drag on the pace of change, Evans believes the agency is moving faster than it ever has before in trying to address current tech innovations.

#5
MASTER DATA MANAGEMENT

WHAT IT IS: Master Data Management refers to controlling the definition and use of data to improve quality, access, consistency or sharing for improved operations and efficiencies.

WHY IT WAS CHOSEN: Without a bigger picture toward and the incremental steps taken already to make data better or increase its usability, getting to the transformational clinical trial is impossible.

IMPACT: Current

#6
INTELLIGENT ENTERPRISE/ BIG DATA

WHAT IT IS: Large volumes of easily accessible, high quality Big Data from multiple, disparate sources.

WHY IT WAS CHOSEN: The downstream effects of Big Data cannot be underestimated and will be evolutionary, as the foundations for Cognitive Computing/AI and the Healthcare Environment controls are built by high quality, high volume data.

IMPACT: Transformational

More controls in the Healthcare Environment were around the effects of population health decisions, payer decisions, care delivery, evidence-based medicine, and more. These entities may not be transformational, but their influence must be factored into R&D of tomorrow. Personalized medicine was placed in the Healthcare Environment because it is currently in use—and a control to how decisions are made. Information gained through personalized or precision medicine, including images, tumor markers, genome sequencing, and the 'omics will feed and grow both cognitive computing and big data.

While it did not appear on the final matrix, personal health data sharing is a downstream use of HL7's Fast Healthcare Interoperability Resources (FHIR) platform. It is the chance for patients to share data directly for research. Lipset explained: "It sits at the convergence of eSource and patient engagement, enabling patients to be the source of much more rich and diverse data."

Another innovation on the original list was collaborative care networks. Chadwick, specifically, called out the Chronic Collaborative Care Networks (C3N; https://ImproveCareNow.org). In this project, through objective communication and education, remission rates have gone from 50% to 75% for patients with inflammatory bowel disease.

Operational efficiencies and MDM

The area of least interrelatedness to the Engaged Patient was the Master Data Management category. Louie suggested that some of the technologies on our original list—such as electronic trial master file (eTMF)—were strictly for the operational efficiencies they deliver. "They are operationally-based, and make the process more efficient and allow companies to respond to regulators; that's not patient-related, but process-related," he noted.

Getz agreed. "eTMF is one that is being rapidly adopted or more market-ready to adopt in 2017. It would deliver a higher level of efficiency, could contribute to faster cycle time, and provide more data to track what historically has been in documents that have been siloed. It's a technology that will have a notable impact this year." Making documents available in a single source is a plus for future uses, as are standards.

Louie added that the EMA's approved implementation of ISO standards for the identification of medicinal products (IDMP)—a set of common, global standards for data elements, formats, and terminologies to uniquely identify and exchange information on medicines, is driving data access and standards.

Evans concluded that without standards, innovation is impossible. "There are maturing standards that have been driving that activity—across any of the categories. Without having the foundational standards in place, you are not going to be able to innovate or have widespread adoption of the innovation."

Big Data: It is what it is

The Intelligent Enterprise/Big Data theme encompassed the items listed on the original list, and were included as a source of data that can be mined to answer larger questions. For example, Chadwick noted pharmaceutical companies performing data mining on social media. "What pharma is doing with social media content is amazing. It is scraping data to get to the most subtle references out of social networking to find potential adverse events."

As noted earlier, Big Data isn't in the Impact stage, meaning it's not here yet. But it is going to be evolutionary when it hits its stride. The panel mulled the term "Big Data" because it conjures the hype vs. reality factor that Lipset says exist with some technologies. But as Kubick pointed out, "it is a recognizable term, it is a theme in literature, and it can be applied to clinical trials and R&D."

We hope the matrix helps apply what you do now in clinical trials to where the future of R&D is going, and shows the interrelatedness of the many technologies and stakeholders in the R&D space.

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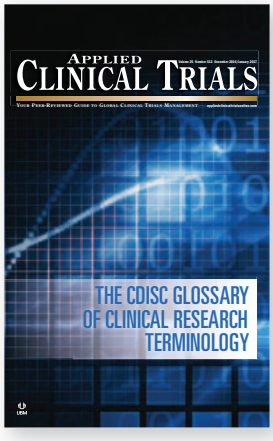


GLOBAL REPORT

INVESTIGATORS' FINANCIAL TIES COME UNDER CLOSE SCRUTINY

It's an old chestnut: does a cozy, cash-based arrangement between the investigator and the drug's manufacturer produce positive clinical trial results? "Yes" is the clear answer, according to a new study by researchers at University of California San Francisco (UCSF).

Financial links between researchers and companies that make the drugs they are studying are independently associated with positive trial results, suggesting bias in the evidence base, concludes the study, published online by *The BMJ* in January.

Salomeh Keyhani, MD, associate professor of general internal medicine at UCSF, and her colleagues evaluated the association between financial ties of principal investigators (PIs) and study outcomes in a random sample of 195 drug trials published in 2013. They focused on trials that examined the effectiveness of drugs.

The group, lead author of which was medical student Rosa Ahn, found that financial ties between principal investigators and the pharmaceutical industry were present in 132 (67.7%) studies. Of the 397 PIs, 231 (58%) had financial ties. Of all PIs, 156 (39%) reported advisor/consultancy payments, 81 (20%) reported speakers' fees, 81 (20%) reported unspecified financial ties, 52 (13%) reported honorariums, 52 (13%) reported employee relationships, 52 (13%) reported travel fees, 41 (10%) reported stock ownership, and 20 (5%) reported having a patent related to the study drug. The prevalence of financial ties of PIs was 76% (103/136) among positive studies and 49% (29/59) among negative studies.

Trials authored by PIs with financial ties to drug manufacturers were more likely than other trials to report favorable results, even after control for confounders such as funding source and sample size (odds ratio 3.37, 95% confidence interval 1.43 to 7.9). Ahn and Keyhani point to possible mechanisms linking industry funding, financial ties, and trial results such as bias by selective outcome reporting, lack of publication, and inappropriate analyses.

An unexpected finding was the lack of association between industry funding and favorable trial results in multivariate analysis, noted Andreas Lundh, PhD, a post-doc researcher at the Center for Evidence-based Medicine, Odense University Hospital and University of Southern Denmark, in a *BMJ* linked editorial. Interpretation of this finding is complicated, however, because Ahn's study used a definition of industry funding that grouped company-run trials with independent academic studies that also received industry funding, he pointed out.

Also, financial ties are often unreported, and although Ahn and colleagues did make efforts to identify undisclosed financial ties, the databases available for such purposes are still limited, Lundh wrote.

Ahn, Keyhani, and colleagues stress that their analysis is observational and cannot be used to draw conclusions about causation, but given the importance of industry and academic collaboration in advancing the development of new treatments, they think "more thought needs to be given to the roles that investigators, policymakers, and journal editors can play in ensuring the credibility of the evidence base."

Lundh and co-author Prof. Lisa Bero, from the Charles Perkins Centre and Faculty of Pharmacy, University of Sydney, Australia, agrees more research is needed to identify how industry funding and financial ties could influence trial results. They urge trial authors to share their data and participate in industry-funded studies only if data are made publicly available, and they suggest journals could help by rejecting research by authors who are unwilling to share their data and by penalizing authors who fail to disclose financial ties. The role of sponsors, or companies with which authors have ties, in the research must also be transparent, they stated.

"Trials with industry funding or authors with financial ties should be interpreted with caution until all relevant information is fully disclosed and easily accessible," they concluded.

— Philip Ward

WASHINGTON REPORT

'CURES' IMPLEMENTATION, USER FEE RENEWALS KEY TO BOOSTING R&D AND APPROVALS

Congress surprised policymakers and the research community in December by enacting the 21st Century Cures bill after two years of debate. Final enactment was secured by adding language to fund state opioid treatment programs, expand mental health services, and promote research on regenerative medicine.

The new law shores up FDA operations and funds biomedical research at the National Institutes of Health (NIH), including the Obama administration's Cancer Moonshot and personalized medicine initiative. Key provisions support patient-focused drug development, pediatric research, biomarker qualification, and the development of needed antibiotics and treatments for rare conditions. Most important for FDA officials are policies designed to help the agency hire more scientists and experts to evaluate new products and research programs.

A theme is to encourage researchers to apply novel adaptive designs and statistical modeling to clinical trials and to permit wider use of real-world evidence in approving added indications for marketed medicines. Medical device makers gained a new approval pathway for "breakthrough" devices, and there's language reducing diverse conflict-of-interest reporting requirements for researchers. NIH's National Center for Advancing Translational Sciences (NCATS) received authority to support Phase II clinical trials on promising therapies. And experts at NIH and other federal agencies applauded curbs on red tape designed to facilitate staff participation in scientific and medical meetings.

Now FDA faces the daunting task of preparing the many new guidances and establishing new procedures within the tight timeframes specified in the legislation. One complication is that the additional $4.8 billion provided over 10 years for NIH and $500 million for FDA is authorized by Congress, but not appropriated, opening the door to future cuts in promised resources for FDA to carry out these many requirements.

User fees critical

FDA's need for additional resources to implement "Cures" and to efficiently evaluate new medicines makes it doubly important for Congress to reauthorize user fee programs for drugs (PDUFA), biosimilars (BsUFA) and generic drugs (GDUFA) well before they expire on Sept. 30. Normally, enacting legislation as extensive as Cures would make the process easier, as the new law already tackles some controversial issues, such as greater reliance on real-world evidence in regulatory decision-making, expansion of priority review voucher programs to incentivize drug development, and increased flexibility for pharma companies to present information on unapproved drug uses to knowledgeable payers and formulary committees.

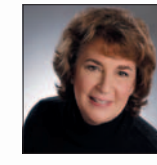
But the user fee bills need to be moving forward by summer for FDA to avoid issuing pink slips to staffers supported by fee revenues. Legislators on both sides of the aisle are looking to add on provisions to curb high prices on new and old drugs, and new Trump administration officials in HHS and FDA may want to revise the fee packages—something that FDA and industry representatives adamantly oppose after spending the last two years negotiating the new fee program agreements.

Approval blip?

Timely renewal of user fees is important for maintaining an efficient system for evaluating and approving clinical development protocols and market applications, which suffered a decline last year. The Center for Drug Evaluation and Research (CDER) approved only 22 novel medicines in 2016, a significant drop from the near-record 45 new drugs in 2015, reported John Jenkins, long-time director of CDER's Office of New Drugs (OND) before his retirement last month. This may be a temporary blip in the process, as Jenkins noted that CDER continues to approve most new drugs in the first review cycle and provides expedited action on innovative drugs and breakthrough therapies.

A key factor in the decline, however, was a drop in new applications filed by sponsors in the first place. And more of those were incomplete or inadequate, as seen a sharp rise in Complete Response letters (CRs)—14 in 2016 compared to just a few in most years. Most CRs reflected inadequate safety and efficacy data, but manufacturing problems halted action on a notable number of new drugs.

CDER Director Janet Woodcock hopes to address some of the review and approval issues by implementing a pharmaceutical platform for new drugs, along with clear data standards for drug submissions and effective IT policies, to better manage the review process.



— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

1/10/17: Recommendations for Assessment of Blood Donor Eligibility, Donor Deferral and Blood Product Management in Response to Ebola Virus

1/10/17: Current Good Manufacturing Practice Requirements for Combination Products

1/12/17: Multiple Endpoints in Clinical Trials

1/12/17: 180-Day Exclusivity: Questions and Answers

1/12/17: Nonproprietary Naming of Biological Products

1/13/17: Referencing Approved Drug Products in ANDA Submissions

The following committee meetings are among those scheduled in March:

- Vaccines and Related Biological Products Committee Meeting Announcement ***March 9***
- Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting Announcement ***March 15***

EU REPORT

TIMES CHANGING FOR ETHICS GUIDELINES, TOO

It's not just science that is leaping ahead and taking clinical trials into new territory. The world is changing around science, and one of the consequences is that there are changes, too, in the ethical context for medicine. What was until recently considered ethically sound is now no longer so adequate—and that is why, in February, the Council for International Organizations of Medical Sciences (CIOMS) is publishing its final version of its revision of one of the texts underlying all modern trial protocols, its 2002 International Ethical Guidelines for Health-related Research Involving Humans.

