RISING COSTS
Are Top of Mind in Phase III

Denise Myshko

Industry experts say there are multiple reasons why clinical trial costs are increasing, including patient and investigator recruitment challenges and protocol amendments.

The good news: more drugs are entering Phase III trials. The bad news: clinical trial costs continue to rise. The number of drugs in Phase III development in 2011 increased by 13%, representing the largest year-over-year improvement seen, according to Citeline's 2011 Annual Review of Trends in Pharmaceutical R&D. At the same time, per-patient costs for Phase IIIa and Phase IIIb saw an average increase of 88% and 86%, respectively, and now top $40,000 compared with about $25,000 three years ago, according to a study by Cutting Edge Information.

Per-patient costs are rising due to the lack of up-front planning before study start, says David Kelly, president of Kellman Pharmaceutical Services.

"CROs and sponsors need to use a data-driven evaluation process to ensure that the most qualified investigators are chosen for a study," he says. "The metric of 30% of chosen sites not able to produce a single patient in a trial surely does not help the per-patient costs. CROs and sponsors alike pass the same investigator lists from study to study choosing the wrong investigators over and over again."

Sponsors need to be less linear in the start-up process and focus more on the up-front diligence vs. being reactionary after a trial's enrollment is lack luster, Mr. Kelly says.

With per-patient costs at an all time high, it is even more important that each patient recruited for a trial remains in the trial, says Stacy Doce Patterson, M.D., executive VP, director of medical affairs, at ICC Lowe.

"Often patient recruitment is a focus, but perhaps not as top of mind, but equally critical, is patient retention," she says. "One of our clients was faced with a year-long trial where children had to get monthly injections. The risk of patient drop-out was huge so we developed a patient retention program to keep both the parents and children motivated to complete the trial. This program improved the efficiency of the trial."

Dr. Patterson says companies are looking for new channels to help identify and recruit appropriate patient types.

"Social media portals and online monitoring service are used to identify specific online patient and caregiver communities to help in-

DR. STACY DOCE PATTERSON ▪ *ICC Lowe*

"As recruitment becomes more challenging due to increased competition among companies targeting similar prospects, companies are looking for new channels to help identify and recruit appropriate patient types."

10 Steps for More Efficient Phase III Trials

- Be realistic about the time requirements/demands of a protocol to the site and patient.
- Understand what specifications in the protocol affect the patient population (e.g. target countries, institutional or community based sites).
- Clearly understand the patient population being targeted in the protocol.
- Allow adequate time for study design. Moving too fast to achieve protocol approval while the design elements are still under discussion or under regulatory review will cause avoidable rework.
- Include steps to check feasibility during study design. This is critical to achieving better country allocation and investigator selection, thus resulting in a true understanding of the patients best suited for the study.
- Understand the competitive landscape.
- Ensure a clear and efficient process is in place for site startup.
- Develop and implement effective advertising and retention programs.
- Select only those investigators with the appropriate experience, site infrastructure, and commitment to quality.
- CRO and sponsor must clarify roles and responsibilities up front; a strong partnership leads to success in terms of trials completed with quality, on time and on budget.

Source: Jeffrey Kasher, Ph.D., Eli Lilly and Company

ANDREA SCHIEFER ▪ *Clinipace Worldwide*

"The FDA now expects the industry to apply a more diversified, risk-based approach, by building monitoring plans and employing monitoring modalities."

form recruitment efforts in the United States and globally," she says.

Scott Connor, VP of marketing at Acurian, argues, however, sourcing people who are interested in and close to a clinical trial has never been an issue, even in the United States where trial awareness and understanding is still a challenge.

"Too much focus is being put on new strategies and technologies for solving the enrollment problem, but the underlying fundamental issues behind the problem go unchecked to this day," he says.

He says sponsors and regulators need to come to grips with the fact that protocol design is increasingly untenable, sites can no longer source all the patients from their own databases, sites are not properly compensated for processing external patient referrals, and CROs are not experts in patient enrollment.

"It's too easy for any of us to believe that the fantasy nexus of technology and social media will magically solve trial enrollment," Mr. Connor says. "That is dangerous and irresponsible thinking. The good news is that disruptive innovation is already available. Sponsors have the opportunity to invest in proven enrollment solutions, and they can objectively analyze that these investments are more financially prudent when compared with extending enrollment or adding more sites."

Best Practices for Patient Recruitment

Andrea Schiefer, VP, European clinical operations, executive director, pharmacovigilance, at Clinipace Worldwide, says companies can overcome difficulties in recruiting subjects by conducting thorough and meaningful feasibility studies.

"In-depth understanding of the opinions of the regulatory authorities and other stakeholders, such as the health insurance funds in the different regions where the study is conducted, is required," she says. "Additionally, a poorly designed or ambiguous protocol or case report form (CRF) may introduce systemic errors that can raise costs of a trial tremendously. A well-planned and designed protocol and CRF are key."

Ms. Schiefer says companies have to also reduce the amount of unnecessary protocol amendments that stem from protocol inconsistencies and design flaws.

