

Pharmaceutical Executive

FOR GLOBAL BUSINESS AND MARKETING LEADERS

PERSONALIZED MEDICINE MEETS THE REAL WORLD

A WAVE OF GENOMIC MEDICINES IS COMING DOWN THE PIPELINE, AND THEY'RE GOING TO BE EXPENSIVE. CAN COMPANIES PROVE THEY'RE WORTH IT? MAYBE: BUT THE CLAIMS PAYERS SEEK AREN'T COMING FROM TRADITIONAL CLINICAL TRIALS.

BY NANCY DREYER



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HE ERA OF PERSONALIZED MEDICINE

was heralded long before its arrival. But not until Herceptin (trastuzumab) came onto the market in 1998 to treat breast cancer in HER-2 positive patients did companies understand just how much genomics could alter the healthcare landscape.

Since then, companies have advanced the science, and have even brought a few tailor-made therapies to market. NitroMed, for example, figured out that BiDil (isosorbide/hydralazine) works best in African Americans. But while pharma has pushed this and other personalized medicines through clinical development, much of the data that proves these drugs' utility in real-world settings can't be obtained through the traditional route of experimental medicine. Instead, payers are demanding clinical and cost-effectiveness information for these very expensive medicines, as well as long-term safety and efficacy information. So great is the need for coverage of these pricey, but often life-saving, therapies, that it is changing the traditional research paradigm.

Now, the industry is looking toward observational research to fill in the gaps. Observational research includes epidemiology, the scientific study of the distribution and determinants of disease, and outcomes research, which evaluates the status of participants after receiving care. Both of these disciplines look at patients and drugs outside of controlled lab settings. Instead of dictating practice, researchers observe, record, and build a body of evidence that shows how drugs are used, whether they work, and if so, in which patients. Pharma no longer controls all aspects of treatment, but instead relies on scientists who know how to design and analyze data collected in non-experimental settings like doctors' offices.

Certainly, there is an urgent need for this type of research. Pharma's pipelines are filled with personalized medicines, and private and public payers are hinging their coverage on the all-

important value claims this research is uniquely positioned to address. However, most companies are still in the thick of clinical development, and aren't thinking about the observational research they will need to demonstrate value to buyers. This article helps executives get out in front, by outlining the challenges personalized medicine poses to the research framework and offers advice on how to design research programs to ensure maximum uptake of the product.

Intrinsic Challenges

The very nature of personalized medicine challenges the way scientists normally handle drug development. There are some unique issues that characterize research for tailor-made therapies.

The right patients are hard to find Even large disease categories look like a collection of rare diseases when patients are grouped based on common polymorphisms and biomarkers. For example, although lung cancer is the leading cancer killer of both US men and women, Iressa (gefitinib) and Tarceva (erlotinib) are most successful when given to a subset of just 10 percent of lung cancer patients with a particular set of mutations in their epidermal growth-factor receptors.

Although advances in technology for examining DNA, proteins, and other biomarkers allow companies to understand and describe these patient subgroups, genetic testing is not yet a widespread or standard part of most physicians' armatorium. As such, many patients who can be helped by personalized medicines are simply not recognized.

Informed consent is more challenging The Office of Human Research Protections (OHRP) and the Office of Civil Rights (OCR) offer confusing and, at times, conflicting information to guide research practices with respect to informed consent and privacy. However, researchers of genomic medicines have the added burden of requirements outlined by the Centers for Disease Control, which don't necessarily conform to those required by OHRP and OCR.

The complexity of multiple requirements often leads researchers to provide two different consent forms—one for the overall research project and the other specifically focused on issues relating to genetics (see "Biology of an Informed Consent Form," page 84). For example, in the general consent form, patients would agree to provide a sample of blood. However, the genomics consent form must identify the specific types of genetic testing to be performed, what happens to the samples should a subject withdraw from the study, and whether or not patients will be notified of results.

