Carolyn Gretton

The Dynamics of DATA MANAGEMENT

From growing regulatory requirements and submission standardization to the advent of adaptive trial designs, pharmaceutical companies and their clinical trial partners are facing a host of data management challenges.

Carrie Coutre, director, study standards implementation (SSI) operations, for Millennium: The Takeda Oncology Company, says while the traditional data management resides with the CRO, Millennium's SSI operations department works with the CRO as the liaison for data quality and all data-related activities from study start-up through database lock.

"At Millennium, we focus on oncology drug development; as a result, we collect data from many sources — imaging, randomization and supply management, specialty lab, central lab, patient reported outcome, and so forth," Ms. Coutre explains. "Because we work in a fully outsourced model, from a data perspective it is our CRO's responsibility to take the data from the multiple sources and send us the data in our specified standard format, which is consistent with our global oncology standards."

Over the past year, Ms. Coutre says Millennium has also invested in building preferred relationships with IXRS (interactive voice/Web response system) vendors as well as central lab vendors that can be used by the company's CRO partners.

"This allows us to capitalize on additional efficiencies through process and data standardization," she says.

Heather Wolff, director of data management, Infinity Pharmaceuticals, notes that operational data such as tracking of subject visits, time to enter data into electronic data capture (EDC) systems, and current status of source document verification are important for managing studies and coordinating timelines for a cross-functional study team.

"Some of these data can be extracted from automated systems, such as IXRS for randomization or drug supply, or the audit trails of an EDC system," Ms. Wolff says. "In other cases, it can be entered manually by study team staff, such as a clinical trial manager entering subject status in a CTMS."

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"Our philosophy has been to make sure we are collecting the data in the best way to ensure high quality and data standardization along with ease of collection for our patients and sites," Ms. Coutre says. "For example, if we are collecting patient reported outcome data, we need to evaluate the ease of entry to ensure compliance and ultimate data quality for analysis."

According to Ms. Wolff, most subject data for a clinical trial is collected by clinical trial sites and reported to the sponsor through paper or electronic CRFs in an EDC system.

"Many trial sponsors have moved to EDC for operational advantages, including faster data collection and a faster review process, among other benefits," Ms. Wolff says. "Since data are entered into EDC from source documents, sponsors must verify that the collected data match their sources."

For trials that use at-home dosing or patient reported outcomes (PROs), additional data can be collected directly from the subject in a diary or questionnaire, Ms. Wolff says.

CARRIE COUTRE
Millennium: The Takeda Oncology Company

"For example, in a pain or arthritis trial subjects may be asked to evaluate and record their level of pain on a daily basis," she explains. "This type of data may be entered into an EDC system later, but is typically not queried by the sponsor."

Better Recollection

Patient diaries is one area where electronic-record adoption has been particularly well-re-

DR. MINGXIU HU *Millennium: The Takeda Oncology Company*

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DR. JANE FANG
MedImmune

ceived. According to Johann Proeve, Ph.D., head of global data management, Bayer HealthCare, the traditional paper diaries used by patients were problematic for data managers because of the difficulty deciphering the various forms of handwriting, as well as the problem reconciling certain data entries with real-life experiences.

"It makes much more sense that patients report these data electronically," he says. "I think patients these days, regardless of age, for the most part have access to electronic systems, or at least can use the devices that ePRO vendors provide for those trials."

Dr. Proeve adds that these electronic patient diaries also help combat what he calls parking-lot syndrome, where patients end up filling out several weeks' worth of PRO forms all at once on their way into the doctor's office or clinic site.

"We all know that the recall of what happened 10 days ago is probably not that exact," he says. "We also noticed when patients entered data like the minutes or seconds it took a drug to act, this was not compatible with the drug profile. In the paper diary scenario, we would just have to accept those answers, while in an electronic option, we can ask the patient if that's really what he or she meant to tell us, giving the patient the opportunity to correct the data before the information is recorded in the database."

Junfang Li, Ph.D., senior director, biostatistics and data management, for Mitsubishi Tanabe Pharma America, notes that while ePRO collection provides cleaner data and faster collection, it also presents some challenges.