This 120-page document will have to become the new bible for everyone working in clinical trials, observational research, biobanking, and epidemiological studies. Its chapters cover virtually every aspect of trial design and conduct, from informed consent to compensation for research participants, and from ethics committees to cluster randomized trials. Almost all guidelines are newly drafted, and major revisions have been introduced to guidance on risks and benefits, choice of control, and women. Its scope has been expanded from "biomedical research" to cover all health-related research, and it has been merged with CIOMS' 2009 International Ethical Guidelines for Epidemiological Studies.

Protecting the general good

Most notably, the doucment brings a new emphasis to what can best be described as the general good, in line with the development of more socially aware public discourse on health over the last two decades. There are now extensive guidelines on scientific and social value and respect for rights, on equitable distribution of benefits, on community engagement, on public accountability, and on conflicts of interest. CIOMS decided on an update because of developments since 2002, both in the field of biomedical research itself and in research ethics—including, notably, the revision of the Declaration of Helsinki in 2008.

So a new provision, right up at the front of the guidelines, is that "the ethical justification for undertaking health-related research involving humans is its scientific and social value." To be ethically permissible, health-related research with humans, including research with samples of human tissue or data, must have social value, CIOMS insists. It explicitly outlaws "seeding trials" if their purpose is to influence participating clinicians to prescribe a new medication rather than to produce knowledge about the merits of these interventions. Similarly, even a well-designed, late-phase clinical trial could lack social value if the endpoints measured are not sufficiently related to clinical decision making.

Responsive to community needs

Keeping research relevant also gets new attention in these guidelines. "Before instituting a plan to undertake research in a population or community in low-resource settings, the sponsor, researchers, and relevant public health authority must ensure that the research is responsive to the health needs or priorities of the communities or populations where the research will be conducted," says CIOMS. And benefits must be shared, the guidelines demand.

Pregnancy

Women, and particularly pregnant and lactating women, benefit from additional attention in the new guidelines. Because they have distinctive physiologies and health needs, research designed to obtain knowledge relevant to their health needs must be promoted, says CIOMS, adding that research in pregnant women must be initiated only after careful consideration of the best available relevant data. In any research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women, the risks must be minimized, and the purpose of the research must be to obtain knowledge relevant to their particular health needs or those of their fetuses or infants.

Specimens and data

The rise in privacy concerns over recent years also informs new guidelines on biological materials and related data. In addition to provisions on governance for collection and storage of everything from tissue specimens to health records, CIOMS requires that when specimens are collected for research, either specific informed consent for a particular use or broad informed consent for unspecified future use must be obtained from the person from whom the material was originally obtained. If any residual tissue is stored for future research, a specific or broad informed consent may be used, or may be substituted by an informed opt-out procedure.

— Peter O'Donnell

EMA NOTES

LANDMARK CONDITIONAL MARKETING AUTHORIZATION REPORT: The European Medicines Agency (EMA), to mark 10 years of experience with conditional marketing authorization (CMA), published a wide-ranging analysis of the positive impact this tool has had in providing early access to new medicines for patients. Since 2006, a total of 30 drugs have received a CMA. Medicines that were granted a CMA target debilitating and life-threatening conditions such as HIV infection, breast cancer, severe epilepsy in infants, or multi-drug resistant tuberculosis; 14 were orphan drugs.

EC PUBLISHES BIOSIMILARS Q&A FOR PATIENTS: The document (see http://bit.ly/2jZCGnV), available in seven languages, provides a simplified view of the biosimilars landscape, answering questions that patients might have, such as what is a biologic or a biosimilar and how do they compare to generics. The European Commission is organizing its third annual multi-stakeholder workshop on biosimilar medicines, set for May 5.

CLINICAL TRIAL INSIGHTS

MEASURING ADOPTION AND VALUE OF PATIENT ENGAGEMENT

Recent studies may help break down barriers to implementing patient-centric initiatives

Ken Getz

The adoption of select patient engagement initiatives is making steady progress but not without encountering substantial headwinds.

According to a 2016 CenterWatch survey of 95 major and mid-sized pharmaceutical companies, nearly two-thirds of sponsors report that they are facing pushback on implementation. Survey respondents identified three primary challenges: 57% reported internal resistance to modifying current drug development practices and processes; 40% noted the lack of internal expertise required to manage adoption; and 35% reported that there was insufficient funding to cover the investment required.

Although the virtues of patient engagement are profoundly obvious to many, according to that same survey, internal resistance was strongly associated with senior management concern and uncertainty around the financial value of patient engagement. Two recently completed studies—one a retrospective assessment and the other a prospective modeling exercise—should help inform senior management about the financial return on patient engagement.

Retrospective assessment

Throughout 2016, the Drug Information Association (DIA)—in collaboration with the Tufts Center for the Study of Drug Development (Tufts CSDD)—met with 22 pharmaceutical companies and contract research organizations (CROs) to gather baseline data on patient engagement practices and their impact. The study also looked at guidelines and frameworks designed to assist implementation planning. The results of this study are being presented at conferences and webinars and can be accessed on the DIA website (http://www.diaglobal.org/en/resources/how-we-think/patient-engagement).

The working group conducted surveys and interviews, collected case studies of actual patient engagement initiatives and reviewed the published peer-reviewed and trade literature. The most widely adopted engagement initiatives among the working group companies involved soliciting input from patients and professionals to inform protocol design feasibility, clinical trial positioning and implementation. Seventeen of the 22 companies reported routinely implementing and piloting patient advisory boards. Sixteen companies reported implementing and piloting advisory panels with investigative site staff and health care providers.

Thirteen of 22 organizations reported that they are routinely implementing and piloting the distribution of non-technical plain language clinical trial results summaries to their clincial study volunteers.

Other more commonly adopted initiatives include the use of home nursing networks (9 out of 22); the conduct of surveys among study volunteers during and after clinical trials (9 out of 22) and the use of wearable devices (8 out of 22). Seven companies reported piloting, and 11 companies indicated that they are planning to use electronic informed consent.

The working group observed a wide variety of organizational models used to manage patient engagement initiatives. The most prevalent model was a dedicated and centralized function with the following primary responsibilities:

- Facilitate cultural change within the organization
- Build policies, guidelines, processes and tools
- Share effective practices across the company
- Advance more systematic patient-centric practices company-wide
- Facilitate and coordinate implementation
- Manage internal alignment of patient engagement and advocacy outreach efforts

In total, 121 case examples of patient-centric initiatives were gathered and analyzed. These case examples produced 650 metrics in total, of which 260 were quantitative in nature.

The working group was unable to aggregate the quantitative metrics across the case studies to derive average impact measures and to make meaningful comparisons.

> Internal resistance was strongly associated with senior management concern and uncertainty around the financial value of patient engagement.

At this time, companies have neither defined nor collected metrics uniformly.

Patient and professional advisory boards, social media engagement and patient education programs were among those offering the highest return on engagement. These initiatives required minimal investment, were relatively easy to implement and had a significant reported impact, including faster study planning, approval and initiation time lines; higher randomization, recruitment and retention rates; fewer disruptions and delays; and more positive study volunteer satisfaction levels.

Wearable devices, home nursing networks and telemedicine generally provided a strong but relatively lower return on engagement, as they required larger upfront investment and more substantial technical and operating support to implement. Im-

CLINICAL TRIAL INSIGHTS

pact measures showed improvements in enrollment and retention rates.

The DIA website provides a detailed summary of 12 patient engagement initiative categories for which case-example metrics were gathered. The website also provides a Return on Engagement Toolkit for sponsor companies to apply to measure the impact of their own initiatives.

Prospective valuation modeling

The Clinical Trials Transformation Initiative (CTTI) funded a project in 2016 to model the value proposition of patient engagement. Project members included representatives from several pharmaceutical companies, Duke University and Tufts CSDD, and CTTI. The aim of this study was to apply a widely accepted financial modeling method commonly used by high-risk, R&D-intensive industries to guide portfolio planning and investment.

The model components include factors that drive project value or net return—such as the revenue generated following a successful commercial launch; the direct and indirect total development and commercialization costs; the cumulative development cycle time duration; and the probability of success due to technical and regulatory risk.

The CTTI team developed base-case models of typical Phase II and Phase III oncology development programs using benchmark cycle time, cost and risk data gathered, maintained and published by Tufts CSDD. The model outputs included both net present value (NPV) and expected net present value (ENPV) estimates. The former is defined as the after-tax, inflation-adjusted present value of incoming and outgoing cash flows, assuming regulatory approval and market launch.

NPV estimates vary depending on the outcome of clinical trials at each phase of development and the risk that each potential outcome represents. ENPV combines all of the individual NPV estimates to derive an average, aggregated, risk-adjusted measure.

Base-case NPV and ENPV measures were compared to those following adjustments to the model. Patient-centric initiatives are expected to improve the relevance and executional feasibility of study protocols and to enhance the study volunteer experience. The CTTI team assumed that select patient-centric initiatives (e.g., patient and professional advisory panels) may result in the avoidance of one Phase II or Phase III protocol amendment.

> Using the base-case model, the net present value for a typical successfully launched oncology drug increases dramatically: +$25 million if the impact is realized in Phase II and +$32 million in Phase III.

On average, according to a 2016 Tufts CSDD study, a single amendment adds 90 days to the development timeline and requires $141,000 and $535,000 in direct Phase II and III costs, respectively, to implement.

Using the base-case model, and assuming that a modest $50,000 expenditure to implement a patient engagement initiative will result in one less Phase II and III protocol amendment, the NPV for a typical successfully launched oncology drug increases dramatically: +$25 million if the impact is realized in Phase II and +$32 million in Phase III. The ENPV also increases substantially (+$15 million) when the protocol amendment is avoided in Phase III.

The ENPV increase in Phase II is more modest—+$4 million—since the measure penalizes earlier stage projects that will encounter later stage risk. Still, in all cases, a modest investment in a given patient engagement initiative that leads to the avoidance of a protocol amendment will yield a return on that investment many magnitudes greater.

The CTTI team also tested the prospective NPV and ENPV impact on patient engagement initiatives driving faster recruitment rates and higher retention rates. The results again indicate very high increases in NPV and ENPV based on modest investments. It's important to note that the model is not measuring the strategic value of patient engagement initiatives—such as improvements in relationships with patient communities and better long-term positioning within a given market.

The results of this prospective valuation model will soon be published in a peer-review journal. Refer to the CTTI website (https://www.ctti-clinicaltrials.org) to find this paper among a listing of papers published there.

Removing headwinds

For the majority of biopharmaceutical companies and CROs, patient engagement practices are in their early stages. The retrospective assessment provides initial baseline adoption data, resources, insights and case study-based impact measures. The prospective assessment offers a financial modeling framework that sponsors can systematically apply and test to inform their decisions to invest in and support patient engagement initiatives. Combined, these two studies may help alleviate the headwinds that many organizations are encountering.

— 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

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Q&A

DISRUPTIVE INNOVATION AND THE TECHNOLOGY STRATEGIES NEEDED

Applied Clinical Trials spoke with Christine Hurley, chief operating officer for 4G Clinical, a new entrant into the randomization and trial supply management (RTSM) space, about making the transition from the industry sponsor side, where she was most recently associate director of clinical systems and technology with Biogen Idec, to the supplier business. She also discusses the evolution and challenges of technology innovation and its implementation across the drug development enterprise.

Q: It's been over a year since you left the sponsor side for the vendor side. What is the most important thing you have learned—from either viewpoint—that you didn't know before?

That there is no single best technology solution, or strategy, for every company. What does that mean? While it might be considered an emerging best practice to use a particular type of technology to support a certain business process. For example, buying and implementing a centralized temperature deviation database to manage cold chain excursions. It isn't necessarily right for every organization to buy one at this moment to meet their business goals. In fact, it can have the opposite effect and be so disruptive to the business that it backfires and turns companies off to innovation.

