Carolyn Gretton

Decoding Data DYNAMICS

The shift in life-sciences development toward more personalized therapeutics is driving a need for proactive clinical data management (CDM) strategies that take into account the volume and complexity of information emerging from today's clinical trials.

Data management is being impacted by a number of variables — more data, technology, expertise — but one of the biggest trends is that of personalized medicine.

According to Gil Fine, Ph.D., senior director, statistics & data management at SuperGen, the advance of personalized medicine has significantly increased the amount of data being collected in the drug development process.

"There are a vast number of variables that clinicians are interested in, ranging from genotyping, which requires a complex data field or response, to cytogenetics, which tends to involve long text strings of symbols that have a structure that experts can make sense of right away," Dr. Fine says. "But it all equates to more data that have to be managed. The number of fields that we examine, collect, and store has gone up unbelievably in the last few years with the personalized medicine initiative."

Corey Dunham, VP of data management and statistics, North America, at Aptiv Solutions agrees.

"Personalized medicine makes the randomization and screening process far more involved," he adds. "Data management must develop custom Web services or APIs to integrate with external genetics, biomarkers, or imaging labs." (Please turn to the Showcase: The Impact of an Integrated Execution Environment on Data Management in Adaptive Clinical Trials.)

Joseph Kim, clinical operations director for Shire Pharmaceuticals, offers another view. He says rather than asking how the growing personalized medicine market will affect data management, he says it's time to look at how data management will affect the future of personalized medicine.

"When one thinks about it, practicing medicine has always been a personalized activity; physicians will often create their own treatment paradigms to fit the patient in front of them," Mr. Kim adds. "The question then becomes, how data capture and analysis technologies can better serve physicians to help them make personalized medical decisions based on statistically significant data borne out of rigorous clinical research. Development of these elements needs to go hand in hand with new diagnostic tools to help physicians characterize patients using new labels."

"It is well-known that finding truly effective and general methodologies for accomplishing breakthrough therapeutic discoveries is a major challenge," says Guy Mascaro, president of the nonprofit Metrics Champion Consortium (MCC). "With personalized medicine, which will require new methodologies for identifying, testing, and managing study eligibility, the complexity and rigor with which sites, sponsors, and CROs will need to document and maintain accurate data become significantly greater. New CDM tools and practices will need to be developed to manage this burgeoning field."

In addition, according to Mr. Mascaro, personalized medicine will impact the way companies determine appropriate sample sizes for statistical analysis and validation.

Susan Howard, assistant director for GlaxoSmithKline, and vice chair of the Society for Clinical Data Management, predicts the specialized tests required to determine eligibility for personalized medicine studies will result in longer periods of time from informed consent to first dose of study medication.

"Many of these tests must be done by specialty labs, which increases the number of external data sources and vendors," Ms. Howard says. "In data management, we are routinely seeing studies with five or more external vendors and data sources, so we are well-prepared to handle this work."

Theresa Musser, VP, development operations, at Rigel Pharmaceuticals, says one challenge is integrating all of the information about a given patient to create a personalized medicine for that individual.

"We're beginning to see gaps in how a patient's medical information is collected into one large database," she says. "For example, if I'm taking part in a clinical trial and I give consent for certain genetic biomarkers to be identified, does that information just reside in the clinical-trial database? Or can I access that information and provide it to my doctor?"

"EDC is changing the role of CRAs and the activities they perform while visiting a site."

THERESA MUSSER *Rigel Pharmaceuticals*

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LINDA SULLIVAN *MCC*

"The multiple players involved in conducting today's increasingly complex global clinical trials can tax even the most effective CDM systems."

Barriers to Collection

Linda Sullivan, VP, operations, for MCC, says the multiple players involved in conducting today's increasingly complex global clinical trials have made for complicated command, control, and communications processes that can significantly tax even the most effective CDM system currently available.