"Clinical trial protocols have on average 2.3 amendments," she says. "Undetected design flaws, inconsistencies, or errors in the protocol, and difficulties recruiting subjects are obstacles that sponsors could have avoided with better upfront protocol planning and review."

Almost 60% of all protocols used in clinical trials for new drugs are amended during the trial, and one-third of those changes could have been avoided, according to an analysis conducted by the Tufts Center for the Study of Drug Development. The study found that more than half of all protocols require one or more amendments, with Phase III studies requiring the highest number of changes per amendment at 8.5. One-third of all amendments relate to protocol description and patient eligibility criteria. Median total cycle time to identify and resolve a protocol problem is 61 days.

Mr. Connor says sponsors need to be honest with themselves regarding a site's ability to source 100% of the patients.

MARKETING COMMUNICATIONS IN PHASE III

KEN KRAMER, PH.D., is Senior VP and Medical Director, Alpha & Omega Worldwide, part of The Core Nation, a family of healthcare marketing and medical communications companies that offers strategic, branding, and creative consulting services. For more information, visit thecorenation.com.

"A very wise international marketer once told me that our job was not to uncover need but to create need. Thus, it is very important to plan market-shaping activities to coincide with the end of the Phase II trials and the commencement of Phase III. In creating need, we must be able to identify what all stakeholders believe are missing from currently available therapies. In many cases, these multiple audiences will have different sensibilities that will have to be explicitly addressed during this period. A one-size-fits-all approach no longer works, as we need to speak to these audiences in a language that will resonate the most with them if we are to have a reasonable expectation of an impact. If this is done correctly, and well, all parties will anticipate the approval of a new drug and this will speed up the very crucial periods of trial and adoption."

DAVID REAR, R.PH., is President of Advanced Clinical Concepts, a medical agency founded on the idea that scientifically sound content leads to informed prescribers who are more able to make better decisions and deliver better care for patients. For more information, visit advancedclinical.net.

"At this stage of development, important product attributes are becoming increasingly clear and it's important to begin to identify the context within which messages need to be adapted to ensure that the brand is correctly positioned. Although the implementation of the plan itself may seem very tactical in nature, the process to complete the plan requires validation and alignment of strategies that impact everything from future clinical objectives to marketing and sales activities. It's important to keep in mind that the science behind the brand drives the content and provides the foundation on which the rest of the communication plan rests. All of this needs to be developed within the context of regulatory and compliance requirements; however the foundational role of the communications plan as a common thread that unites all these efforts remain steadfast."

"A site's ability to be at 100% is an increasingly rare occurrence, and therefore sponsors can actually drive down the price by investing in specialty enrollment services designed to maximize the productivity of existing sites within the existing enrollment timeline," he says. "Best practices are in place today to help sites be more efficient at processing the external patient referrals they need to enroll and retain. These practices include fairly compensating sites for the extra work required to evaluate and matriculate external patients and providing sites with staff support to triage potential patients."

Mr. Connor says per-patient costs can be held in check or lowered if sponsors better understand the economics of patient enrollment compared with the economics of adding time and sites.

"In the past, there has been suspicion over patient recruitment and enrollment as a business," he says. "But today there are plenty of enrollment metrics that objectively underscore that sponsors can be cost neutral at worst, and certainly cost positive."

Carla Radke, senior director, clinical monitoring, at Clinipace Worldwide, says one way to cut costs is to design a trial so that an interim analysis is conducted after a certain percentage of subjects have enrolled or completed the trial.

"A decision is then made sooner whether to continue the trial," she says. "Sites can commit to enrolling a certain number of subjects contractually. Even if there are competing studies, if they have agreed contractually, hopefully, sites will reach their quota."

Ms. Schiefer says good planning and feasibility studies and applying risk mitigation plans that describe how recruitment issues are detected at the very beginning are critical for addressing patient recruitment and per-patient costs.

"Sponsors have to implement monitoring plans to identify and exclude sites that are not performing well," she says. "They have to train the investigators and plan to implement alternative training and communication methods — teleconferences, webcasts, or online training modules — for providing and documenting ongoing, timely training and feedback."

Ms. Schiefer says sponsors also should conduct analyses of site characteristics, performance metrics, for example, high-screen failure rates, high frequency of eligibility violations, and delays in reporting data, and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance.

"Pharmaceutical companies should conduct aggregate statistical analyses of study data to identify sites that are outliers relative to others and to evaluate individual subject data for plausibility and completeness," Ms. Schiefer says.

Ramana Reddy, practice leader — life sciences, at Cognizant Business Consulting, says a mix of marketing and management, together with scientific expertise, can make a Phase III recruitment campaign more productive and cost-effective.

"Hands-on subject support and personal attention must be implemented to retain participants," he says "Almost 40% of all prequalified volunteers fail to continue in programs due to lack of responsiveness of investigative site personnel." PV

SCOTT CONNOR ▪ *Acurian*

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