

## Insider Insights

### Outcome Sciences

CWWeekly's semi-monthly company profile feature, Insider Insights, interviews executives of companies and organizations in the clinical trials space. Writer Ronald Rosenberg sat down with Richard Gliklich, M.D., president and CEO of Outcome Sciences.

**Q** What can CROs learn from disease patient registries that sponsors, disease associations, patient advocate groups and medical professional organizations don't already know about the major researched diseases?

**A** Patient registries basically offer a view of treatments and their actual results in the real world. It's an area that links together manufacturers, providers, patients and payers as, ultimately, everyone is invested in understanding what works and for which patients. The other key point is because so many groups not only benefit from registries but need them for the quality of their decision-making on many levels, these programs are best leveraged across different stakeholder groups rather than staying in silos. That's a concept we have been pushing for. In other words, we are building models in a number of disease areas to have multiple stakeholders, including sponsors working around registries together.

**Q** Post-marketing approval studies—your company's specialty—are growing as sponsors seek to gain evidence for higher reimbursements or submission for expanded labeling, as well as to show safety and fill regulatory requirements. What changes are you seeing in phase IV study requirements from the FDA, Canadian and European regulators from five years ago?



**A** The first major change has been a shift from relying on spontaneous adverse event reporting to seeking systematic collection of post-marketing safety data almost routinely for new drugs and devices using observational methods, including the FDA's Sentinel Initiative and a large number of registries. For example, in addition to asking manufacturers to develop registries, the CDRH (Center for Devices and Radiological Health) is beginning to develop some of its own registries and we are involved in some of that work.

The second major change has been a much more clear focus on benefit in addition to risk. With FDAAA in the U.S., risk management guidance changes in Europe and the proposed changes to the approval process in Canada, all three groups of regulators are converging on the same concept—that approval and maintenance of approval for products depends on a positive ratio of benefit to risk. So when a product is first approved, there is limited information on its real-world safety and effectiveness, but as experience accumulates, whether more is learned about the product's safety profile or sponsors and physicians find new uses for the product or other benefits, that ratio will change over time.

Thinking of it as a benefit-to-risk ratio is what regulators are now trying to do. Five years ago regulators didn't think a lot about benefit, but now that has changed. That's

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*Richard Gliklich, M.D., president and CEO, Outcome Sciences*

the reason the FDA will sometimes describe what it is doing as comparative effectiveness research, or why Canada has the Drug

#### Outcome Sciences

**Headquarters:** Cambridge, Mass.

**Year founded:** 1998

**Description:** Provides services and technologies for evaluating the safety, effectiveness, value and quality of healthcare products, therapies and services, including patient registries, post-approval studies, data and integrated technologies for evaluating real-world outcomes. Teams have designed, developed and managed patient registries including many of the largest and most well-recognized programs for disease outcomes, safety and risk management.

**Officers:** Richard Gliklich, M.D., President and CEO  
Bob Kaufman, Chief Operating Officer and Senior Vice President  
Dan Levy, Chief Technology Officer  
Nancy Dreyer, Ph.D., MPH, Chief of Scientific Affairs and Senior Vice President

**Offices:** Cambridge, Mass.; Washington, D.C.; Chicago; London; St-Prex, Switzerland; Sydney; Mumbai and Tokyo

**Employees:** ~250

**Customers/clients:** More than 2,500 customers including pharmaceutical, medical device and biotechnology companies, healthcare organizations and government agencies.

**Clinical studies:** More than 250 phase IIIb, phase IV and other types of studies.

**Web site:** [www.outcome.com](http://www.outcome.com)

Safety and Effectiveness network, whose stated purpose is to evaluate the safety and effectiveness of pharmaceuticals when used by a diverse patient population outside the controlled environment of clinical trials.

**Q** Phase IIIb studies, which are additional therapeutic exploratory and confirmatory studies, are also conducted on marketed drugs to search for a new indication. In your experience, what are some of the strategies and new operational chal-

lenges you are facing?

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lenges sponsors and CROs have to consider in pursuing phase IIIb studies?