"The confluence of these factors now strains even the most venerable of sponsor organizations, causing a continual movement toward the outsourcing of more data management services to help manage gaps and improve continuity in clinical trial operations," Ms. Sullivan says. "This current paradigm gets further complicated as more and more mergers occur in the industry, resulting in newly formed organizations that have to potentially manage legacy studies as outliers. This trend may greatly impact the efficiencies that companies are trying to drive with new CDM systems."

One important technology issue cited by many data-management experts is the integration of data from multiple source systems. Many of the EDC tools available today still have inadequate integration platforms, and their user interfaces do not allow data managers to easily reconcile data from multiple sources, Ms. Howard says.

Dr. Fine says his company has run into that challenge most often with large academic centers, which often develop their own data management systems for specific projects, each of which tends to be a bit different.

"Our big challenge is being able to integrate the systems and have them talk to each other," he says. "At some point, the challenge of managing so many different systems is going to be overwhelming."

From her perspective, Ms. Howard considers the perpetually changing and evolving technology to be somewhat of a barrier to effective CDM because clinical studies in her sector, oncology, can often span several years.

"By the time one of my staff members is assigned to a study, several pieces of the technology, as well as associated policies, may have changed," she explains. "It is a huge challenge to stay current with new tools while ensuring a study is set up in the timelines allocated."

Ms. Musser says she has observed a greater onus on the sites to enter data, and this has shifted the role of the CRA or site monitor relative to what monitoring actions are taken both before and during a site visit.

"EDC is changing the role of CRAs and the activities they perform while visiting a site," she says. "And this all ties in with source document verification, especially as more and more sites go to automatic electronic input.

"It's not about barriers so much as recognizing that there are ongoing changes to roles and responsibilities, and about how much data a data manager is reviewing," Ms. Musser continues. "Many companies are doing cross-training for CRAs and data managers, because that leads to a more seamless type of approach to how data are reviewed emerging."

While some industry observers may take aim at the FDA for not keeping pace with the technological advances in CDM, Dr. Fine says they need to remember that the agency is dealing with the same growing onslaught of clinical-trial data as life-sciences data managers.

"While we aren't increasing trials to higher numbers of patients enrolled, we are increasing the amount of information that comes from each patient, and the FDA has actually taken steps by standardizing data structures," Dr. Fine says. "While the FDA didn't originate CDISC, it has joined the CDISC committee and participated in meetings, and regulators are on board with the standardization."

Mr. Kim believes one of the biggest barriers to CDM implementation is philosophical, not technological.

"There's the 'we've always done it this way' type of thinking, and an overemphasis on 'how do we get the data out,' rather than focusing on how we can make it easier to get the data in," he explains.

In addition, Mr. Kim says he is amazed at the length of time it still takes to build a CDM for a clinical study.

"I have a suspicion that the latest generation of IT professionals would approach this activity in a completely different way, which could greatly streamline the process while providing a more user-friendly interface," he says.

New Technology Frontiers

Dr. Fine says while today's EDC systems are a vast improvement over the systems available just a few years ago in terms of capacity and features, the category will continue to evolve.

"I can envision a few ways in which EDC could improve; one exmple would be integrat-

FAST FACT

THE GLOBAL MARKET FOR CTMS IS EXPECTED TO BE VALUED AT $1.76 BILLION BY 2017.

Source: Global Industry Analysts

VIEWPOINTS

Interfacing for Optimal Operations

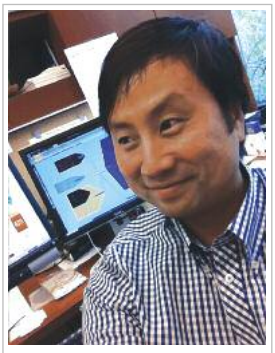
Web integration of external systems through Application Programming Interfaces (API) is having the biggest impact. This requires customized programming solutions that can be deployed quickly in a reliable and regulated manner. This means there must be clinically savvy programming resources that recognize the regulatory rigors required. This is difficult to find and operationalize.

