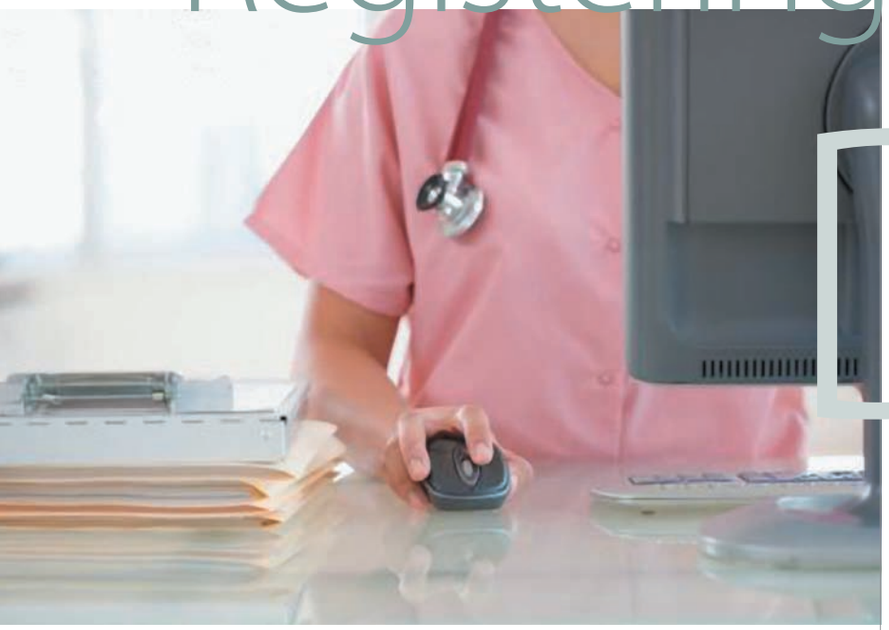
BY KIM RIBBINK

Registering SAFETY



As the emphasis on drug development shifts toward improving risk management, **NEW TOOLS HAVE EMERGED TO EVALUATE SAFETY BOTH PRE- AND POSTAPPROVAL.** Increasingly, companies are looking at patient registries as an integral part of their safety arsenal.

Drug safety has become the focal point among patients, their doctors, regulatory bodies, and pharmaceutical companies. Efforts to minimize risk have companies looking for alternative ways to uncover adverse events early on and to monitor a drug's safety even after approval.

As this issue was going to press, the importance of patient safety was brought to bear when Pfizer suspended a large, Phase III trial evaluating the investigational cardiovascular therapy torceptrapib/atorvastatin (T/A) because of an increased rate of mortality in patients receiving the combination compared with those receiving atorvastatin alone. The study was halted based on feedback from an independent data safety monitoring board (DSMB) that found, as part of its monthly analysis of mortality data and a quarterly analysis, there was an imbalance of mortality and cardiovascular events, including stroke, heart attack, and revascularizations (e.g., coronary stents or bypass surgery).

A DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. Similarly, a patient registry is an organized system designed to address important safety questions for a specific product using observational study methods to collect uniform data to evaluate specified outcomes.

The goal is to identify risk and a product's safety profile earlier in development or as early as possible after marketing, says Robert Reynolds, Sc.D., executive director and head of epidemiology, in Pfizer's safety and risk management division.

"From the focus on improving risk management have emerged new tools for evaluating safety after a medicine is approved, and registries are one tool," he says.

Elizabeth B. Andrews, Ph.D., MPH, VP of pharmacoepidemiology and risk management at RTI Health Solutions, agrees that during the first few years of marketing a product, there are few satisfactory alternatives to patient registries for providing credible, quantitative data on the safety of a product.

As part of an increased focus on safety, the FDA has noted in its guidance document, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, that through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources and evaluate the factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics.

"Certainly, through their inherently observational approach, registries offer a valuable methodology for collecting real-world data on a product's safety in a postapproval setting," says Leanne R. Larson, MHA, VP of strategic consulting at Ovation Research Group.