When technology implementation fails, it is often perceived as a fault of the system itself, when it is more often a change management failure. I am a huge proponent of applying technology wherever you can, but it is essential that an organization develop a technology strategy that enables their business goals and prioritizes technology implementation carefully. It is crucial that technology vendors understand their clients' business and technology strategies and how their particular software fits into that strategy so they can best partner to help their clients succeed.

Q: When it comes to innovation, many seem ambivalent that it equates to real change or improvement. When do you know that an innovation is truly impactful? How is that measured?

I do think there is some weariness in industry about the term "innovation." I've heard many comments along the lines of "oh, everyone says their system is innovative or they are innovating"—what does that even mean? Impactful innovation in our industry at the highest level, to me, means directly improving the lives of patients. How do you measure that? Does your software significantly shrink timelines and speed up a business process? Does your software improve the quality of data collected, which then, in turn, speeds up data cleaning and analysis? When clinical professionals are in the critical stage of starting up a clinical trial, have we simplified things for them? Have we removed steps in the start-up process? Have we made something simple that used to be feared—or simply wasn't understood? The measure is a challenge for sure; if you can tie improvements to faster start-up timelines, you have a metric that everyone will relate to.

Q: It's well discussed that the pharma industry does not quickly embrace change. How can people get more accepting of technological change in clinical trials?

What immediately comes to mind is how crucial it is that technology is built on a deep understanding of the business process it is enabling. When offering technical solutions in the clinical space where your customers are clinical experts, not software development experts, it is paramount that the software support their processes. In order to provide a compelling argument that the technology will improve their process/jobs/time-to-patient impact, you have to demonstrate that you understand their processes and the challenges of their jobs.

This might sound simple but too often in this industry we see biotech and pharma organizations working their process around the system that they have and, inevitably, it doesn't work as expected, or worse, there are quality issues. In an industry as regulated as ours, successful technology change must start with business expertise.

Christine Hurley

Q: There are clinical trial processes or areas that are ripe for technology innovation, which is how your company launched in the RTSM area. Do you see other processes that could be positively changed with new approaches?

Absolutely. As you've said, our industry has a reputation for being slow to change, especially in the technology area, and certainly there are opportunities across all aspects of clinical development that we could consider automating or improving. A few trends/areas that I've been especially interested in this year relate to clinical sites. I've been fortunate enough this year to work directly with clinical sites to get their input into our RTSM product, and I can't stress how valuable that feedback is. Clinical sites, with tens of trials running at a time using multiple systems for each—all doing different things—layer onto that site processes that all must be followed independent of sponsor requirements.

After many years in the industry, it was truly eye-opening for me. One investigator, with about 30 years of experience, noted they had never been asked by a sponsor for feedback about the tools that they use. I think site engagement and communication related to clinical technology—both at start up and ongoing—is an area of deep possibility.

— Staff Report

Editor's note: Watch Christine Hurley discuss advances in clinical trial supply management on the ACT TV player on our homepage.

CLINICAL SITE MONITORING

FDA MOVES TO IMPLEMENT NEW SITE INSPECTION PROGRAM

FDA's Office of Regional Affairs (ORA), which manages the agency's 5,000 field inspectors, plans to "stand up" its much-anticipated Program Alignment (PAG) initiative by May 15. The aim is to implement this major reorganization of the FDA field force in fiscal year 2017, as promised. The new program will alter bioresearch monitoring (BIMO) of clinical research operations, as well as inspections of manufacturing facilities for drugs, biologics and medical devices.

The change involves shifting to a commodity-based, vertically integrated inspection program, with specialized inspection cadres for FDA-regulated products and inspection operations. ORA will maintain 20 district offices across the U.S.; some will concentrate on certain product areas, such as food or drugs, with additional specialists covering other areas. BIMO inspectors will be distributed among the district offices to meet program needs.

The PAG was announced in 2014, and FDA Centers issued PAG Action Plans in 2015 for shifting to the new structure. The initiative seeks to establish teams of specialized, highly trained investigators able to identify and respond effectively to questionable conditions and to provide more timely information on operations at regulated entities. There was talk of a PAG launch last November, and there remains uncertainty that it will move ahead now with a new commissioner heading up FDA and other new officials who may seek to review such a major organizational change.

ORA already has named senior-level program directors at FDA headquarters to oversee operations for six main product areas: food, biologics, drugs, medical devices, BIMO and tobacco, plus operations involving imports and ORA laboratories. Chrissy Cochran is BIMO program director, responsible for working with FDA product centers to establish and manage the new BIMO inspection program. Ginette Michaud is program director for products regulated by the Center for Biologics Evaluation and Research (CBER). Alonza Cruse is pharmaceutical quality program director and leads PAG collaboration efforts for drugs regulated by the Center for Drug Evaluation and Research (CDER) and by the Center for Veterinary Medicine (CVM). And Jan Welch directs changes affecting medical devices and radiological health. Each district office will have a director, plus program managers to head inspection cadres at that location.

— Jill Wechsler

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ONCOLOGY

THE MERGING OF CANCER RESEARCH & CLINICAL TRIALS

The convergence of cancer research and clinical trials holds an insurmountable weight in the healthcare realm during the 21st century. With new technologies rapidly evolving each day, the speed of research and trials is at an all-time high. This convergence has the ability to forge a new path in the ways innovations are encouraged and cures are secured.

Cancer research is sharpening the focus on how the industry may succeed in solving complex health problems, but requires that the clinical trial process must be changed. Several factors are coming to light that will color the way scientists should do research. Cancer treatment is the prototype for the new research model, as oncology gets most of today's research investment. According to the IMS Institute for Healthcare Informatics, cancer remains the biggest portion of the overall drug development pipeline in the earlier phases with four times the number of drugs in the pipeline than the next largest therapeutic class.

While cancer gets the most investment, fewer cancer drugs are progressing to Phase II and III trials, which indicates both the high levels of early-phase activity and the difficulties in generating successful results in the clinic, according to IMS. About 80% of cancer pipeline drugs are potentially first-in-class treatments and a portion are the first of their kind, according to the PhRMA Report on Medicines in Development. This means potential treatment options are becoming available and fewer of them are succeeding initially.

There are currently more investments and products in the funnel, resulting in oncology treatments that are new and novel. The issue is that there is not enough recent or real-time information available. Competition for patients is ever present, and attention and collaboration need to be up front in the research cycle to share learning for the benefit of the patient.

Breaking gravity on Cancer Moonshot

A prime example of this convergence is the Cancer Moonshot. Two advances are required to break gravity for this initiative. Both are directly related to collaboration. The first is organizational, removing the space between clinical practice and research. This involves agent availability and patient matching. The old paradigm of phased studies and sponsor-lead trials is being outpaced by the urgency of research and the availability of new potential cures, particularly with immunology and oncology. Now, there are multiple agents engaging multiple targets at each of those steps. Some agents accelerate the immune system (pressing on the gas) while others interfere with a tumor's ability to evade the immune system (releasing the brake). There are a multitude of hypotheses on not only how best to combine mechanisms, but also how to sequence them.

Allowing clinical research to move at the most efficient pace possible will require skilled researchers to have open access to all of the agents and the data, with current, evidence-based decision support. In combination, this will allow the best patient enrollment decision-making based on available evidence. Review risks and results as a collaborative team and communicate the evidence as quickly and as clearly as possible, without bias of commercial competition or who gets credit. The body of knowledge grows exponentially with clinical research and patient care.

Fully collaborative research

The traditional research model results in researchers working with one or two potential treatments, competing for patients and enrolling them in studies based on inclusion/exclusion criteria defined by the understanding of those products. A fully collaborative model allows researchers to understand all treatment options and have real-time data concerning patient profiles and outcomes, as the data is obtained. Screening, inclusion and enrollment decision support is tweaked with the constant receipt of new data, successes and failures. Enrolling patients in different treatments will be based on the most recent data across patients and treatment options, without limitations or sole focus on a few specific therapies. The commercial rewards can be addressed away from the Launchpad, based on outcomes as the picture of success emerges.

The timeline for sharing research results and presenting interpretation of the results is accelerated, as research plays out, not as it concludes. Again, the resistance to this earlier and open sharing is prevalent in the existing commercial model, where this information is shared later in the research cycle to avoid early exposure of results of product testing and allow time for competitive marketing. In some cases, sharing results following closure of the study is simply the traditional model for research where conclusions are made in summary. In the new world of the Cancer Moonshot, earlier sharing of results data is allowing everyone to see value in each therapy and either increase or decrease investment accordingly. This early sharing of data is also allowing therapies to be redirected to other targets, different cancers or chronic diseases.

The second revolution is a technical infrastructure that will allow identification of patients, enrollment and exchange of clinical data in collaboration. Implementing this infrastructure is no longer an innovation as much as it is using technologies that are already available to be used globally in broad collaboration. Patient registries, study enrollment criteria, site locations and potential treatment options all need to come together in a collaboration platform to make cancer research reach its fullest potential for positive outcomes.

Genomic data's role

Genomic databases currently exist for both patients and tumors as well. Individually, these data and tools exist and are accessible via the internet, fragmented in silos of commercial and public research. A concerted effort must be made to integrate solutions and aggregate data. Incentives can be drawn up to share data which leaves important players out of the equation.

The National Cancer Institute's (NCI) Genomic Data Commons (GDC) is a significant step in this direction. NCI's Center for Cancer Genomics (CCG) maintains the GDC, which requires contribution of genomic sequence data to the databank where the research is funded by the NCI and includes genotyping of patients and/or tumors. This data is anonymized to protect privacy of patients. It also holds a substantial amount of information on demographics, race and physiology which can be used to analyze disease and health patterns.

— Mark Vermette, Principal Consultant, Halloran Consulting Group

CLINICAL DATA MANAGEMENT

ACHIEVING END-TO-END TRACEABILITY USING TRACE-XML

Traceability is an essential element of data quality and a regulatory requirement for studies submitted to the FDA and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). Because a study's strength hinges on the integrity of source data as well as the quality and reproducibility of the processes used to generate the results, traceability plays a crucial role in reinforcing clinical research analysis results. In regulatory submissions, sponsors must demonstrate that the content of a submission database can explicitly trace back to the original source data in an unbroken chain, including any transformations or derivations that may have altered the data.

The Clinical Data Interchange Standards Consortium (CDISC) has developed the models, Operational Data Model (ODM-XML) and Define-XML, to represent metadata for data artifacts, such as case report forms (CRFs) and datasets created for use in clinical research. Define-XML is required as part of a standards-compliant, regulatory submission to the FDA and PMDA and plays a key role in establishing traceability for submission datasets.

Define-XML 2.0 provides most of the metadata needed to enable software traceability. Specifically, it provides descriptive metadata that displays the previous step in the clinical research data lifecycle. However, it does not provide the explicit references to source variables that would enable computable end-to-end traceability. Without these source variable references, automated end-to-end validation and traceability queries are not possible.

Trace-XML is a new extension to Define-XML v2.0, which delivers end-to-end, clinical data lifecycle traceability from data collection through final analysis. The Trace-XML extension enables standardized clinical study metadata to be represented as a graph, displaying the complete history of each data element to facilitate assessing audit trail completeness and correctness. The metadata supplied by Define-XML v2.0 and ODM-XML v1.3.2 includes the variables, datasets, sub-forms, forms, and computational methods that become the nodes in the graph representation of the study metadata.

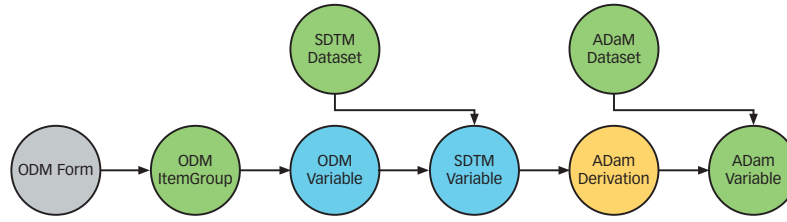

Figure 1. Conceptual example showing the type of Trace-XML content created for a variable trace.