COREY B. DUNHAM
VP, Data Management and Statistics, North America
Aptiv Solutions

Mission Critical: Clinical Study Report

People often forget that the first critical step is getting all of the stakeholders involved from the very beginning, starting with protocol design, and remembering to keep the final goal in mind: a well-written clinical study report. The old and inefficient model of managing multiple databases, including safety, and vendors by manually compiling data from disparate systems with multiple places to go for review of information is an

"The question is: how can data capture and analysis technologies better serve physicians to help them make personalized medical decisions based on statistically significant data borne out of rigorous clinical research?"



JOSEPH KIM *Shire*

ing the ability to view some of the data that might be better portrayed graphically rather than numerically," he says. "For an ECG, it's important to be able to view the actual heartbeat wave in its entirety, rather than being given some summary parameters, such as QT intervals, to summarize that wave numerically.

"The same thing would be true in my field of oncology development," Dr. Fine continues. "We collect responses to treatment in solid tumors based primarily on a criteria called RECIST, or response criteria in solid tumors. It would be much better if we could actually see a patient's scan or digital image as part of the data we capture, allowing anyone who needs to interpret the data to do so directly from the source, rather than depending on numbers that summarize what was collected."

Ms. Howard foresees the use of electronic health records (EHRs) in clinical research as having great potential for streamlining trials, noting that there already have been successful demonstrations of this use.

"The industry must adopt standards to use EHR on a large scale, and strict privacy standards must be maintained so the public has confidence that their data are being used appropriately," she adds.

inefficient and costly way to do business in today's world.

CARRIE CAMERON
Senior Director, CRO Services
Clinlogix

Study for Success

The technologies that are currently having the greatest impact on data management are those that reduce study setup time through study specification and EDC-built automation. Tools that hold the most promise in terms of content data management for streamlining clinical trials are those that facilitate the production of study design libraries, thus allowing vendor neutral reuse with preferred CROs and EDC vendors as well as with downstream submission tools.

MARK WHEELDON
CEO
Formedix

Standardizing Data

The Web/Internet is clearly the biggest technology game changer because it is globally accessible and is increasing participation with CDISC, which has become the standard. This is vital because it creates a common language across data exchange and processing. Going forward the tablets and apps that go with the standards will have a significant impact on trials because it makes the data immediately available anywhere — on the subway or in the room with the subject. It makes the access and sharing of that data more efficient. Input data once, then use or share it many times. Wireless networks will substantially speed the access as well because a wireless hub will no longer be necessary.

GREGORY J. BAILEY
Director of IT
IVR Clinical Concepts

Harness the Power of Standardization

Most companies involved with drug development have multiple systems with data generating and storing capabilities. The difficult piece is timely data integration across multiple platforms with appropriate presentation of the data in a way that makes sense to the customer and is easy to use, digest, and interrogate. Many of the systems, be they off-the-shelf or developed in-house, are difficult to integrate due to siloed designs, process variability, or differences in underlying data structures. Harnessing the power of standardization in structure, design, and content leads to increased potential for transforming data into information, reuse of programming and display elements, greater efficiency, and shorter times to decision.

STEVE POWELL
Senior VP, Clinical Informatics and Late Phase Services
PRA

It's All About the Cloud

Simply put, in clinical safety data management, the cloud is the biggest trend. Technologies such as Web-based safety portals will streamline or eliminate manual processes that inhibit cycle times and may delay detailed analysis. So as these technologies are adopted, manufacturers will have the opportunity to repurpose highly skilled talent into roles that directly support commercial value creation. This is key, because this will help drive rapid reimbursement approvals and accelerate appropriate use.

MICHAEL O'GORMAN
President and General Manager
Sentrx

Collision of Conflicting CDM Trends

The big challenge today in CDM systems use and implementation is the collision of two strong industry trends: the desire for simpler systems based on EDC/CDM schemes and the increased outsourcing of the data management function. This double whammy of flux disrupts dataflow, work processes, SOPs, validation, staff training, and efficiency. These trends often end up in conflict, and the DM profession has not been prepared historically to cope with these type of issues.

