Denise Myshko

Optimizing *Clinical* TRIALS

Experts say optimizing the various processes in clinical development is critical for the timely and efficient approval of new products.

Over the past several years pharmaceutical companies have been facing increases in costs and delays in conducting their clinical trials. Research professionals are challenged to find ever increasing ways to make development more efficient and effective.

Andy Lee, deputy head of clinical sciences and operations at Sanofi, says an imperative is to optimize the various processes supporting clinical development. This is called process excellence and requires the association of various methodologies, including lean Six Sigma, along with business process management suites to model, optimize, and automate the clinical processes.

"While most clinical trial sites today have made great advances in terms of having access to computer and Internet-based technologies, there are still certain areas of the world that struggle in this regard."

JIM MURPHY / Almac

FAST FACT

40% OF PROTOCOLS ARE AMENDED BEFORE THE FIRST SUBJECT/FIRST VISIT AND ONE-THIRD OF THE AMENDMENTS ARE AVOIDABLE.

Source: Tufts

"What is at stake is the speed and the cost of the development of a drug," he says. "The challenge here is change management, which requires leading an organization to new ways of working by leveraging the BPM technology to wire (or rewire) the clinical operations value chain."

A second imperative, Mr. Lee says, is related to the transformation of data that is collected, validated, and assimilated in order to draw inferences and conclusions about a products efficacy and safety.

"The driver behind this transformation is the optimization of R&D productivity and the decision-making process in advancing a compound through the various stages of development and, ultimately, being able to quantify the benefit/risk profile of a drug," he says. "One challenge here is the integration of data resulting from the lack of unified standards — internal or external — and the siloed approach that has been used over the years, while deploying applications in an R&D organization."

Mr. Lee says the solution will start from the adoption of standards reinforced with the management of metadata and master data and will grow through the adoption of architectural principles, such as service-oriented architecture (SOA), that will reduce the silos of the application landscape.

Data Needed for Up-Front Planning

- **Treatment data:** Leading drug regimens, dose administration, treatment location, etc.
- **Patient prevalence**
- **Regulatory feasibility:** MOH/IRB/EC approval timelines, local documentation requirements, drug shipment requirements, translation requirements
- **Medical feasibility:** Use and availability of comparators, rescue medication, placebo
- **Benchmark around procedure cost and resource requirement**
- **Study design parameters:** Inclusion/exclusion, objectives, endpoints, assays, standard of care

Source: Nagaraja Srivatsan, Cognizant

Protocol Development

Knowing how to effectively develop a clinical trial protocol is essential to a compound achieving IRB approval, ensuring the success of the study, and ultimately achieving market approval.

Recently published data from the Tufts Center for the Study of Drug Development show that 40% of protocols are amended before the first subject/first visit and one-third of the amendments are avoidable. This represents a significant impact on study costs and cycle time productivity.

Mr. Lee says simplifying a protocol is not an easy process.

"It requires an appreciation of many factors, such as the impact on the clinical site, burden on the patient, medical practice, and standard of care, disease epidemiology and associated prevalence/incidence rates, historical recruitment durations, competing trials, and country/site performance, to mention a few," he says. "In

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>
> **MICHELLE MARLBOROUGH** / Medidata Solutions

addition, it is essential for sponsors to partner with investigational sites and patient groups. These groups provide invaluable input into the study design and operational conduct. If feedback is sought well in advance of the final version of the protocol, sponsors can prevent costly and time-consuming flaws in the protocol design that result in delays in recruitment and/or costly protocol amendments."

Mr. Lee says early input on the protocol from investigators, study coordinators, and patient focus groups will help sponsors focus the research question being asked and balance the scientific hypothesis with medical and operational practicalities, thereby reducing protocol complexity.

"Past experiences have shown that conducting this level of feasibility early in the synopsis stage has led to dramatically increased recruitment rates and accelerated program decision making," he says. "Sponsors who have exercised these practices late in the planning process tend to demonstrate longer recruitment timelines and an increased number of protocol amendments. This type of early partnership with investigative site staff and patient groups can greatly reduce protocol complexity and avoid a large percentage of avoidable protocol amendments."

Michelle Marlborough, director, product management, at Medidata Solutions, says a recent study from the Tufts Center for the Study of Drug Development examined the economic impact of non-core procedures in a protocol provided the industry not only with some eye-opening metrics on the quantity of unnecessary procedures in a protocol, but also with a framework for assessing the importance of data in the protocol.

"Sponsors will adapt new techniques to ensure alignment of procedures and data capture with the most important objectives in the study and will find that, as a result, trials see better enrollment, retention, and compliance rates," she says.

In fact, clinical data gathered from 25% of the procedures administered to patients may be unnecessary, and, in the aggregate, are responsible for $3 billion to $5 billion in overall clinical trial costs annually, according to the Tufts study, which was sponsored by Medidata Solutions.

The study collected and analyzed more than 115 clinical trial protocols and categorized more than 22,000 medical procedures. The costs of "core" procedures — those supporting study end-points or safety objectives — and non-core procedures were measured using Medidata's benchmarked clinical trial cost database.

The study found that about 25% of all clinical trial procedures are considered non-core, i.e. are not directly tied to the trial end-points as agreed upon prior to the study by the FDA for demonstrating the safety and efficacy of the drug or therapy in question. The non-core procedures represent roughly 20% of a clinical trial's budget, an estimated $1 million in non-core procedure costs per clinical study.

Ms. Marlborough says to avoid protocol amendments, companies have to change their success metrics.