Trace-XML adds the metadata needed to connect a variable, represented as a colored shape called a node, to its source as illustrated in Figure 1. It can retrieve much of the additional metadata needed to produce the explicit connections between variable nodes, called graph edges, from the CDISC SHARE metadata repository's forthcoming Application Programming Interface (API), or from SHARE exports.

Source variables and connecting edges generated by the Trace-XML software are derived directly from CDISC standards, enabling it to graphically illustrate how these standards are interconnected based on variables used across different standards and versions of those standards. Once the graph representation of the study metadata has been created, an analysis variable can be traced back to its source providing traceability across a full study.

For reviewers, Trace-XML allows end-to-end querying, validation, and visualization of metadata across the data lifecycle. Traces generated by Trace-XML can be referenced in Define-XML to package full lifecycle traceability in a regulatory submission. Moreover, Trace-XML can broaden the concept of end-to-end by beginning with eSource data (electronic healthcare records) and flowing through to analysis results. CDISC will make Trace-XML (the software and Define-XML extension) freely available on our web site in early 2017.

— Sam Hume, Head of Data Exchange Technologies, CDISC

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CLINICAL TRIAL OVERSIGHT

REVISED 'COMMON RULE' DROPS CUMBERSOME INFORMED CONSENT REQUIREMENTS

Clinical investigators, in most cases, will not have to obtain new consent from clinical trial participants to study their stored identifiable data or biospecimens, an important change from an earlier proposal for updating the federal government's "Common Rule" governing biomedical research. Instead, researchers will be able to rely on an initial broad consent for future research involving a subject's blood or tissue, according to the final update to the Common Rule affecting the Department of Health and Human Services (HHS) and 15 other federal agencies (see https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects).

The revised final Rule drops a number of controversial policies included in a rulemaking proposal issued in September 2015. Researchers and patient advocates filed more than 2,000 comments on the plan, with scientists and investigators raising strong objections that certain new requirements would impose added regulatory burdens on research institutions and study sponsors.

Patient privacy advocates had championed a requirement that researchers obtain written patient consent before using any biospecimens obtained during earlier medical procedures to protect individual privacy. The aim was to prevent situations where an individual learns later that a specimen was used in research without their knowledge, as in the infamous Henrietta Lacks case involving unauthorized use of cancer cell tissue in the 1950s without permission or patient knowledge.

To avoid excessive roadblocks to future research, however, the updated Common Rule drops the need for added informed consent for research involving non-identified biospecimens. And it continues to permit investigators to obtain waivers to consent requirements.

The revised Rule further clarifies that informed consent must include a clear description of a study, its risks and benefits, and appropriate alternative treatments. And it requires researchers to inform patients if a study might include whole-genome sequencing, which could be used to identify donated specimens.

But a clear aim is to reduce the length and complexity of consent documents to help research subjects make informed choices about participation in a study. The government "is very hopeful that these changes and all the others that reduce unnecessary administrative burdens will be beneficial to both researchers and research participants," commented Jerry Menikoff, director of the HHS Office for Human Research Protections.

In addition, the final Rule supports the use of a single institutional review board (IRB) for multi-institutional research studies and reduces the need for additional IRB approval on future research where consent had been obtained earlier.

— Jill Wechsler

CLINICAL RESEARCH NETWORKS

BOOST FOR CLINICAL RESEARCH FROM EUROPE'S NEW REFERENCE CENTERS

Clinical research into rare respiratory disorders is likely to get a boost from a new grouping of specialists in more than 60 centers across Europe. The "European Reference Network on Rare Respiratory Diseases," which has just won formal approval under a European Union funding scheme, is creating a five-year program of activity that includes maximizing the efficiency of clinical trials in Europe.

Initially, the network, known as ERN-LUNG, will aim to create an infrastructure to promote research in the different sub-themes of rare respiratory diseases that it is focusing on. "Recruitment of sufficient numbers of patients for clinical and other investigations or availability of data or bio-samples will be eased dramatically," it predicts.

ERN-LUNG will particularly target pulmonary hypertension, cystic fibrosis and other forms of bronchiectasis, primary ciliary dyskinesia, alpha1 antitrypsin deficiency, interstitial lung diseases, mesothelioma, and chronic lung allograft dysfunction. In each of these areas it has brought together acknowledged expert centers in 12 European countries—mostly university hospitals—to make the best use of them in providing care to the scattered population of patients with these conditions. The project also has input from patient organizations, policymakers, foundations, trade organizations, and ethics specialists.

In each of these sub-themes, support will be given to ongoing clinical trials of new drugs or other therapeutic interventions. A specialized committee on research and clinical trials "will make best use of the extremely positive experience of several of the pre-existing networks (CF, PCD, AATD, nonCF-BE) in pushing new orphan drug development forward, by establishing clinical trials networks in collaboration with the European Clinical Research Infrastructure Network," says the network. It will also develop tools and training for protocol review for doctors and patients. In addition, each sub-theme will be encouraged to develop registries, and close links have been established with the European platform for rare disease patient registration, at the EU's joint research centre in Ispra, Italy.

The grouping is one of 23 similar networks that the EU will pump more than $20 million over the next five years. Each will explore a broad area of a rare disease cluster. In addition to ERN-LUNG, other networks (with equally catchy acronyms) cover different aspects of cancer—in adults with solid tumors, genetic tumor risk syndromes, or pediatric cancer with a focus on haemato-oncology. Some will deal with craniofacial or congenital anomalies and malformations, organ transplantation in children, skin or metabolic disorders, endocrine conditions, or epilepsies.

— Peter O'Donnell

NEWS NOTES

J&J TO ACQUIRE ACTELION, SPIN OUT NEW R&D COMPANY

Johnson & Johnson and Actelion Ltd. entered into a definitive transaction agreement last month under which J&J will acquire the Swiss biotechology company for $30 billion. As part of the deal, Actelion will spin off its drug discovery operations and early-stage clinical development assets into a new Swiss biopharma company, which would be listed in Switzerland.

In a bid to become a leader in medicines for rare diseases, J&J, the world's biggest maker of healthcare products, adds Actelion's specialized focus in developing treatments for pulmonary arterial hypertension, or high blood pressure in the lungs.

JDRF launches early-stage investment fund around type 1 diabetes

JDRF, the leading global organization funding type 1 diabetes (T1D) research, unveiled the launch of the JDRF T1D Fund, a new venture philanthropy vehicle that is the first and largest of its kind devoted to identifying and funding early-stage high impact T1D commercial opportunities in active partnership with venture and industry capital sources. The fund is inititated with a $32 million investment commitment from JDRF, plus about $10 million in pre-launch contributions from donors.

Given the recent passing of Mary Tyler Moore, who was the international chairman of JDRF since 1984, the creation of the T1D Venture Philanthropy Fund takes on added importance. There are 1.25 million Americans currently living with T1D, a figure that is expected to rise to five million by 2050. There is currently no way to prevent or cure the disease.

Tufts CSDD study explores low recruitment rates

A recently published analysis by the Tufts Center for the Study of Drug Development (CSDD) stated that physicians and nurses only refer a fraction of their patients for clinical trials. The study also found that this result reflects failure by sponsors, CROs, and investigative sites to engage healthcare providers as partners in the clinical research process.

The study, based on a survey of 2,000 physicians and nurses primarily in the U.S. and Europe, found that nearly all physicians (90%), and the majority of nurses (70%) feel "somewhat" or "very" comfortable providing and discussing clinical trial information with their patients, but physicians refer less than 0.2% of their patients into clinical trials, and nurses refer even fewer.

Other key finds include: Physicians and nurses cite the inability to access information and insufficient information and time as key reasons for not referring patients into trials; only 9% of physicians and 2% of nurses say fear of losing patients influences their decision not to refer; and physicians in clinical practice are 2.7 times more likely to refer their patients into clinical trials than physicians in hospital-based settings.

EMA issues summary of 2016 highlights

The European Medicines Agency (EMA) published a four-page document to summarize its main achievements relating to marketing authorizations of new medicines and the safety monitoring of authorized drugs during 2016. The following items are highlighted in the report:

- The agency's Committee for Medicinal Products for Human Use (CHMP) recommended 81 medicines for marketing authorization, including 27 new active substances. A total of 17 out of the 81 had an orphan designation.
- Seven medicines received a recommendation for marketing authorization following an accelerated assessment.
- Eight drugs received a recommendation for a conditional marketing authorization, one of the possibilities in the EU to give patients early access to new medicines.
- 59 extensions of indication were recommended in 2016.

Cancer Research UK joins ACRP standards group

Cancer Research UK has become a member of the Workforce Development Steering Committee of the Association of Clinical Research Professionals (ACRP). The group's main goal is to review and approve core competence standards for clinical research professionals. Its members comprise industry and academic organizations across the global clinical research sector.

As its first initiative, the committee will request public comment on a competence framework for clinical research associates (CRAs). The framework will define standards for clinical trial monitors/CRAs within the eight core competence domains for clinical research professionals, as defined by the Joint Task Force for Clinical Trial Competence.

Astellas signs up for Access Accelerated

Astellas Pharma is the latest company to announce its participation in Access Accelerated, a global, multi-stakeholder initiative to advance access to non-communicable disease (NCD) prevention, diagnostics and treatment in low-income and lower-middle income countries. Access Accelerated comprises 22 pharma companies, who, in collaboration with the World Bank Group and the Union for International Cancer Control (UICC), will work toward the United Nations Sustainable Development Goal target to reduce premature deaths from NCDs by one-third by 2030.

Takeda to acquire Ariad Pharmaceuticals

Ariad Pharmaceuticals Inc. accepted a $5.2 billion takeover offer from Japan's Takeda Pharmaceuticals Inc. in a deal that will bring two innovative targeted therapies to Takeda's existing oncology portfolio. Takeda will leverage Ariad's R&D capabilities and platform, and largely absorb its R&D costs within Takeda's existing R&D budget. The deall will also broaden the Japanese company's portfolio of hematology drugs.

Almac Group launches Almac Clinical University

Almac Clinical Technologies, part of the Almac Group, has launched Almac Clinical University, a web-based training and educational platform designed for clinical development professionals. The platform offers a library of resources for industry best-practices and current challenges.

— Staff and wire reports

A Practical Overview of Patient-Centric Trials

Hélène L. Svahnqvist, Anna Skabeev

A how-to guide for clinical trial managers in implementing patient-centric approaches using today's clinical study model.

PEER REVIEW

Clinical trials often serve as the first point of interaction between a patient and a sponsor company. Nevertheless, clinical teams can lose sight of this fact when designing the technical components of clinical studies. The outcome can be cumbersome trial protocols adding unnecessary burden on patients already in a challenging situation, and, therefore, unhappy patients, low recruitment and high dropout rates, as well as low scores on company perception surveys.

The intent of patient-centric clinical trials is to lessen the burden of participation by making the participant journey as convenient and pleasant as possible, and, therefore, help in addressing the issues above.

While terms such as "patient centricity" and "patient-centric trials" have become industry buzzwords and made their way into various publications and oral presentations, there is still much to do when it comes to implementation. The aim of this article is to provide practical overview on what clinical trial managers (CTM) can consider in their work to take a step toward patient-centric trials today using the current clinical trial model.