According to a draft guideline, Registries for Evaluating Patient Outcomes, prepared for the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, patient registries serve many purposes, including: to describe the natural history of dis-

Registries provide the company and the healthcare community a channel **TO CAPTURE VALUABLE DATA ABOUT THE "REAL-WORLD" UTILIZATION OF THEIR PRODUCT**, in addition to the evaluation of safety.

DR. ELIZABETH ANDREWS
RTI Health Solutions

ULTIMATELY WE WANT TO BE ABLE TO CONDUCT THE BEST SCIENTIFIC STUDY POSSIBLE while still providing safety knowledge to regulators and patients and physicians in a timely manner.

DR. ROBERT REYNOLDS
Pfizer

ease; to determine clinical effectiveness or cost-effectiveness of healthcare products and services; to measure or monitor safety and harm; and/or to measure quality of care.

Many in the industry recognize that patient registries are a valuable way to monitor safety because they can provide data on a broad population.

"Patient registries can act as surveillance systems to monitor a population for any occurrence of an unexpected or harmful event," says Richard Gliklich, M.D., president and CEO of Outcome, and senior editor of the AHRQ report.

Increasingly, companies are looking closely at various ways to include patient registries as part of their risk-assessment plans.

"Some companies are being proactive and conducting a registry or a large streamlined trial at the time of product launch to better evaluate the risk in an actual use setting," says Annette Stemhagen, DrPH, FISPE, VP of epidemiology and risk management at United BioSource Corp. "Other companies may decide to be even more proactive and initiate a study during Phase IIIB, the period between the NDA filing and approval."

The study may take the form of a randomized clinical trial (RCT) or an observational study or registry, she notes.

Safety **FIRST**

When a new drug application (NDA) is filed, companies must demonstrate, among other things, that the drug is safe in its proposed use. Once a product comes to market, the FDA depends on a reporting system to monitor spontaneous adverse event reports or case reports. The FDA receives adverse drug reaction reports from manufacturers as required by regulation. Healthcare professionals and consumers send reports voluntarily through the MedWatch program. These reports become part of a database.

The FDA defines adverse events (AEs) as any untoward medical occurrence in a patient administered a pharmaceutical product, whether related or considered to have causal relationship with the treatment. AEs are categorized according to the seriousness and expectedness of the event.

But the AHRQ report says spontaneous reporting relies on a nonsystematic recognition of an AE by a clinician and the active effort of the clinician to make a report to the manufacturer and health authorities. Moreover, these events are generally reported without a denominator — the exposed population — making it difficult to determine an incidence level.

"By providing a system for reporting AEs, outside of the current practice of spontaneous reporting, and by gathering information on the exposed population, registries can help to both quantify and properly attribute the risk," Dr. Gliklich says.

Dr. Reynolds says registries and epidemiology studies can complement safety information from clinical trials and spontaneous reporting.

"One of the important aspects of registries and epidemiology studies is that there are many relevant safety questions — rare events in large populations, studying long latency periods, and looking at vulnerable populations — that can only be answered using these methods," he says. "That said, however, it's important that these results are never viewed in isolation from other data sources. We need to look at results from clinical trials, spontaneous reports, epidemiology studies and registries, and sometimes preclinical data sets to evaluate fully a particular safety question."

Peggy McHugh, VP of strategy and development at Registrat Inc., agrees that registries allow manufacturers to cast a broad net to collect valuable information on a marketed product's use, effectiveness, and safety.

"These data can extend the clinical-trial matrix and safety profile to further establish the ratio of benefit to risk for a product and support product education and risk management throughout the product life cycle," she says.

Safety scares, such as the one that ultimately led to the withdrawal of Vioxx, have led many in the industry to look at ways to improve post-marketing safety surveillance.

One option is a two-stage approval process for new drugs, which, according to Dr. Gliklich has received strong support from industry and academia and has sparked growing interest from regulators. This has the potential to not only improve AE detection, but also to shorten times to the first stage of approval.

In this evolving area, Dr. Gliklich says companies are taking a three-pronged approach.