RONALD S. WAIFE
President
Waife & Associates Inc.

Ms. Musser says there is a question of exactly who should bear the responsibility for pulling and/or integrating EHR data into the clinical data process.

"A lot needs to be done about defining the responsibility and then deciding on process and systems, if there is a decision to bring all the data together," she says. "Should the industry be responsible for ensuring that clinical trial information gets to the private physician? Or is it the physician's responsibility to know his or her patient has been in a clinical trial, and to find out from the patient whether any resulting data or information should be provided to the physician? Some of this is emerging science, and it might not be clear how the information translates to taking better care of a patient. We need to determine the implication of telling a patient about a certain genetic disposition, because conveying that requires some context of medical history and medical diagnosis, and we don't know what that connection or that context is yet."

Mr. Kim predicts mobile technology will radically alter the face of CDM before the decade is out as smartphone adoption rates surpass those of hard-line Internet connectivity.

"Coupled with biometric advances and sophisticated app development, mobile technology could create new statistical analysis models that can better examine efficacy and safety over more precise temporal scales," he says.

"EDC and data management enable us to look at data on an ongoing basis and then make a judgment as the profile of the drug is emerging," Ms. Musser says. "Medical monitoring has become a more proactive role; not that it was passive in the past, but sometimes we didn't receive data until three months later. Active management of patients on even a daily basis can be better conducted because we now have real-time access to data, and I think that's a boon for everybody."

Most experts agree the CDM innovations have only just begun.

Ms. Musser cites e-clinical suites as changing the face of CDM from a clinical operations perspective.

"These suites enable both sites and sponsors to have one portal where they can access warehoused information and be able to generate reports in whatever form needed to assess progress and safety in a study," she says. "This is creating some major efficiencies in project management, as well as site management and communication."

Dr. Fine says the arena is very dynamic, and there will be new players in the game that will come up with innovation technologies. PV

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EXPERTS

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THERESA MUSSER. VP, Development Operations at Rigel Pharmaceuticals Inc., a clinical-stage drug development company that discovers and develops novel, small-molecule drugs for the treatment of inflammatory and autoimmune diseases, as well as muscle disorders. For more information, visit rigel.com.

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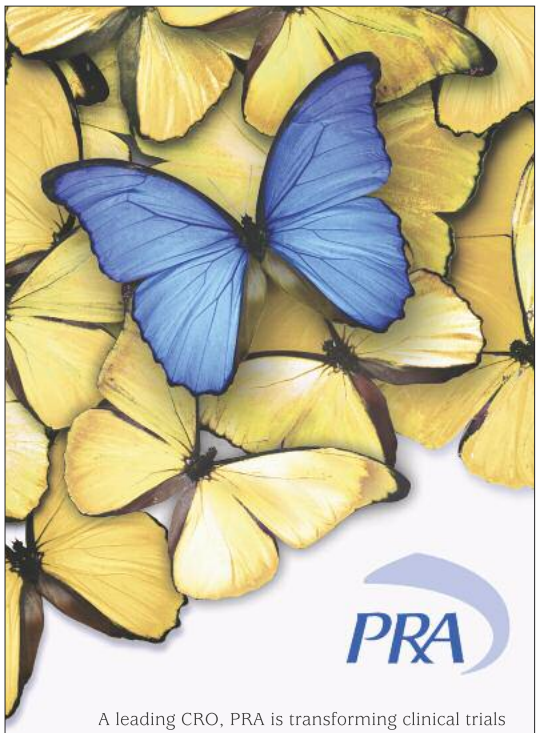

Standardizing METRICS

The Metrics Champion Consortium is leading the development of standardized performance metrics that improve the quality of process efficiency, while supporting the scientific nature of clinical research.

One of the keys to data management is standardization and ease of use.

According to Guy Mascaro, president of the nonprofit Metrics Champion Consortium (MCC), these are two of the association's goals.

Mr. Mascaro notes that the MCC's mission is to help the pharmaceutical, biologics, and medical device industries achieve greater efficiency and effectiveness through standardization of performance metrics.