A Typical CTM experience

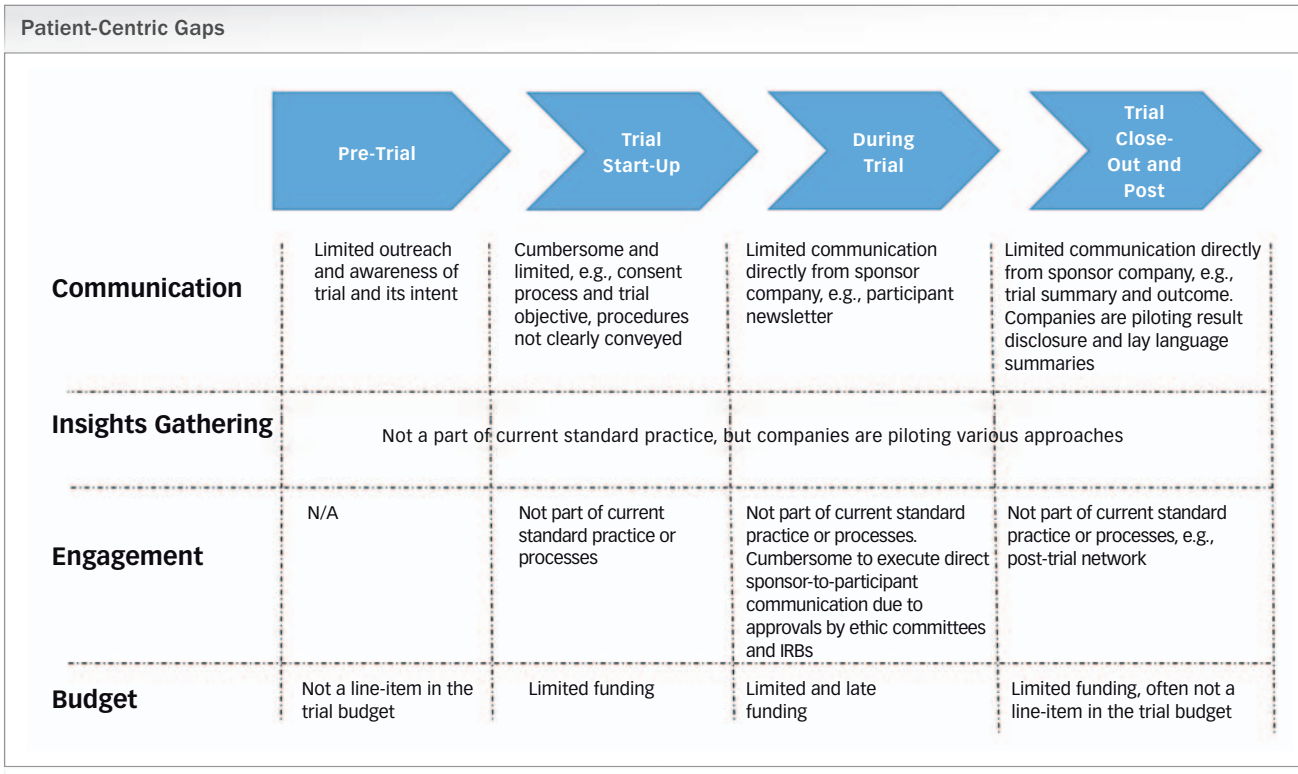
In a theoretical example, a CTM is accountable for a high-profile trial within a new therapeutic area for their organization. The company's 2017 corporate goal is continuously on display throughout the office: "all staff are to implement goals and measures related to patient's satisfaction and loyalty." By measuring patient satisfaction across the organization, executive leadership anticipates the establishment of a baseline understanding of how the company is perceived by its most important stakeholder, the patient.

It is easier said than done: the only patient satisfaction data you have, in this example, is from an orphan drug Phase III trial a year ago, in which retention rates were disappointingly low. Participants complained of challenging visit schedules and poor communication of the trial intent, design, and outcomes. Consequently, the study was delayed and over budget. Most companies have looked only at cost, timelines, and quality of results, not patient or site experience. But patient and site experience plays an important role in all of these factors. You want to execute a successful trial by implementing a more patient-centric approach. How can you make the clinical trial journey more efficient and less cumbersome for the participants and clinical staff?

Figure 1 (see facing page) illustrates gaps in the trial continuum from a participant perspective. By adequately addressing the gaps at every phase of the process, a CTM can help ensure that their trials are designed in a way that is not just scientifically rigorous, but also incorporates patient perspectives.

Plan ahead

Improvements in patient-centricity can be made throughout drug development and life cycle management, from trial planning activities to product launch. Trial planning activities may include live protocol simulations, patient advisory boards and other ways of soliciting patients and caregiver input on what a trial should include, and protocol review committees with key cross-functional stakeholders outside the organization (including patients and patient advocacy organizations). Some companies use crowdsourcing at the protocol development stage to gain patient insights on the protocol, including endpoints and procedures. By thorough planning that prioritizes the



Source: Modified March 2016, by Kenneth A. Getz, Patients as Partners Conference

Figure 1. Overview of typical clinical trial phases and examples of patient-centricity gaps throughout.

participants' trial experience, CTMs can help ensure that they are considered stakeholders in the trial experience and results.

The quality, timelines, and, therefore, the cost of a trial is significantly affected by the commitment of the participants to achieving a successful trial. This commitment increases with a deeper understanding of trial requirements, and, thus, willingness to follow all trial routines, such as regular attendance of trial visits, timely and detailed reporting in patient diaries, and the quality of patient-reported outcomes. Although the FDA has not developed specific guidance on all possible aspects of patient-centric trials, the agency does emphasize the importance of incorporating patient perspective in the development and evaluation of new medicines and has several patient engagement initiatives underway.[1]

Incorporating the patient perspective into trial planning and activities is not an easy task that can be done by the CTM alone. However, unless an organization has a function dedicated to patient-centricity, the CTM will need to be the driver and ensure that the appropriate internal and external stakeholders are at the table. The person may also need to assist in the development of guidance and policies for his or her organization, particularly regarding compliance and the selection of third-party vendors. Success depends on the support of multiple groups in the organization, including legal and compliance, regulatory, corporate communications, medical research, and medical affairs. Outside the company, buy-in from external patient advocacy groups and clinical trial sites will be needed to complement the company's support. If a CTM runs their study with a contract research organization (CRO), it, of course, will need to be involved from the get-go.

Unless an organization has a function dedicated to patient-centricity, the CTM will need to be the driver and ensure that the appropriate internal and external stakeholders are at the table.

For maximum impact, the CTM can do the following:

- Review patient-centric approaches used by other companies in the same therapeutic area: what can you earn from current practice and outcomes?
- Mindfully assess eligibility criteria to ensure they are not too restrictive
- Make the consent process interactive

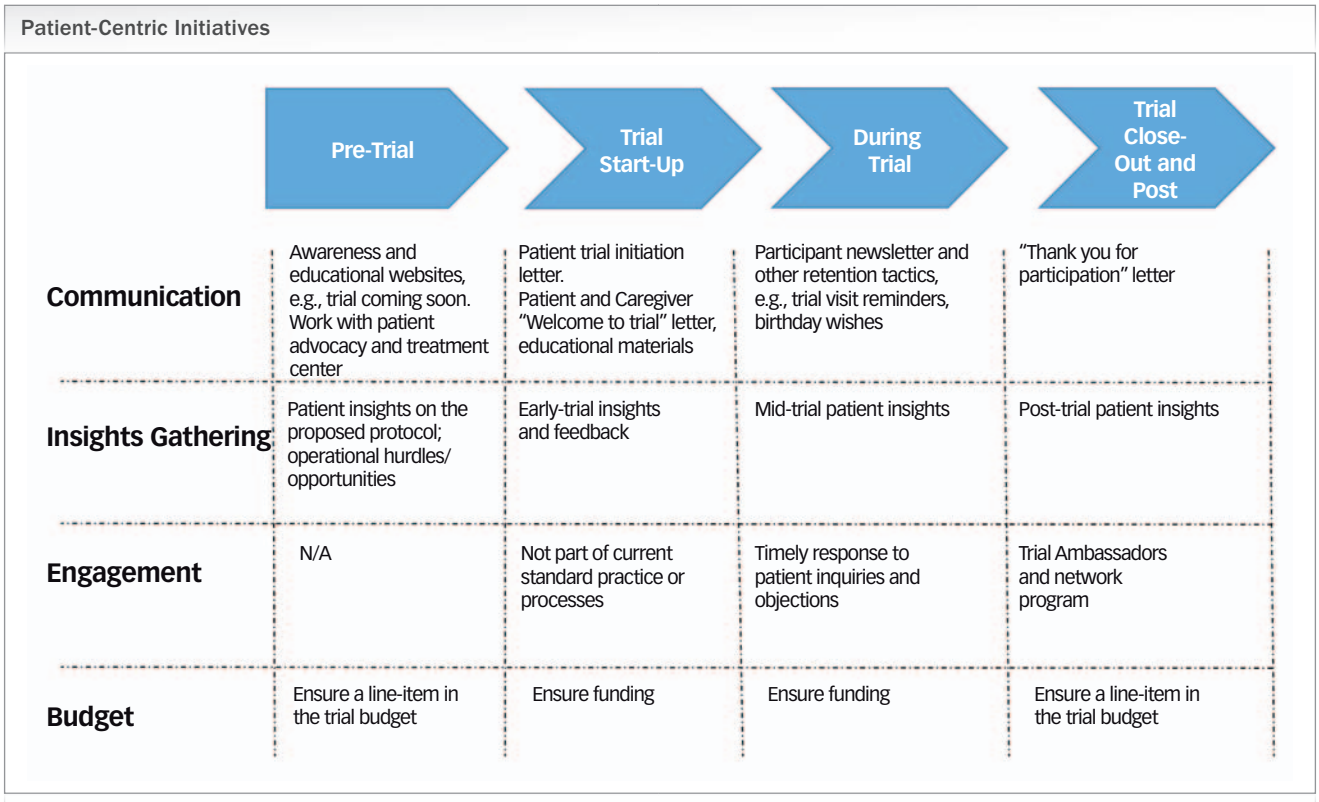


Figure 2. Overview of typical clinical trial phases and examples of patient-centric initiatives to incorporate throughout.

- Mitigate unnecessarily complex protocols by involving the patient in the design process
- Start the clinical trial planning process early, ideally 10 months prior to trial launch, to ensure time for refining and implementing the patient-centric approach
- Build in additional time and budget for training of site staff
- Track the changes that incorporating a more patient-centric approach makes to timelines and budget
- Collect evidence to make the business case for patient-centric measures to your supervisors: enrollment and dropout rates, budgets, timelines
- Above all, consider the clinical trial patients' journeys—how patients are making their decisions about trial participation—throughout the planning process

During the planning process, cultural differences should be considered. In the era of global clinical development, patient communication and trial materials must be created with cultural differences in mind and available in multiple languages. Better results at local sites will be achieved if staff are empowered to put necessary customizations in place. Patient registries can also help sponsor companies improve the post-trial relationship with participants. The role of a global CTM is to work with local colleagues to ensure these nuances are considered throughout the clinical trial phases.

Throughout trial start-up, recruitment, and retention, thoughtful communication with participants is essential to the establishment of patient-centric practice. Before the trial even begins, companies should publicize the trial appropriately, through government websites, patient advocacy and treatment center websites, and, as appropriate, mass advertisement.

> Only the CTM will know if their job satisfaction is improved by implementing a more patient-centric clinical trial approach.

Take the lead

Make your sites partners in the trial by soliciting their input and providing training and materials before recruitment begins. Their role is critical; they can make the journey for the patient less complicated and more rewarding. From the start, remind your sites to convey the concrete benefit to a participant in culturally-appropriate ways: that he or she is often getting even more attention and oversight of their

care while they are in a clinical trial, even if they receive the placebo. Schedule regular patient experience evaluations in addition to standard clinical assessments. The CTM can help ensure that the sites (with the support of the sponsor) can provide input on local culture and have the materials they need to include participants as active partners in advancing critically important research. Acting mindfully, a CTM has a chance to help sites make participants true partners in the trial process.

Above all, emphasize that two-way communication between site and participant is the priority. This principle should inform the "toolkit" a CTM provides to their sites so that they can do the following effectively:

- Get participant feedback before executing by asking questions about scheduling, etc.: "Will this be onerous for you?" Sites need to look several steps ahead to allow for patient schedules (work/family)
- Set participant expectations: these are the responsibilities and rights as a participant. Always offer to include the participant's caregiver (if any)
- Discuss and explain protocol endpoints and other scientific aspects of the trial with participants before, during, and after the trial
- Explain expected protocol operational hurdles and opportunities to participants; solicit their advice on addressing these issues
- Ensure that the sites have easy means of providing feedback throughout the trial. Timely feedback can help the CTM and sites address unforeseen problems that arise before the trial is negatively impacted
- Explain that it is the participant's responsibility to keep the study blind. They are essential members of the team
- Cultivate patient loyalty: anticipate their questions and objections and have answers ready in lay language

Retain participants

Once the trial is underway, similar strategies and tools can improve patient retention. In addition to providing standard appointment reminders, CTMs can use e-diaries, wearable devices, and even "bring your own devices" (BYOD) to make participation easy, collaborative, and interactive.