"First, companies that are approaching approval are actively discussing with the FDA the use of patient registries as part of the Risk Minimization Action Plans (RiskMAPs) or other commitments for the post-approval phase," he says. "Second, companies that sense a question of safety in the marketplace are developing multipurpose registries that address both effectiveness and safety. Third, companies with drugs earlier in development are creating patient registries to determine background safety signals before introducing their products."

A RiskMAP addresses risk-assessment activities and risk minimization actions.

Equally, registries provide assurance and often help to refute signals that emerge from single case reports or from spontaneous AE reports, according to Dr. Andrews.

"Hundreds of potential safety scares arising from single or small clusters of case reports have been avoided by having prospectively collected data on a large patient population already at hand," she says. "Because these examples don't make the news, they are easy to forget. The value to the public, however, is huge."

Trial or **REGISTRY?**

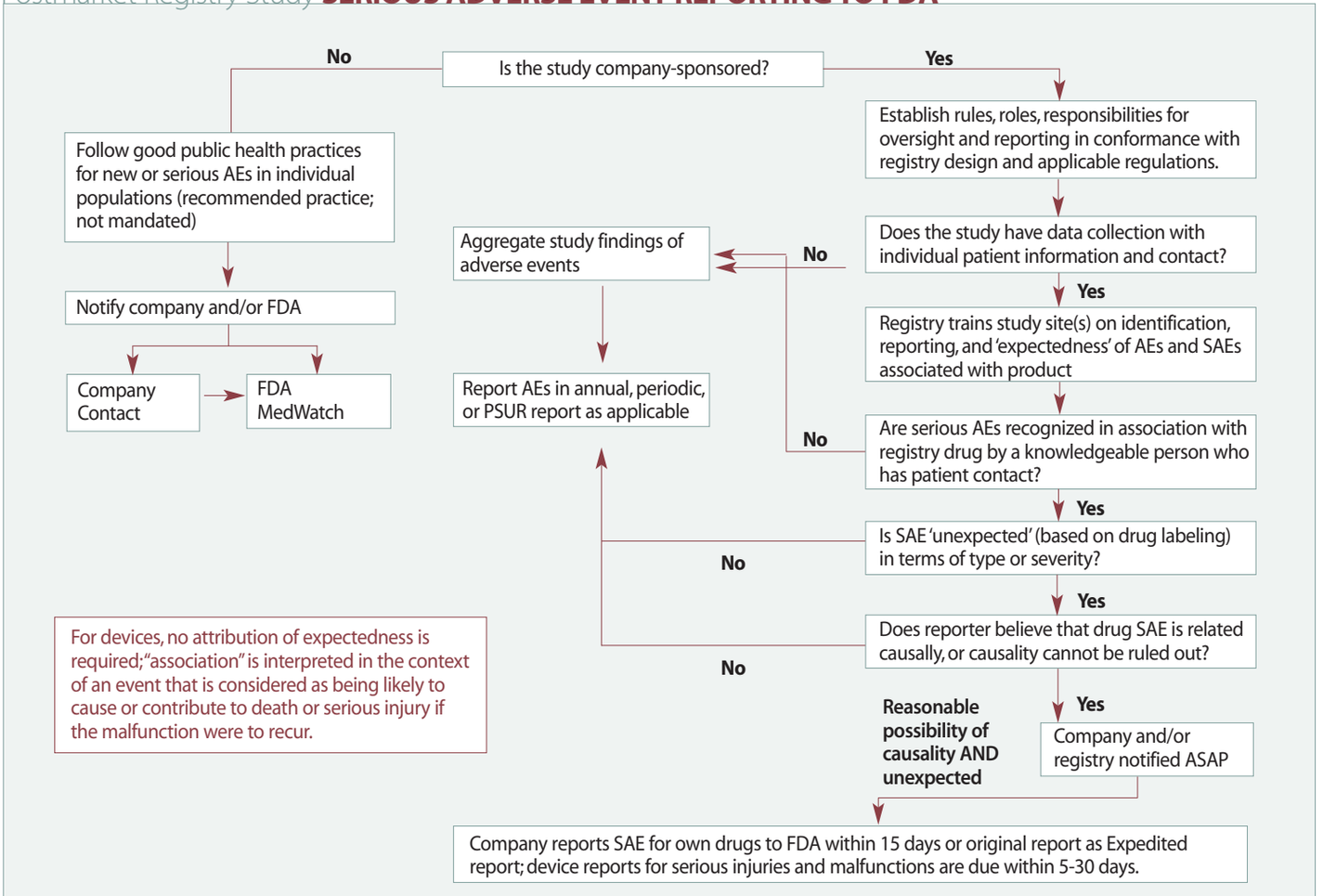
Industry experts point out that it's not a matter of choosing between one or the other when it comes to RCTs versus patient registries.