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> **ANDY LEE** / Sanofi

"The focus on first subject in as a measure of successful study start up does little to prompt good protocol design and limits the time available to do feasibility assessment," she says. "The accessibility to social media will also provide companies with new means of assessing feasibility, not just from the sites' perspective, but also from the patients' perspective."

Protocol amendments are often necessary for a variety of reasons, argues Jim Murphy, president of Almac Clinical Techologies.

"One key reason is that clinical trials are a combination of art and science rather than pure science," he says. "While even the most proficient protocol writers do their best to conduct

feasibility studies to avert amendments, once the trial begins, such studies are often not rigorous enough to predict the issues that arise during a trial. For example, even patient recruitment is a key area that feasibility studies cannot accurately predict. Amendments often prove necessary, whether we like them or not."

Michael Kirchengast, Ph.D., VP, scientific affairs, at PRA, says clinical trial protocols should always be developed on a solid basis of data and advice.

"All safety and efficacy data related to the compound, as well as a thorough analysis of protocols in the same or similar indication, are a given," he says. "That — combined with careful evaluation of the state-of-the art treatment, the use of an active comparator or placebo on top of best medical practice, and the current competitive study environment — should form the basis of a protocol draft. Regular interaction with key opinion leaders and the FDA and EMA will help carve out requirements and reduce later frustrations."

Dr. Kirchengast says an initial assessment of protocol feasibility should be done with the help of mining both publicly available and proprietary databases.

"This informatics-based approach should allow for identifying research-experienced sites globally and getting up-to-date information about competing trials, as well as regional variations in standard of care and medical practice," he says. "After having formed such basis and having verified the solidity of the protocol synopsis, individual site performance has to be assessed by looking into past site performance known to the CRO that will conduct the planned study and by close cooperation with each site to pre-identify eligible patients wherever possible in a chronic disease setting. In any acute care-related study, it will be of primary importance to identify patient pathways at each site and ensure seamless communication and cooperation between all parties involved."

Ms. Marlborough says sponsor companies should be looking to unlock the wealth of information they already have at hand that could drive more accurate study planning.

"By capturing metadata about a protocol design and feeding that information into a study or investigator database alongside the operational outcome of a trial, planning and impact of protocol design decisions can be based on real data rather than algorithms or best guess," she says.

Ms. Marlborough says every study completed should be having key information about the study collected, including design information, causes of amendments and metrics on enrollment, drop outs etc., so that protocol feasibility is built into the design process as well as being conducted directly with sites and subjects.

"There are many very simple indicators of feasibility that are completely overlooked on most studies, for example, using industry benchmark data or standard-of-care data to assess if there is an abnormally high frequency of an invasive procedure in the protocol that will indicate if patients will be willing to consent," she says.

Patient Recruitment

Experts say another critical area is patient recruitment. In 2010, clinical study sponsors, investigators, and their partners spent more than $2.3 billion on patient recruitment, and such expenditures are growing 15% annually, says Steve Hoffman, a registered pharmacist and chief pharmacy officer within McKesson Patient Relationship Solutions.

"Despite these efforts, two-thirds of investigator sites fail to meet the patient enrollment requirements for a given clinical trial, according to a Tufts study," he says. "Given these conditions, it's no surprise that the clinical research industry is looking for new ideas."

Mr. Hoffman says an innovative, patient-centric strategy showing considerable promise involves leveraging community pharmacies as a recruitment channel. With their access to and personal knowledge of patients and their medications, community pharmacists are uniquely qualified to add value to the targeting and overall effectiveness of patient recruitment initiatives, with the potential to greatly enhance R&D productivity.

Using only technology to identify patients for clinical trials can be challenging because medical records don't always tell the entire story, Mr. Hoffman says.

"Patients don't always take their medications as prescribed, and using just the prescription claims data to infer diagnosis can be misleading, he says. "For example, a trial candidate may recently have become pregnant; another might be on a medication for a different indication than what the records seem to show; others may have mobility, language, or personality barriers that would make them a poor fit for certain trials."

Mr. Hoffman says filters need to be applied to get an accurate picture of the patient.

"We're finding that community pharmacists are in an excellent position to help identify and engage patients based on their close relationships with their customers and the unique insights they can apply to the filtering process," he says.

Ryan McGuire, research team leader at Cutting Edge Information, says accurate patient demographic data are essential for proper clinical trial planning.

"A detailed understanding of the target patient population aids protocol development inclusion/exclusion criteria, site selection, and patient recruitment," he says. "Knowing age, gender, and other socioeconomic information is invaluable to protocol development and patient recruitment. A properly designed protocol will account for all of these variables. Working with patient advocacy groups can help clinical trial managers identify disease clusters and modify incentives to accelerate recruitment. PV

Four Approaches to Enhance Collaborations with Clinical Sites

Industry data related to investigator site performance have shown that sponsors are casting too large a net and engaging many nonperforming investigators to capture a small subset of high-performing centers. One strategy showing early signals of improved productivity at Sanofi is the development of strategic operational partnerships with known high performing centers. Based upon feedback from these partnered sites, Sanofi has identified four strategic approaches to enhance collaboration with such sites.

- Provide the company's long-range vision. Historically, sponsors have only sought investigator feedback just before recruitment of the first patient. Sponsors that provide investigational sites with longer insights into their research/development programs tend to have greater recruitment success due to better study anticipation, better site resource planning, and better patient identification.
- Partner with experienced clinical trialists to develop study designs that are medically and scientifically sound but also operationally achievable.
- Ensure that operational feasibility is an integral component of the protocol feasibility process to minimize complexity and site/patient burden.
- Work with sites to develop customized recruitment strategies that reflect their strengths and challenges.

Source: Andy Lee, Sanofi

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