BYOD allows participants to use their own devices, like smartphones and tablets, to complete study assessments, such as monitoring daily activity and collecting patient reported outcomes (PRO) and quality of life data. The BYOD devices approach may also be used to enhance communication with study participants through easy and virtually no-cost measures, such as sending out study visit reminders or sharing individual trial data.

BYOD has recently been evaluated, by Bracket, in a Phase II Parkinson's disease clinical trial. Results were presented at the Annual DIA Meeting in June 2016. Participants used an application that included a mix of surveys and tasks. The active phone sensor collected and tracked their progress. Over the course of the study, adoption went up and, by the end of the trial, 80% of the data was submitted via the app. Adam Butler, Bracket's Senior Vice President for Strategic Development, expects to see a "tipping point of very heavy adoption" of BYOD in clinical trials over the next three to five years.[2]

Participants that feel involved in the process through these strategies may even offer more and better feedback. With sufficient funding and staffing for the sites, CTMs can go even further by incorporating home visits by site staff and/or healthcare professionals. Including these strategies in trial design can help CTMs create and manage patient-centric programs that can lessen the burdens on the participants and improve results.

Once participants are chosen, communication toolkits for the sites can help staff establish a more personal relationship between patients and the company through basic low-cost components such as a welcome letter and information about the trial in lay language. Other ways in which the CTM can improve the participants' experience include the following:

- Engagement and community building, via patient associations, face-to-face advisory boards via third parties, surveys, social listening, and other channels
- Communication (through the sites)
  - o Participant newsletters and brochures written in lay language
  - o Talking points for the sites to supplement these materials
  - o Online communities

As simple and inexpensive as these measures are to execute, surprisingly, most companies do not provide them to participants consistently. CTMs can step up and fill this gap to begin establishing a patient-centric experience for participants from the first interaction.

> Creating clear metrics to evaluate patient-centric methods is fundamental to track organizational improvements in this arena.

Close out and follow up

Carrying the patient-centric principle through the post-trial period is critical. CTMs can play a role managing this process. For example, a simple "thank you" for trial participation can go a long way and help a patient consider participation in a future study. Sharing trial results in a lay language improves the company-participant relationship. It is also the right thing to do from an ethical point of view. Still, most patients do not receive information regarding the outcome of the trial they participated in or of the important role that they played.

Patient-centricity may lie beyond the scope of a typical development program. Collecting real-world, long-term data is critical and can be achieved via patient registries. While the idea sounds simple and not new, there are still a lot of questions when it comes to how. The Clinical Trial Transformation Initiative (CTTI) has a work-stream underway to develop recommendations with the aim to increase use of patient registries in clinical research.[3]

Measure outcomes

The main intent of assessing these measures is to understand the percentage of participants touched by patient-centric tactics. This will

Management Check

Checklist / Questions	
✓	Did I assess the clinical trial market place, including sites, patients, and competition early on in the process (~10 months prior to study start)?
✓	Did I describe the clinical trial patient journey (assess how patients are making their decisions about trial participation)?
✓	Did I ask potential participants for input on protocol hurdles and opportunities?
✓	Did I implement good communication patient practices (GCPP) throughout the study and did I thank the participants/patients at the end of the study?
✓	Did I collaborate outside my function?
✓	Did I leverage learning?

Source: Svahnqvist, Skabeev

Table 1. Questions for clinical trial managers to consider during the study process to make trials more patient-centric.

guide CTMs for upcoming trials by identifying what innovations work best. A CTM can also, at the end of a trial, ask for direct feedback from participants, via a third party, on the patient-centric activities that were implemented. Keep in mind that you might see cultural and regional differences for which you should account in reviewing results. The following participant information from the sites can help a CTM understand results, refine techniques for future trials, and report learnings to colleagues:

- Percentage provided insights on protocol, endpoints, and operational hurdles to overcome
- Percentage educated about the general trial journey and the one they are to consider joining
- Percentage informed about trial progress
- Percentage that were part of a trial community
- Percentage that received a thank you from the sponsor via the site
- Percentage that received lay language summary reports of trial outcome via the sites

Follow-up by sites, with a CTM's guidance, can include the following:

- Identifying areas in which participants need further education on the clinical trial journey in general and for the protocol specifically
- Conducting participant surveys during and after the clinical trial

Creating clear metrics to evaluate patient-centric methods is fundamental to track organizational improvements in this arena. We recommend that the CTM select just a few measures to test at a time so that yearly comparisons can be done with trials within and outside their organization. The CTM's findings can then showcase the successes and, thereby, influence practice throughout their organization, and, potentially, the industry.

> CTMs can make a difference not only for the stakeholders involved in clinical trials but also to set the stage for their organizations to be viewed as companies that are truly putting patients first.

Performance measures

The following are some major areas for CTMs to consider measuring to assess trial progress and success:

- Performance measures (time, quality, and cost)
- Participant/patient-reach measures, assessed via sites
- Participant/patient satisfaction

We recommend that the CTM collect and share these data points to compare studies that are implementing a patient-centric approach vs. the ones that are not:

- Number of protocol amendments
- Number of trial design challenges
- Retention and discontinuation rates

- Return on investment, measured via cost per patient; speed of recruiting; and speed achieving last patient In (LPI) and last patient out (LPO)

Feedback measures directly from participants are useful indications of their overall satisfaction with their individual trial journey. We recommend that CTMs incorporate this feedback when assessing the effectiveness of the patient-centric measures that they implement. For example, surveys of trial participants throughout the study are good ways to track progress. These should be done (preferably by an independent third party) at these points in the trial:

- Start of study
- Mid-point of study
- End of study—especially important to understand overall satisfaction with the trial experience
- Net Promotor Score (NPS), which illustrates overall satisfaction with participating in trial "x." Measures whether participants would recommend participation in a similar trial to other patients

It is important that CTMs incorporate the feedback into the trial process in a timely manner. For example, as part of the first survey taken during the study setup, CTMs might learn that the consent process is complicated and the educational material provided to the patients is too detailed. CTMs can take immediate action to improve the participant's experience by adjusting these processes and materials for the current and next trial.

Only the CTM will know if their job satisfaction is improved by implementing a more patient-centric clinical trial approach. We hope that this approach results in "wins" for the CTMS, the clinical trial participants, the site staff, and the trial leadership within the sponsor company.

Discussion

For clinical trial research, patient-centricity efforts should focus on how to deliver a higher level of engagement and involvement as participants enter into and progress through the trial journey. Ideally, these measures will lead to a less burdensome experience for participants and site staff, creating higher satisfaction, improved data quality and overall performance, and loyalty and trust for the sponsor company.

Patient-centric clinical trials are here to stay. To ensure that sponsors and clinical teams will make this approach an integral part of their work, CTMs can start assessing and proposing an array of patient and caregiver engagement and communication processes and initiatives for their trials.

Table 1 (see facing page) summarizes key questions for CTMs to consider during the study process to make trials more patient-centric.

Anticipated benefits

By incorporating a patient-centric philosophy throughout the development process, the CTM may expect the following benefits that reflect improved satisfaction among site staff and participants:

- Improved collaboration and trust among sponsor, site, and participants
- Improved compliance
- Quality/reliable data and feedback
- Improved patient retention
- Favorable timelines, getting medicines to patients in need faster, and reduced budgets
- Building a learning organization adaptable to stakeholder needs
- Work satisfaction (CTM/trial team)
- Competitive edge vs. trials/companies who are not implementing a patient-centric approach

Summary

CTMs will need to be the driver and implementer of patient-centricity for clinical trials. As described in this article, to be successful, CTMs will need to accomplish the following:

- **Plan ahead:** Early in the development process, map out ways in which all stakeholders, from participants to sites and internally, can make trials more patient-centric
- **Track your progress:** Incorporate ways to measure improvements in patient centricity so that you can monitor, and eventually demonstrate, success
- **Drive the process:** Provide your sites with training, resources, and encouragement for their implementation of patient-centric protocols
- **Engage your participants:** From welcome packets to thank-you letters, support the creation of simple, low-cost innovations like patient associations, surveys, and literature in lay languages
- **Develop/implement performance and feedback measures**

The term, "patient-centric trials" has been out there for some time; however, few companies have implemented the approach throughout the development arena. Why not be one of the pioneers in the field? CTMs can make a world of difference not only for the stakeholders involved in clinical trials but also to set the stage for their organizations to be viewed as companies that are truly putting their key customers—patients—first.

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Improving Patient Engagement through eCOA

Susan M. Dallabrida, PhD

How the adoption of electronic clinical outcome assessment in trials can drive increased communication and patient reporting of events.

PEER REVIEW

The use of electronic clinical outcome assessment (eCOA) represents a mechanism of capturing both patient and clinician reported outcomes digitally instead of on paper. The most common use of eCOA is for data capture in clinical trials. The evidence for obtaining improved data quality with digital systems over paper has grown substantially and as such, avenues for using eCOA in healthcare are being explored. eCOA captures data on handheld smartphones, tablets, browsers, interactive voice response systems, and patient's own devices (bring-your-own-device, or BYOD), using secure systems that meet regulatory guidelines for electronic capture of clinical data. Consent for clinical trials details patient privacy, explains how the trial will be conducted, and confirms that the clinical site owns all clinical research data. The patient may authorize trial access to their lab, imaging, and electronic medical record (EMR) data for integration with their study data.

As adoption and the use of eCOA grows, additional learnings have provided a more complete understanding of how to use it effectively in order to derive the benefit of improved data quality. Herein, we will discuss the evidence of how the use of eCOA can promote increased communication between patients and clinical staff, increase patient reporting of events, and how tools such as training and patient engagement should be implemented to deliver maximal benefits from the use of technology. Collecting high quality data for clinical research requires a blend of clinical science and technology. Clinical science influences patient engagement behaviors with study design, collection schedules, predictive instruction, and assessment selection.

Patient-site communication

As more questions arise about improving patient engagement in clinical trials, many sponsors are finding that the answers may lie in the use of technology. Most pharmaceutical companies are considering methods for implementing novel technologies (e.g., activity trackers and mHealth devices) in their trials, in order to maintain better, more consistent interaction with study subjects. Many of these devices are still in proof-of-concept testing. Whether they will find their place in clinical research will be the decisions of global regulators. The US 21st Century Cures Act mandates that FDA regulate accessories based on their intended use, instead of based upon the parent device with which the accessories are associated.

What many sponsors may not realize is they already have access to regulatory-approved technology that can address current patient engagement challenges. Researchers will find that the use of eCOA not only improves data quality, but also offers the potential to improve patient engagement during clinical development.

The benefits of capturing high quality clinical trial data via eCOA have been widely recognized for more than a decade. Researchers have documented significant improvements in patient protocol compliance and data quality, a reduction of missing data and data "noise," and, most importantly, increased study power with fewer patients.[1]

Here we review some of the well-established literature demonstrating how eCOA can also improve patient/clinician communication and candor vs. traditional paper-based COA, helping sponsors to keep patients better engaged during clinical development.

Patient/clinician interactions

eCOA prompts and increases patient/clinician interactions and enables subjects to think through their symptoms prior to meeting with site staff. As a result, patients are more likely to bring up clinical events in discussions with the clinical site, since the eCOA completion prompts their memory of additional details. For example:

- In a head-to-head comparison of electronic vs. paper completion using the EORTC-QLQ-C30, 48.9% of the symptoms reported electronically were addressed at the clinic visit vs. only 23.6% on paper.[2]
- In a study of 660 cancer patients, patients were given touch-screen tablets to complete electronic self-report assessments, which included items on symptoms and health-related quality-of-life. The results indicated that electronic patient-reported outcome (ePRO) reports to clinicians fostered discussions with patients at visits, clinicians were more likely to discuss issues flagged by the automated system at visits, and visit duration was unaffected.[3]
- Electronic COA ensures that every patient is asked the same questions in the same order at every visit without bias, halo, error, leniency, variation, interpretation, or mood. These electronic data are then available for site staff to intervene, augment, and guide care.