"Registries are designed to answer important scientific questions," says Vikram Dev, M.D., VP of U.S. clinical drug safety at AstraZeneca Pharmaceuticals. "Registries will not replace RCTs, but they may provide additional safety information that is unavailable from other sources. They could be an important public health resource assessing the effects of drugs in a wider population than was assessed in RCTs, such as risk factors, comorbidities, concurrently administered medications, and long-term outcomes."

Patient registries offer a potentially more representative perspective of what is achieved in real-world settings because they evaluate care as it is actually provided, which is not assigned, determined, or recommended by a protocol, the AHRQ report notes.

"In a controlled trial, patients are closely monitored, but once a medicine is being used in the real world physicians may prescribe the medicines differently from the label, or patients don't always take the medicines as intended, so the value of closely monitored patient registries and epidemiology studies is to understand the drug's safety in the real world, not in the controlled environment," Dr. Reynolds says.

Postmarket Registry Study **SERIOUS ADVERSE EVENT REPORTING TO FDA**



Source: Registries for Evaluating Patient Outcomes, prepared for Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, Washington, D.C. For more information, visit ahrq.gov.

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DR. RICHARD GLIKLICH
Outcome

But interpreting the information gathered by patient registries requires analytic methodology geared to addressing the potential sources of bias that challenge all observational studies.

"To draw credible conclusions, it is critical to have the analytic capabilities to address observational data, missing data, and confounders that can arise in large, complex patient registries," Ms. Larson says. "With that caveat in mind, it is possible to learn a lot from a registry population and have access to data that aren't available in other settings."

According to Dr. Dev, a registry is very much like a cohort study, with a limitation that its usefulness is dependent on enrollment.

"Additional limitations include recruitment biases, confounding by indication, and a lack of randomization and a placebo control," he says.

Patient registries also cover a wider population than would be possible in clinical trials. And while the vastness and duration of registries do pose challenges, both financially and logistically because of the need for extensive cross-functional input, experts say they are generally more cost-effective than RCTs.

"Although there may be more sites and patients, generally registries require less extensive data collection and reduced site monitoring requirements," Ms. McHugh says.

It also may be difficult to quantify data from a clinical trial. For example, the sample size may have been too small to observe more than a couple of cases of a potential safety issue or the risk factors may not have been well-understood. Thus, by creating a registry it is possible to get a clearer understanding of critical safety issues.

"Studies need active plans to maximize patient retention over time," Dr. Andrews says. "And the analyses should be planned differently from those used in clinical trials. The biggest mistake made in the design of registries is to treat them as if they were modified clinical trials. This approach leads to an unnecessary burden on clinical sites and patients, poor compliance with the study, and incomplete follow up."

There are clear differences between clinical trials and registries, and companies are looking to new approaches to address study-related issues in a naturalistic setting.

"Companies are incorporating objectives, such as signal detection and trend analysis, into studies that are broadly described as observational or epidemiologic, allowing them to monitor product outcomes and effects across large patient populations," Ms. Larson says. "They also recognize the critically different statistical methodologies that are required to fully understand registry data that address issues around missing data, nonrandomized treatment groups, and other analytical factors."

Dr. Andrews says registries often require different tools from those used in clinical trials.