**A** Phase IIIb studies face the challenge of operating in a regulated environment but ideally mimicking real-world conditions as much as possible. In some ways it is an oxymoron. The challenge for sponsors and groups like us is to simplify and streamline the procedures in a manner that provides representative data from a real-world perspective while meeting the regulatory requirements.

From a logistical perspective, this limits the number of centers you can work with. For example, true community-based practices will have trouble participating in highly regulated studies. Yet you want to have those types of groups represented because they may see a different patient population and have different practice patterns. It's a balancing act that requires a fair amount of expertise and logistical strength.

Groups like ours have invested in developing networks of real-world centers that can function with simplified phase IIIb studies without it manifestly affecting what they do day to day. That sometimes means applying different methodologies, like cluster randomized and pragmatic designs, designs that enable you to meet the regulatory requirements but still get the real-world view of how the product can be used for purposes during and after the approval process.

**Q** You've said non-traditional trials likely will be equal if not more important than randomized, double-blind, placebo-controlled studies in comparative effectiveness research (CER), as drug makers need to spend more time in the drug development cycle to figure out and assemble the evidence needed to better determine the therapeutic value of new therapies in real-world settings. Explain.

**A** When you think about CER, you are dealing with different types of decision makers. They are not just regulators, but

payers, physicians and patients who face many different types of questions. Each requires data fit for the purpose of making that particular decision. Some might want different information as well as use different evidentiary standards, depending on the questions. It is very question dependent and decision-maker dependent.

That's why CER is different. You have to understand all the stakeholders and their needs, and what they are thinking about when they make decisions. And while randomized clinical trials are the gold standard for evidence from an internal validity perspective, meaning the small group of patients you are testing, they give you information that is close to truth, but also they have many limitations critical for decision-makers.

For example, many studies have shown that randomized trials might not reflect true results in real-world settings, and studies on narrow populations can not be generalized to even large sub-groups of patients. In one case, CMS (Center for Medicare and Medicaid Services) made a determination against national coverage for CT colonography because even though the randomized studies were really strong, there wasn't enough information about older patients to inform making a decision for the Medicare population.

Randomized clinical trials (RCTs) are also limited when patients don't use the drugs as intended. For example, if there are adherence issues in the real world, you might not obtain useful results from an RCT and a traditional intent-to-treat analysis. By the intent-to-treat approach, I mean that if a patient is randomized to receive drug A, he is analyzed based on the assumption that he took drug A. But if turns out a particular patient never took drug A and had an adverse event, is it appropriate to link that adverse event to the drug he never actually took? Randomized trials also are not useful for studying off-label uses of drugs, which are very common. In fact, more than 60% of oncology drug use is off-label.

Finally, there are just too many questions

than can be answered by RCTs alone. Every clinical or market-access decision requires information, and there are not enough dollars in the world to do everything through randomized trials, even it were the best way to do it. As a result, experimental and non-experimental approaches are both necessary and complementary. As a sponsor, you need to understand why you would choose one over, or in addition to, another, depending on the goal.

**Q** In the near future, researchers for some rare disease registries are likely to collect and store biosamples for future analysis, as the genetic origin of these disorders, such as cystic fibrosis, becomes better understood. How will this advanced research be developed amidst new legal, ethical and logistical issues?

**A** There are many issues around biosamples, including obtaining permission that covers potentially varying purposes or obtaining repermission, protecting confidentiality when the samples themselves may be identifiable and dealing with very specific legal issues, such as the Genetic Information Non-Discrimination Act (GINA).

Bio-specimens, and DNA in particular, are inherently unique, and there are a number of routes by which DNA information can be linked to an individual. Even if you have de-identified biological information, if it is tied to highly sensitive clinical information it might provide a match to the biological information, say, in a forensics setting.

At the same time these legal, ethical and logistical issues are arising, solutions also are being created, such as methods to separate bio-specimens with one directional linkage with clinical data, methods to obtain permission electronically for new purposes and others. These problems require specialized solutions. Some solutions exist and others are rapidly emerging. It is really a hot area of discussion and innovation that is very closely linked with patient registries. 