



Bio-IT World

Indispensable Technologies Driving Discovery, Development, and Clinical Trials

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Sponsors Getting 'Proactive' About Phase IV Studies

By Deborah Borfitz

For a multitude of reasons, it's a good idea for sponsor companies to spend more energy on so-called "Phase IV" post-marketing studies. A maturing drug pipeline is at risk of generic erosion unless new indications are found. Medicare and private health plans are demanding more real-world data as a condition of coverage for specific subpopulations. High-profile recalls have drawn unflattering public attention to blockbuster products.

Oh, and the FDA is a bit more interested in seeing companies follow through on their promise to do Phase IV studies as a condition of marketing approval. Even the average consumer probably now knows that adverse events aren't fully discoverable until a product is mass marketed.

It is no surprise then, that — based on annual spending levels — Phase IV trials are the fastest-growing category of clinical research. In 2007, development spending on Phase IIIb and IV trials is projected to be over \$5 billion - near-

ly four times the 2000 figure, according to Kenneth Getz, senior research fellow at the Tufts Center for the Study of Drug Development. The number of participants in Phase IV programs also skyrocketed to a median of 920 in the 1990s, up from 123 a decade earlier.

The chief goal of Phase IV studies is to satisfy regulatory demands or, sometimes more important, to increase a product's profit potential. Overall growth in ethical pharmaceutical sales has been sliding for more than a decade, reports Getz.

"We're seeing companies take a proactive approach to post-marketing data acquisition in the form of [disease/patient] registries," remarks Jeff Williams, CEO of Clinipace in Research Triangle Park, N.C. The primary aim is to collect "new data for new indications...and [off-label] applications." Many new companies are popping up that do nothing but search for alternative indications for existing products.

"Previously, post-approval studies were primarily funded either through the NIH [National

Institutes of Health] or as investigator-initiated trials funded by industry, but now we see more sponsor-initiated phase studies and registries," says Richard Gliklich, president and CEO of Cambridge, Mass.-based Outcome. The NIH has also been shifting more attention to Phase IV trials, however, as a search of its clinicaltrials.gov Web site attests.

Interest in registries is driven by high-profile recalls, such as the Vioxx incident. "Post-marketing surveillance is primarily dependent on the voluntary reporting of adverse events by providers — meaning they need to not only recognize the event, but know that it's not on the label — and that doesn't happen with great predictability or with a denominator for determining rates [of particular adverse events]," says Gliklich. The New England Journal of Medicine never succeeded in its push to follow the first 20,000 recipients of every released product. But the FDA has moved towards recommending or requiring "risk minimization action plan" that has spurred tremendous interest in registries both here and abroad.

Outcome: Tracking More Than One Million Patients

By Deborah Borfitz

Although all electronic data capture (EDC) companies declare they do them, Phase IV studies are in fact a "niche" with regulations, user needs, and technologies that are different from those of pre-approval trials, says Richard Gliklich, president and CEO of Cambridge, Mass.-based Outcome. He expects the niche to occupy "at least a quarter of the market" in the years ahead.

"We have twice as many [Phase IV] programs this year as last," says Gliklich. The volume of patient registries has also doubled. "We're tracking more than one million patients a year now." The sponsors include provider organizations interested in issues such as in-office delivery of anesthesia and the implications of polypharmacy.

Outcome is currently under contract with the Agency for Healthcare Research and Quality (AHRQ) to produce a "how-to" reference guide for public and private sector entities on designing and operating successful patient registries, says Gliklich, the senior editor. A key user will be government decision-makers who elect to provide

coverage simultaneous with the development of further evidence about a treatment, such as implantable cardioverter defibrillators. The registries handbook has 39 contributors with expertise in patient registries, including the FDA. It is soon to reside on the websites of the AHRQ and the Centers for Medicare & Medicaid Services.

EDC was first tested in large Phase IV trials, where Outcome demonstrated 40 percent savings in data management costs in the conversion from paper to the Web, says Gliklich. Still, relatively few Phase IV trials today use the technology because of sponsors' relational issues with practicing physicians and the dearth of EDC systems that clinicians can operate in the absence of an in-house data coordinator and IT support. "Post-approval, investigative sites are sponsors' customers, and [companies] really want to delight them...not force them to use a particular EDC system." For a single Phase IV study, there can be upwards of 1,000 sites to please.

The response of early-phase EDC companies, such as Phase Forward, was to come out with stripped-down versions of their products. But what real-world sites really want is an EDC sys-

tem that's easy to use, since investigators are often minimally experienced and site monitoring is limited. Investigators also want a system that will meet their other needs, such as pay-for-performance data, says Gliklich. "Our system has a very rich reporting side for comparison and benchmarking. With [Outcome 7.0], sites can transmit data and make it available in multiple formats for different end-users, including patients."

The idea is to create "non-monetary" value for sites, says Gliklich. Grant dollars are relatively small for Phase IV studies because of strict regulations and American Medical Association policies guiding payment structures.

Outcome focuses solely on EDC-enabled Phase IV trials, including issues of compliance with the mammoth Health Insurance Portability & Accountability Act. Depending on the primary purpose of the project — research or healthcare operation — investigators may need to obtain informed consent and authorization or they may need to utilize a data use agreement, says Gliklich. If it's impractical to get authorization to use patient data, they need a waiver from the privacy board.

OUTCOME
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