MCC is working toward providing member organizations with a global clinical trial metrics data capture and reporting platform hosted in a cloud environment.

Currently, MCC has more than 25 corporate sponsors and almost 30 corporate members, and collaborates with a wide range of organizations across the clinical trial industry, including the Association of Clinical Research Organizations, CDISC — Clinical Data Interchange Standards Consortium, PhRMA, and the Institute for International Research.

"We are in the process of forming an alliance with IBM's Global Business Services' Healthcare and Life Science team to develop a proof-of-concept database and reporting tool that will leverage its cloud technology to allow MCC members the ability to access clinical trial metrics data in a more proactive and real-time fashion," he says. "Our goal is to someday allow our member companies to bring performance data from disparate data platforms into a blinded database where they can effectively compare their own company performance on various MCC metrics to that of the membership norm."

LINDA SULLIVAN *MCC*

"We envision member companies being able to look at leading and lagging indicators at the site, country, study, and therapeutic level so that areas that warrant improvement can be easily identified."

"We envision member companies being able to look at leading and lagging indicators at the site, country, study, and therapeutic level so that areas that warrant improvement can be easily identified, addressed, and monitored to ensure that efficiency and greater productivity are achieved," says Linda Sullivan, VP, operations, for MCC. "The current performance metrics are designed to foster a balanced approach to evaluating the quality, time, and cost performance of a study." PV

Keeping Patients' Privacy

While personalized medicine is driving many of the changes in clinical data management (CDM), Linda Sullivan, VP, operations, of the Metrics Champion Consortium, notes that a separate, yet equally important issue is the heightened importance and ever-changing role that patient informed consent will play in data collection, and the increased burden and evolving standards this will have on CDM.

"For example, expanded terms of informed consent will need to be accurately married and maintained with patient samples for future use as new genetic assays are developed and companies want to revisit completed trials to reanalyze data to determine the viability of a given therapy for a certain subset of the patient population," Ms. Sullivan says.

Theresa Musser, VP, development operations, at Rigel Pharmaceuticals, says by using sophisticated e-technologies to collect and store deeper levels of patient data, sponsors and vendors have an even greater responsibility to patient safety and patient privacy.

"We now have real-time access to deep information such as genetic coding biomarkers that are being stored in a data warehouse, and I believe the industry needs to be mindful of its responsibility related to personal privacy issues as we move forward," Ms. Musser says.

Gil Fine, Ph.D., senior director, statistics and data management at SuperGen, notes that not only do FDA regulations protect the safety of patient records within the CDM framework, there's an entire industry outside CDM that's built around protecting the information and biological materials patients provide as part of the clinical-trial process.

"The fact that we work in this regulated environment, and we're obligated to follow and adhere to these rules that are put out, is a safety net that lies on top of all CDM systems," he says. "I do believe that the FDA regulations are above and beyond what one might think is needed, so they're really a good barrier of protection for maintaining that information in a secure environment."

FAST FACT

THE U.S. MARKET FOR ELECTRONIC MEDICAL RECORDS (EMR) IS EXPECTED TO GROW FROM $2.18 BILLION IN 2009 TO $6.05 BILLION IN 2015, FOR AN ESTIMATED CAGR OF 18.1%.

Source: MarketsandMarkets

World Pre-Filled Syringes Summit

Considerations for drug developers in adopting pre-filled syringe strategies

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5. Explore current understanding of **protein-silicone interactions**
6. Delve into challenges of **product-packaging interactions**
7. Understand the criteria for successfully **integrating formulation** and **device**
8. Discuss considerations for developing a **dual chamber syringe** and **auto injector**

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Gillespie Professor of Bioengineering, Department of Chemical & Biological Engineering
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Bill Lambert
Senior Vice President, Pharmaceutical Development
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Li-Chun Tsou
Sterile, Vaccine, & Biologic Project Lead, Pharmaceutical Commercialization Technology
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