"Patient reported outcomes have been done extensively in the past in a number of therapeutic areas," Dr. Li explains. "And because they've traditionally been put on paper, it is very important to validate the ePRO-collected data with the historical data."

Another form of data becoming more prevalent, according to Dr. Proeve, is the data generated by data monitoring committees (DMCs), external bodies that are usually comprised of experts who examine certain safety and efficacy data at regular intervals throughout a trial.

"Also, I'm seeing more bioanalytics and pharmacokinetics data generated both in-house and by external labs," Dr. Proeve adds. "In the past, these data were mainly collected for studies driven by clinical pharmacology: Phase I trials, and maybe early Phase II trials. But recently these bioanalytics data have become more important for Phase III clinical trials as well."

At MedImmune, Michele Pontinen, senior director, clinical informatics, says the company is in the process of integrating its clinical trial data with its exploratory biomarker data, and providing support to the translational medi-

Heather Wolff, director of data management for Infinity Pharmaceuticals, lists the following key areas and questions that data managers need to address during the request for proposal (RFP) process:

System Configuration

- Can the system be set up to meet the needs of the study?
- Does the system meet the relevant regulatory requirements (e.g., 21CFR Part 11 compliance)?
- Is the system able to be reused in different disease indications and trial designs?
- How difficult is the system to configure?
- Does the system require deep technical expertise?
- How are changes to the system priced?

Data Transfer

- Does the system allow transfer of the data to the sponsor? Is this transfer manual or automated?
- What is the pricing model for data transfer?
- What mechanism is used for the transfer? Is the mechanism secure?

System Support

- Is the support provided by the vendor in line with the needs of the sponsor company and the specific trials?
- How are technical issues resolved?

Governance

- Who are the key points of contact at the vendor?
- What is the escalation path?

cine division to help answer complex questions about clinical trial subjects. Going forward, MedImmune sees the need to integrate those data sets with other types of genomics data, such as PCR and microarray data.

"We're also looking to integrate with electronic health records and with payer and provider records," Ms. Pontinen says. "We're beginning to address the issues of data interoperability both at the semantic and the syntactic level to make sure we are all speaking the same language and that everyone understands the intent of the questions we're asking, so that we don't ask a question about an apple and get a reply that gives us information about an orange."

Experts note that third-party vendors can be used to collect other data, such as laboratory, ECG, and imaging information.

"External data transfers typically occur electronically throughout a trial, but the format and method of transmission should be agreed upon up front," Ms. Wolff says. "Ideally, a test transfer is performed before the start of the

VIEWPOINTS

MARK WHEELDON
CEO
Formedix

Software from Start-Up to Submission

Just as EDC changed the way we conduct clinical trials today, new emergent standards-based clinical trial automation software further optimizes the end-to-end clinical trials process from study start-up to submission. Typically, this software enables universal design and execution of studies across multiple EDC systems, multiple platforms (EDC, ePRO, IVRS) with multiple partners offering a paradigm shift in terms of flexibility, agility, and choice. In addition, end-to-end content reuse drives time and cost savings.

EILEEN MOYER
Senior Principal
IMS Health

Data Demands

Beyond the sheer volume of transactional data that's rapidly becoming available is the fact that much of it is unstructured, and some of it is incomplete and of less-than-perfect quality. Companies have to reserve such data for analytical purposes and tread carefully when incorporating it into systems that actually drive business operations. Additionally, many companies' current information management frameworks cannot support the new demands that will be made on them without creating redundancies and inconsistencies.

Master of Their Data

Most importantly, they should have a strategy for managing their master data — data that are needed by multiple functions — to ensure that it's accurate, presents one "version of the truth," and is readily available to all who need it. Even companies that use master data management as a service need to retain responsibility for data governance. Ideally, a cross-functional team sets standards, dictates policies and procedures, and defines responsibilities around the data.