Reporting of more (and more severe) events

eCOA has been proven to increase patient candor. Patients are more likely to report more (and more severe) events electronically than on paper. This principle applies across a spectrum of indications and is generally applicable to patient-reported data. Patient reporting on diverse topics such as medication compliance and blood glucose levels are common examples.

- Diabetes subjects under-report hypoglycemic and hyperglycemic events on paper COAs 67% of the time.[4] Further, diabetic patients using paper COA capture blood glucose values but fail to record them. A systematic review encompassing 11 diabetes studies showed that among these three categories of errors, nearly 50% of paper COA data was inaccurate.[5] Electronic COA mitigates any such errors because the blood glucose readings being captured via fingerstick monitoring are wirelessly transmitted to the eCOA device.
- Several studies examined the impact of electronic and paper patient diaries on glycemic control and HbA1c levels. These studies found that increased monitoring in the electronic version may have encouraged positive behavioral changes and/or provided additional information on which patients could take action to improve their glycemic control. The use of a mobile electronic diary vs. conventional clinic visits were compared in patients from a diabetes clinic in a 12-week crossover design study.[6] In the electronic diaries, subjects recorded meals and blood glucose levels, then received immediate feedback on their nutritional intake. There was a significant improvement in HbA1c for the time that subjects were using the electronic diary vs. the control period (HbA1c levels reduced 0.83%). Overall, the authors concluded that use of eCOA improved HbA1c levels.
- In another study comparing paper vs. electronic diaries, HbA1C levels decreased more in the electronic than the paper group. Furthermore, those who reviewed their electronic screens with their healthcare providers tended toward better glycemic control than those who did not.[7]
- The eCOA diary has proven to be an important and better tool than paper for patients and healthcare providers to improve clinical care. Good control of blood glucose levels is well recognized as a key element to attenuating disease progression for patients with diabetes. Studies show that for each percentage point decrease in HbA1c, microvascular complications are decreased by 35%.[8]

Suicidal ideation and behavior

Self-reported electronic data capture (EDC) enables increased patient candor in suicidal ideation and behavior. Patients are more likely to reveal a higher frequency and severity of symptoms than ascertained by site interviewers. These phenomena are also well documented for topics including sex, drug/alcohol abuse, obesity, HIV, and mental health.

- In major depressive disorder and bipolar disorder, self-reported questionnaires were two to four times more likely to reveal higher frequency and severity of suicidal ideation than clinician-ascertained.[9] In an eight-year study in children and adolescents, 98 families were followed (ages 5-18). Subjects completed a youth clinical interview and youth self-report assessments on suicidal ideation. Reports of suicidality were higher for the self-report group (25% and 30% in the younger and older cohorts, respectively) than the interview version (11% and 24% in the younger and older cohorts, respectively).[10]
- 68 patients admitted to a hospital or treatment facility for treatment of mood or anxiety disorders completed the Beck Depression Index (BDI) and clinician interview. Nine (18%) of the 50 participants who responded positive on the BDI were rated by clinicians as negative for suicide ideations following the face-to-face interviews.[11]
- Primary care physicians reported that an online electronic monitoring tool helped with engaging their patients because their patients were more willing to share how they were feeling in terms of symptoms, side effects and their suicidal ideation online. This enabled the clinicians to better address their health issues.[12]

> Researchers have documented significant improvements in patient protocol compliance and data quality, a reduction of missing data and data "noise," and, most importantly, increased study power with fewer patients.

Compliance and engagement

There is considerable evidence that using eCOA instead of paper is a mechanism for achieving improved compliance with patient reported outcomes collection.[13] In addition to providing greater accountability

The Patient Training Imperative

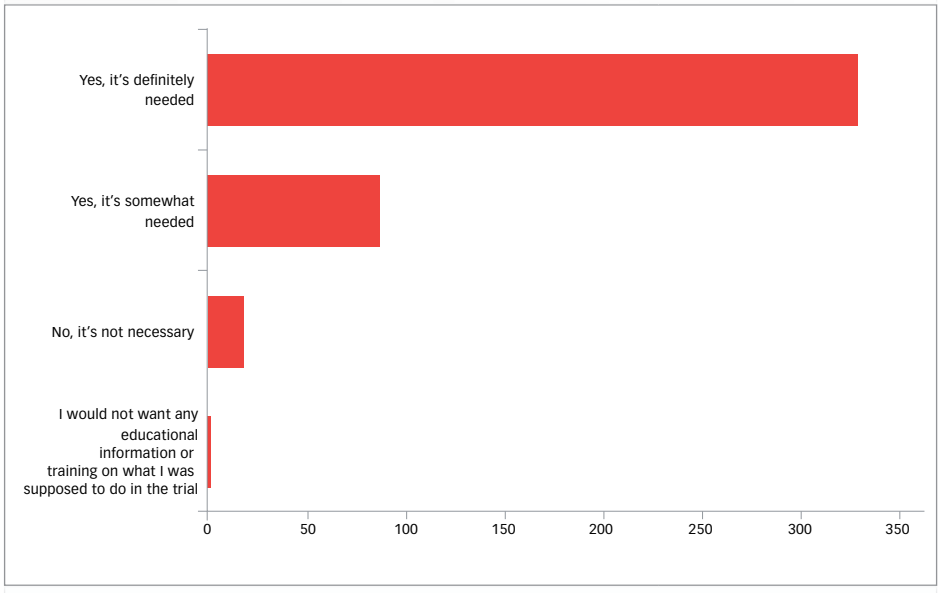

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Figure 1. Prospective patients were asked, "If you were participating in a clinical trial, do you think it would help to be provided educational materials and training on your role in it, what to expect, and the purpose of the study?"

in reporting, electronic media is noted by patients in general as more engaging compared to paper. For example, patient preference for using eCOA technology over paper has been shown across therapeutic areas and demographics; whether a population is technologically savvy or not, there is universal preference for using eCOA over paper. This is noted in published studies such as in oncology,[14,15,16] diabetes,[17,18] headache,[19] inflammation/arthritis,[20,21,22] pain,[23] respiratory,[24,25] and gastrointestinal disorders.[26]

Training needed for patients, caregivers, and clinical site staff

Programming a patient or clinician reported outcome assessment into a digital system reduces errors by avoiding errors in logic such as branching or scoring, but what technology alone cannot address is variability in patient and clinician understanding of how to complete the assessments. From a patient perspective, the total time spent on informed consent is the strongest predictor of patient comprehension in a clinical trial. Comprehension is maximized when consent takes at least 15 minutes.[27] Studies show that training a patient on the instrument's properties and clinical trial expectations is critical to reducing noise.[28] And, regulatory guidances from the FDA and the European Medicines Agency (EMA) recommend training patients, caregivers, and site staff not only on the assessments but also on the EDC elements.[29,30,31] Patients themselves strongly assert a need for training (see Figure 1). Over 95% of 437 patients who express an interest to participate in a clinical trial indicated that training is needed. In addition, caregiver variability[32] and placebo effect[33,34] are also noted to reduce data quality and can be similarly addressed with caregiver. Rater training for site staff conducting clinical interviews and assessments reduces inter- and intrarater variability and improves data quality.[35,36,37]

Didactic training, while useful, is not the most effective mechanism for sustained learning and improved rater reliability. Studies show that interactive training is an optimal mechanism for user engagement, improvement, and retention of learning.[38,39,40] Interactive training—including video modules that reside on the same device as the eCOA assessment—represents a solution whereby training can always be accessible in an offline environment for the subject or site staff.

The use of technology to capture clinical trial data electronically, such as eCOA, can represent a change in behavior or practice for the subjects and site staff using it. This additional factor should be considered such that user interfaces are not only simple, but also engaging and motivate the desired behavior (compliance with patient and clinician reported outcome assessments). Clinical science and the use of patient engagement tools and strategies can provide evidentiary-based mechanisms for maximizing both data quality and quantity. Key factors to drive engagement and compliance include a simplified study design and schedule, collection of key assessments only, minimized burden on subjects and sites,

The use of technology to capture clinical trial data electronically, such as eCOA, can represent a change in behavior or practice for the subjects and site staff using it.

and the combination of useful trial information into a single location, such as the eCOA trial device. Tools such as alarms and reminders, graphics both static and interactive, progress bars during questionnaire completion, adaptive designs, on-device time estimates to patients of how long an assessment completion will take, appointment scheduling, educational information, training, and feedback on data/results during

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- The major technology changes which will greatly influence the day to day work of regulatory professionals
- Process optimisation in regulatory affairs and its effect on global regulatory operational work
- The regional competencies needed for regulatory professionals outside of the major hubs

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the trial all represent mechanisms by which user motivation and compliance with eCOA can be enhanced.

Conclusion

There is a wealth of evidence demonstrating the value of eCOA in fostering better communication and increasing candor between patients and clinical site staff, as well as in improving clinical outcomes. However, in use of technology, there are human elements that need to be considered regardless of the simplicity of the user interface. These aspects include the vital role for training and engagement strategies in parallel with the use of eCOA. There are aspects of obtaining high quality clinical trial data that are dependent on patients and site staff having a unified understanding of expectations and the following of a standard methodology for data capture.

There are aspects of obtaining high quality clinical trial data that are dependent on patients and site staff having a unified understanding of expectations.

This environment is markedly different from that of clinical care in many ways. For example, in clinical care if site staff are nurturing, encouraging and positive and there is a placebo effect, the impact of this behavior is very different than if this same behavior is replicated within a clinical trial where neutral behavior and accurate reporting are paramount to distinguishing placebo from treatment. Similarly, setting these expectations with subjects is also critical. Patients may feel obliged to report feeling better, when they are not, if it is not understood by the subject how important accurate reporting is to clinical trial outcomes.

Overall, combining science and technology can enable better patient-physician communication during a trial; sponsors will have the benefits of higher quality data collection, and tools/strategies such as training and patient engagement are key elements to achieving successful reporting of patient and clinical outcomes.

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An Auditor's View of Compliance Challenges

Seema Garg

A look at the unique compliance and patient safety hurdles—and subsequent interventions—for resource-limited trial sites with no prior experience.

PEER REVIEW

More and more clinical trials are being conducted in resource-limited regions of the world (about 15% to 20%).[1] There are many reasons for this, including a higher concentration of willing and eligible participants; existence of rare and aggressive diseases in certain regions of the world; and socio-economic needs of certain regions to treat, cure and eradicate these diseases. As a result, pharmaceutical companies often collaborate with U.S. government agencies, global health organizations, private charities, contract research organizations (CROs), as well as local and regional governments to launch and execute clinical trials to prove the safety and efficacy of their products in these regions and markets.

All clinical trials present certain operational and compliance challenges. These challenges can have a devastating effect on the study endpoints and data if sites do not have experience in conducting clinical trials or are limited in resources like infrastructure, personnel, training capabilities, safety equipment, etc. This limitation in resources and experience can add an additional layer of complexity to the execution of the trial. In the case of multi-country clinical trials, the regulatory requirements of each collaborating country also have to be considered, which can often hinder the efficiency and speed of the trial.[2] Most of the risks presented by these operational and compliance challenges can be addressed if planning is thorough, and issues are addressed swiftly.

The intent of this article is to bring attention to some of the most frequently encountered compliance and patient safety challenges and to suggest some early interventions. From my experience in auditing clinical research sites, operational challenges often get the most consideration at the resolution table, as operational teams must meet their deadlines to achieve the clinical trial milestones. The compliance challenges, however, often become secondary because of the lack of project milestones to measure compliance and inspection readiness. Follow-up on compliance challenges after the study start often leads to a continuously reactive cycle of addressing compliance issues toward or at the end of the clinical trial in form of corrective actions, deviations, note to files, etc., which can lead to the loss of collected data.

> Some of the compliance challenges observed can be resolved easily with better planning and by creating a compliance risk management plan.

Some of the compliance challenges observed can be resolved easily with better planning and by creating a compliance risk management plan. This plan will allow the clinical trial team to assess the potential compliance risks, determine the severity of those risks to the clinical trial data and the ultimate approval of the pharmaceutical product, and determine proactive actions that can mitigate and reduce those risks to tolerable levels.