REGISTRIES PLAY AN IMPORTANT ROLE IN both risk assessment and in evaluation of risk minimization programs.

DR. ANNETTE STEMHAGEN
United BioSource

"This includes direct contact with patients, tracing services to minimize losses to follow-up, other methods common to survey research, and linkage with other data sources, such as cancer registries," she says.

Best **PRACTICES**

Careful planning needs to go into designing a patient registry and preparing outcomes reporting, ensuring scientific analysis drives how and what data are collected. According to the AHRQ report, points to consider include: selecting data sources, populations, and comparison groups; determining whether sampling is needed and if so, how; identifying possible sources of bias; and addressing them to the extent that is practical and achievable.

Ms. McHugh says concise data-collection forms, study documents, investigator agreements, and employing central IRBs help streamline site and patient enrollment.

Patient registries need to be designed and managed by a crossfunctional team from the sponsor, including representatives from clinical, pharmacovigilance, medical affairs, outcomes research, regulatory, epidemiology, and marketing, experts say.

Bringing these functions together can present challenges for some organizations, and that's particularly the case with safety studies.

"The stakes are high when there's a safety question that needs to be addressed," Ms. Larson says. "Organizations have to look carefully at how to integrate the needs and objectives of a number of different groups."

The potential longevity of some registries means it is vital to engage with external stakeholders, such as clinicians and patients, to assure that the study procedures make sense in a real-world setting, Dr. Andrews notes.

"Most importantly, registries must be noninterventional, must be easy for the site to implement, and must include a strong analytical plan that accommodates the complexities inherent in observational data," Ms. Larson says. "Finally, patient feedback must also be

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Companies will need to **COMPLY WITH SAFETY-REPORTING** requirements within the conduct of registries.

DR. VIKRAM DEV
AstraZeneca

considered because ultimately patients are the best source for information on how they are responding to their treatments."

Those with expertise in the area note that while industry's response is varied, best practices are emerging.

"For example, one thing we advocate is the use of an electronic messaging system from the registry system to the sponsor's product safety group when a potential reportable event has been entered," Dr. Gliklich says. "This speeds the sponsor's response and also ensures that the registry is feeding into rather than duplicating the company's product safety database."

Experts say registry acceptance has grown significantly in recent years but that responses to registries from patients and advocacy groups wanting more safety information vary depending on the demographic and disease state.

"For example, we find that if an expectant mother is aware of a pregnancy registry that involves a product that she has been exposed to she is receptive to learning more and potentially participating in the registry," Dr. Andrews says.

A disease registry that is initiated before product launch and that continues after launch enables a sponsor to gain valuable insights about patients with the condition and then how the product is used in clinical practice.

"There are currently several registries that are being conducted as a part of a risk-minimization program," Dr. Stemhagen says. "For example, the TOUCH program sponsored by Biogen Idec to further understand the risks associated with Tysabri use for the treatment of patients with relapsing multiple sclerosis has two registry programs. The first is a registry of all patients who are prescribed Tysabri to monitor that risk-minimization strategies are implemented at each Tysabri infusion. The second is an in-depth registry, TYGRIS (TYSABRI Global Observational Program in Safety), of a sample of patients in the United States and in the European Union, to gather further risk factor information and to follow patients for up to five years to identify any safety risks associated with long-term use."

Some concerns about the potential use of patient registries by, for instance, the Centers for Medicare and Medicaid Services (CMS) have been raised. For example, in its Guidance on National Coverage Determinations with Data Collection as a Condition of Coverage, CMS describes several examples of how data collected in a registry might be used in the context of coverage determinations.

"A potential concern regarding use of registry data would be that limiting patient access to medications could begin, based on the willingness of prescribers and patients to participate in a registry," Dr. Dev says.

While regulatory bodies continue to review the apposite approaches to tackling safety concerns, industry advisors say as yet there has been no specific guidance from the FDA or CMS.

"Sponsors must weigh their internal objectives alongside the FDA's anticipated response and find a viable middle ground, perhaps even drafting a program design to present to the FDA before any official mandate," Ms. Larson says. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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