ERIC PETERSON
VP, Research & Development
MedNet Solutions

Take it to the Cloud

Aggressive clinical trial timelines, tight budgets, and limited staff support are among the top challenges faced by data managers. Today's cloud-based eClinical technologies can help to cost-effectively address these issues by automating numerous time-consuming and repetitive data management tasks, providing real-time data transparency, and delivering efficient tools to quickly access and analyze the exact datasets desired.

DR. STEPHEN GULYAS
Late Phase Data Services
OptumInsight

PRO Guidelines

Clinical trial data are comprised of demographics, baseline characteristics, dosing and disease information, clinical endpoints, PROs, and AEs. PROs need to follow developer guidelines for data collection, and options often include paper, tablets, or iPads. If daily information (dosing or AEs) are collected while the patient is at home, paper diaries or handheld devices (e-diaries) work well. Other information is efficiently collected through Web-based EDC, when coupled with proper system training, solid help-desk support, and an appealing user interface.

TRACY MAYER
VP, Strategic Resourcing
PharmaNet/i3

Mastering the Basics

Given that timely, cost-effective delivery of reliable data is essential to providing insight around the development strategy for companies, it's critical that data managers have mastered project management basics, including timeline and budgetary oversight. They should also have access to the primary project objectives from the RFP and the governance structure from the communication plan to ensure the data delivery plan aligns with the expectations of the team.

Adaptive Advantages

Adaptive trial design can take many forms, including dynamic randomization ratios, dropping and adding treatment arms, and statisticians using simulations to project trial results mid-study. For data management, this requires frequently cleaned data, flexibility of database design, and on-demand data extraction. Companies can derive the most benefit when research questions are clear, sufficient lead-time for study design is available, and the additional logistics of trial execution can be efficiently managed.

study or shortly thereafter to confirm the appropriate file structure is employed. The ability of a vendor to provide data in a format specified by the sponsor can vary depending on the size and sophistication of these external vendors, and study sponsors may need to adjust the process accordingly."

Jane Fang, M.D., associate director, clinical informatics, at MedImmune, says the real challenge lies with using these data management technologies within the business, as well as creating a solid, consistent process around the technology being employed.

"The partners also have to have the proper discipline to actually embed the standards into the daily conduct of the study," Dr. Fang adds.

"Our industry is beginning to address the issue of data interoperability both at the semantic and the syntactic level to make sure we are all speaking the same language."

MICHELE PONTINEN
MedImmune

Relationship Communication

Relationship management is crucial for companies working in a partnered outsourced model. Ms. Coutre says Millennium trains its SSI operations staff on the importance of building relationships and treating partnered CROs as an extension of the company.

"We reinforce behaviors that maximize effective collaboration on both sides of the partnership, including respect, ownership, accountability, and open and honest communication," she says.

Ms. Coutre stresses that internal relationship-building is equally important.

"Implementing standards at a study level can be challenging when faced with resistance and personal team preference," she says. "Learning how to influence without authority is a key skill that our staff members need to learn when implementing standards, so we work with them on the importance of consistent messaging."

With regard to communication plans in a fully outsourced model, Ms. Coutre says both the sponsor company and the CRO must understand the governance structure and proper channels for communication and escalation.

"Within SSI ops, we encourage direct communication at the team level; we strive for operational consistency among our teams, and use the Millennium-CRO management team forum to develop standard processes, expectations, and timelines," she says. "With these in place, there is increased alignment and fewer opportunities for communication challenges."

Ms. Wolff says Infinity focuses on building long-term relationships with partners that integrate well with its internal approach to data management.

"At Infinity, our commitment to real-time access to clinical data has a direct impact on the selection and management of vendors," she says.

Once a vendor has been chosen, Ms. Wolff says expectations are set before the final contract is executed, with agreed-upon metrics integrated into the ongoing relationship.

Dr. Li says the most effective partnerships pair the swift, close communication and shared objective of in-house teams with the technological capabilities and expanded resources of external vendors.

"If we all visualize this as a partnership, and if we all clearly define our goals, it works successfully both ways," she says.

Dr. Proeve believes giving data managers access to the trial protocol is critical to successfully managing the relationship between study protocol and data standards.