Facilities

Facilities are often a challenge in resource-limited regions due to a general lack of an established research infrastruc-

ture.[3] Limitations may include lack of available built space, electricity, basic equipment, and roads. The operational teams usually focus on preparing to get the enrollment started from an operational standpoint but often do not assess the compliance necessities from the regulatory as well as patient safety aspects. Some information to include in a compliance risk management plan related to facilities should be the following:

Electricity supply

It is not only important to have a generator and a back-up generator, it is also imperative to verify that the capacity of the generators will meet your needs. Project task lists should include time and resources for the documentation of the installation and testing of the generators with proper reviews and signatures. This documentation should be readily available for regulatory inspections and audits. The team should also confirm that there is a written generator maintenance plan and that there are records to show execution of that maintenance plan.

Buildings and roads

If the clinical site is located in a larger building (hospital, university, etc.), the clinical trial team often will need to assess the accessibility of the site for their subject population. This is usually not an issue in the U.S., however, in some resource-limited regions of the world, the operational team needs to carefully consider the need for disability access or emergency evacuation access for the study participants.

The clinical samples, subject files, and/or study product may also need to be transported periodically from one location to another. It is important the clinical teams proactively consider the logistics to ensure regulatory compliance and documented chain of custody on the movement of any clinical trial related samples/files/products. I have observed non-compliance in this area when teams "made do" with the available limited resources and transported study product without temperature monitoring or chain of custody, or transported subject files in personal vehicles without accountability.

This type of non-compliance can result in loss of data/samples/study product.

Basic equipment

Typically, equipment such as refrigerators, freezers, centrifuges, and coolers are either already present at the clinical research site and are in use for other trials or patient care or are brought in specifically for the purpose of a particular study. If such equipment is already in place, it is important to ensure the installation and calibration documentation is complete and available for review by auditors/inspectors. If this documentation is not available, the clinical team must plan proactively to get this equipment qualified and calibrated before using it for their study and ensure documentation is complete and available for review.

If new equipment is added, the clinical team must ensure the installation, qualification, and calibration of this equipment is executed and documented. In all scenarios, monitoring and maintenance of such equipment should be documented and available for review at all times. Staff at inexperienced sites are unfamiliar with strict maintenance schedules and need to be instructed that these maintenance schedules are requirements not suggestions.

Equipment qualification/maintenance has been a challenge for sites that have typically provided routine patient care, but have not participated in a clinical trial. Regulations surrounding routine patient care can be different from country to country but those surrounding clinical trials must meet International Council of Harmonization-good clinical practice (ICH-GCP) standards, which in some cases may be either more stringent or more relaxed than the in-country regulations. The site staff often have difficulty understanding these differences initially, which leads to corrective actions and deviations.

Project teams need to not only plan for the qualification/maintenance of equipment, but also include staff training time and regular reinforcement of required schedules. Typically, in resource-limited areas there is a shortage of local expertise, often requiring a contractor to travel to the region to complete the task and documentation, which will require additional planning, time, and resources.

If a clinical site is processing and storing study samples even for short intervals, lack of documentation of proper functioning of equipment can jeopardize the integrity of collected samples, leading to loss of data. The same applies to the study product; if the site cannot provide evidence of proper and consistent storage of the product, the integrity of the drug can be questioned in the regulatory inspections. Planning can help avoid such high-risk issues.

It is important the clinical teams proactively consider the logistics to ensure regulatory compliance and documented chain of custody on the movement of any clinical trial related samples/files/products.

Document storage and safety

Both FDA and the European Medicines Agency (EMA) have clinical trial record retention policies issued in their requirements;[4,5] however, storage and safety of clinical trial records is frequently an afterthought in many sites, and is especially true at resource-limited clinical sites. In some cases, documents are stored in cabinets and in others they are kept in cardboard boxes. In both cases, documents are at risk from water and fire damage at all times.

Some sites have a designated person to file the documents and account for document removal but at most sites there is no designated document specialist resulting in a risk of losing and misfiling these documents, which again may lead to loss of trial data. Advanced planning is critical, especially because resource-limited sites are more dependent on paper documentation. A file management plan to address document flow and accountability, as well as potential risks such as a leaky roof should be defined before study start and revised periodically

It is critical that ICH-GCP training for personnel at resource-limited investigative sites focus on the study protocol at hand and emphasize the risks of non-compliance with ICH-GCP or data documentation.

in the early stages of a trial and prior to changes in study logistical arrangements.

In addition, there is an issue of long-term storage of documentation, as clinical trial documentation needs to be available for inspections and regulatory filings for many years after the study activities are ceased at the clinical research site. Per experience, long-term document storage plans are usually created at the end of the trial and remain an open item in the audits until then.

Personnel training

The number of ICH-GCP trained personnel available in resource-limited regions is very limited and few have prior experience with clinical trials.[3] Most of the time clinical site personnel are trained on ICH-GCP principles before the study start. These trainings are conducted either face-to-face or via webinars or online courses. Training materials focus on the ICH-GCP principles in terms of human subject protection (HSP) and requirements of GCP, but lack details regarding daily site operations or the potential impact of non-compliance with ICH-GCP requirements on the study. In addition, most training courses have case studies, but they are often not geared toward the disease indication that will be studied at that site. It is important that the ICH-GCP training for resource-limited clinical sites, especially sites that have not conducted research studies in recent years, be geared to the study/protocol at hand and draw out the stake and risks of non-compliance with ICH-GCP or data documentation.

Site personnel sometimes take short cuts in daily procedures because they do not understand the gravity of that procedure and the impact their action on the study data. Periodic reinforcement of this training with real-life examples can also go a long way for staff at inexperienced sites. In most cases, it is prudent to supplement the research-naïve site staff with experienced clinical staff from other regions.[6] That approach can cause some staff blending challenges, but is usually extremely beneficial to have the additional depth of experience to support the inexperienced staff.

Another big challenge is the continuity of training as the protocol and procedures get amended and revised and new information becomes available throughout the study. This information is often not consistently communicated to all clinical site personnel because the site does not have an established training system. Even if the information is distributed, there is a lack of documentation of this training, which makes audits and inspections very difficult. There needs to be a designated training role at the site and a system to distribute and document training on the updates to the clinical trial documentation to maintain compliance as site staff and monitors rotate in-country over the course of the study.

Good documentation practices

Non-compliance to good documentation practices (GDP) is one of the most frequent findings in audits in resource-limited or inexperienced clinical research sites. “Key attributes for good documenta-

tion were first described by US-FDA in the form of ALCOA -attributable, legible, contemporaneous, original and accurate. These are also adapted by World Health Organization (WHO)."[7] GDP training must be treated as its own module, instead of a small sub-set of the overall GCP training. This is because GDP has a high impact on clinical data in resource-limited sites as most of the data are recorded on paper. Some of the common GDP issues include changes in clinical notes without any initials and/or dates, inconsistent use of initials, multiple records of same data etc. These poor documentation practices make it very difficult to reconcile the clinical data in audits and inspections and can lead to loss of trial data. A real-time 100% peer review of all critical data points can significantly reduce loss of data in such cases.

Regulatory file and trial master file maintenance

"A TMF is the collection of documentation that allows the conduct of the clinical trial, the integrity of the 57 trial data, and the compliance of the trial with GCP to be evaluated. The requirement for a TMF is set 58 down in Directive 2001/20/ECi Article 15(5) and the TMF forms the basis for inspection (Directive 59 2005/28/ECii Article 16)".[8]

Maintenance of the regulatory file and the TMF in inspection-ready state throughout the trial has been observed as one of the biggest challenge for resource-limited clinical sites. These trials involve many stakeholders—pharmaceutical companies; one or more government branches from the U.S.; local government agencies; and several different CROs—resulting in a large amount of electronic communication among the different parties involved. This communication is often not centralized, but instead resides in different places at different times, and in almost every trial, gets lost as equipment and devices used for this communication fail. Establishing a central communication forum/site that automatically feeds into the TMF can be helpful in these type of trials.

It is recommended to view the operational plans, procedures, data generated, and timelines from an auditor's viewpoint. Being self-critical can be very helpful in the long run.

It is critical to have an experienced regulatory affairs specialist[4] at each resource-limited clinical site who is responsible for maintaining the regulatory file at the site and submitting all documentation and communication to the TMF. In resource-limited regions that do not have experience in conducting clinical trials, this position may have to be filled by personnel from other regions. In such cases, it is important that there is a long-term plan to train the local site personnel in this task and then eventually transition it to local site personnel with some oversight to ensure compliance. The best results are achieved if this position is created and filled before the trial begins. This position is often created and filled in the middle or toward the end of the trial, which is somewhat successful but some of the losses incurred in the earlier parts of the trial remain irreversible and thus lead to loss of trial data.

Conclusion

Clinical trials are long, expensive, and exhausting no matter where they are conducted, but they become especially challenging when resource-limited clinical sites with no prior clinical trial experience are involved. A little preparation and forward thinking can go a long way in reducing data loss and executing a successful study. It is highly recommended to view the operational plans, procedures, data generated, and timelines from an auditor's viewpoint. Being self-critical can be very helpful in the long run.

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Searching for Innovation in Research

Can't we find ways to use all of our ideas, tools, capabilities and experience to generate some meaningful disruption and actually make some positive great leaps forward?

Wayne Kubick
Chief Technology Officer,
Health Level Seven International

You may have noticed that many conferences lately have been offering "Innovation Theaters," "Innovation Showcases" or "Innovation Corners" that reserve presentation slots for many familiar technology and service companies to "showcase (their) products and services" in a special area on the exhibit floor. The primary entry criterion appears to be being first in line to pay an extra fee—there didn't seem to be any obligation to prove actual innovation value. I believe I heard one presentation at a recent conference was actually touting "paperless" as an innovation.

Of course, it doesn't take much detective work to find claims of innovation. It's difficult to imagine anyone being in this business who wants to label themselves "same old, same old" instead. Indeed, many technology and service providers use "innovation" as just another technological buzzword *du jour*, a kissing cousin, if you will, to "Big Data" or "Cloud Computing."

Sometimes it seems as if jumping on a bandwagon (especially a fast-moving one) is all it takes to be innovative. But if everyone's doing these things (or at least saying they are) can any of them really be all that innovative?

"Innovation" is defined by Merriam-Webster.com as:

"The introduction of something new" or "a new idea, method, or device."

So fine, it's new. But doesn't it matter if it's new to me (such as my shiny new smartphone, which is already a generation old to others), new to you (which depends on how much you knew previously) or, above all, new to a historically conservative industry that desperately needs to embrace dramatic change across the board in order to remain viable?

And if newness is all that matters, I guess every teenager posting today's selfie can claim to be innovative, too.

Which brings me to another, more rigorous definition offered by author Scott Berkun who has railed against misuse of the term for years: "Innovation is significant positive change. This is a high bar, and it should be. To call every little change you make in your work an innovation belittles the possible scale of progress. It's hubris."

Today there's plenty of talk about innovation in medical research. We have efforts to push for more funding for the precision medicine initiative, Congress moving forward with the 21st Century Cures Act, and FDA interacting seemingly everywhere toward the advancement of regulatory science.

But which technology and service providers in the clinical research ecosystem are really offering unique, new solutions that are truly innovative so as to impart significant positive change?

On the other hand, there's plenty of support for the Luddite position. According to the findings of a PA Consulting Group innovation survey, 46% of senior executives describe their innovation activity as a "costly failure." If Mr. Peabody were a pharmaceutical or biotechnology executive, he might say, "Sherman, set the Wayback machine back to yesteryear—and leave it there."

How can we reimagine research using our new capabilities to apply real-world evidence, patient engagement and collaborative technologies while retaining the proven gold standard of a more efficient randomized controlled clinical trial?

Can't we find ways to use all of our ideas, tools, capabilities and experience to generate some meaningful disruption and actually make some positive great leaps forward?

So what truly innovative ideas in clinical research products or services have you seen recently? And do they meet Scott Berkun's high bar? Let's keep the dialogue going.

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