"The study data manager, in my opinion, needs to understand the purpose of the trial if he or she is to combine the protocol with the existing standards," he says. "The manager needs to make sure this can be translated into an electronic case report form that meets the protocol requirements on the one hand, but also adheres to the organization's data standards."

"While the era of EDC affords many advantages to the initiation, conduct, and analysis of clinical trials, there is accompanying, added complexity that needs to be managed carefully," Ms. Wolff says. "Data managers need to be sophisticated in their understand-

MARK PENNISTON
Senior VP and General Manager, Clinical Analytics
Theorem Clinical Research

Critical Thinking is Needed for Each Trial

Critical thinking about the different data elements that will be collected and the most effective way to capture data is required for each trial. EDC is most often assumed, and some EDC vendors are now beginning to offer integrated solutions for other technologies, such as IWR and/or ePRO. Having fewer vendors can be beneficial with regard to communication, cost, and time. Vendor data from many sources must be considered, and plans for DSMB, interim analysis ,and adjudicated data will have an impact on data collection and data availability.

Proactive Management

Data managers are required to understand the specific study timelines and detailed tasks to confirm that study expectations are agreed upon with the entire team. Specific documents, such as data management and communication plans, need to be reviewed by the team. Proactive management is key to maintaining a favorable sponsor/vendor partnership and team cohesiveness. Transparency in timelines, task ownership, understanding of processes and documentation requirements throughout the trial ensures quality and that expectations are met.

DR. JUNFANG LI *Mitsubishi Tanabe Pharma America*

"The most effective partnerships pair the swift, close communication and shared objective of in-house teams with the technological capabilities and expanded resources of external vendors."

ing of not only the trial protocols and disease indications; they must also have strong technical skills."

"I think moving an organization into new ways of working — for example, outsourcing core competencies to partners — requires that the organization take into account the amount of facilitation and the managing of the relationship and the deliverables to constantly make sure all parties are speaking the same language and making the same interpretations," Ms. Pontinen says. "This is something that takes heavy lifting on MedImmune's side to do successfully."

Adapting to Adaptive Trials

Mingxiu Hu, Ph.D., senior director, biostatistics and statistical programming, at Millennium: The Takeda Oncology Company, says adaptive trial design allows modifications that take into account new information emerging during a trial, making the trial more efficient so that effective medicines can be brought to patients more quickly, and allowing for earlier termination of an ineffective drug development program.

"Types of design adaptation include study size modification, patient population change, endpoint alteration, early stopping for efficacy or futility, etc.," Dr. Hu says. "If used appropriately, adaptive design can increase the probability of success for a trial, shorten development timelines, and/or save resources. Prevention of operational bias, statistical bias, and inflation of false-positive rates are key considerations in applying adaptive trial designs."

Dr. Fang says adaptive trial design planning requires a lot of thought up front.

"Downstream events, including changes in design or analysis based upon the safety and efficacy data collected during the trial, need to be prospectively planned and specified," she says. "If something is seen through the data, you can't go back and change your study design without planning; this should be done before data are examined in an unblinded manner."

"The beauty of adaptive design is you can decide early on how to proceed with each dosage step, so you can complete the trial earlier than in the past," Dr. Proeve says. "For data management, it means we need to implement processes that allow us to take data snapshots almost at any point in time, and make the data readily available to biostatistics groups or data monitoring committees so they can analyze them and recommend dropping or adding specific treatment arms.

"To really be able to do that, the requirement is that we always are on top of our trial," Dr. Proeve continues. "This means the data cleaning process is ongoing, that there is no delay in data cleaning, and that all functions involved in a clinical trial work very closely together."

Ms. Pontinen stresses the importance of setting up the roles and responsibilities of the managers involved in an adaptive trial, as well as the appropriate policies to protect the trial subjects. It is also essential that the clinical trial team executing the trial does not become unblinded, she adds.

"I think once you have those details worked out and a solid foundation laid, then adaptive design, which right now is a rather heavy lift at most pharma companies, will become just another way that we deliver trials," Ms. Pontinen says. PV

EXPERTS

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