There's also a host of ethical issues that come along with any research related to patients and their genetic information. Pharma companies must figure out how they will handle the issues associated with screening for "high-penetrance genes"—highly predictive mutations that signal a major risk of disease development—which can cause psychological harm

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to individuals that discover they carry a substantial risk of developing a serious or fatal disease. Consider, for example, age-related macular degeneration (AMD), a leading cause of vision loss and blindness with no known cure. Researchers recently identified the presence of two important genes as culprits in AMD development. Researchers found that 74 percent of study subjects with AMD had either one or both of these genes, but no protective variants of either gene. How should sponsors handle telling patients they have both of these traits?

Little safety information Personalized medicines *should* be safer for patients. Just look at the anti-HIV drug Ziagen (abacavir). About five percent of patients taking the drug experience a serious adverse hypersensitivity reaction. But by testing patients, researchers can determine which ones are more likely to have this reaction, and reduce the risk of that side effect to less than one percent.

In practice, however, personalized medicines come to market without much information about delayed side effects and long-term safety and effectiveness. After all, small patient populations mean smaller trials and less data. Genzyme, for example, received approval for Cerezyme to treat Gaucher disease from a pivotal trial based on data from only 30 patients.

Many personalized therapies are fast-tracked from Phase II to market. They receive accelerated approval because they treat life-threatening or serious debilitating conditions for which there is no satisfactory alternative therapy. That means the total experience with many of these drugs can be based on fewer than 100 subjects. Having so little information about patients' experience means that researchers are less likely to be able to detect safety signals, should any exist.

Good Advice

The cost and complexity of clinical trials are not well suited to understanding how personalized therapies work in the real world, or for providing the value claims payers need to put these drugs on formulary. Observational studies, however, can be an attractive option for companies seeking that information—and a source of continuing connection with a disease community—if designed and executed appropriately.

But small patient populations mean companies must make the most of their interactions with patients and healthcare professionals. Here's some ways companies can make their research proposition attractive, and build lasting relationships with their physicians and patients.

Don't engage in unnecessary experimentation Companies' best chance of attracting participants is to make their research relevant to the marketplace, and attractive to patients and medical professionals. This is particu-

LEARN THE LINGO:

"Efficacy" refers to the extent to which medical interventions achieve health improvements under ideal circumstances, whereas "effectiveness" refers to achieving health improvements in real practice settings.

larly important in order to obtain buy-in from sites for post-approval studies. The Office of the Inspector General guidance highlights the possibility that payments and other arrangements for physicians conducting post-approval research might influence their clinician decision-making and cause overuse or inappropriate prescribing. Therefore, in observational research, site reimbursements are generally minimal, at best.

Keep the protocol in line with physicians' offices When companies are bringing a drug to the market, they typically want to define the study population as narrowly as possible to maximize their chance of showing efficacy: otherwise healthy individuals, who are nonsmokers, and

aren't taking any other drugs. But in observational studies, the population will vary—patients are going to have co-morbidities, use herbal remedies, live in polluted areas, and may even be taking the drug for an off-label condition. Ensuring that the protocol has broad inclusion criteria and limited exclusion criteria allows companies to capture how the drug works across a broad population, in ways that doctors and patients are actually using the drug.

Protocols need to be simple, and work in real-world settings. While extensive genetic testing is typically conducted during clinical development, detailed and unusual diagnostic work-ups are not palatable for post-approval studies—they're expensive, and most costs of testing are born by participants or their insurers. Long CRFs (case report forms) and burdensome patient-reported outcomes also will not work, since study participation is most often motivated by altruism—lots of bureaucratic paperwork is a big deterrent. Thus, studies need to be streamlined to address focused questions about safety and effectiveness, and practical enough to conduct in the context of real-world medical practices.

The strongest protocols are those that include comparative information about patients diagnosed with the disease of interest and treated with the standard of care. Information on competing products, collected at the same time as the data on the product of interest, will add support for analyses on clinical and cost effectiveness, and provide sound benchmark data, should anecdotal concerns about safety arise.

Make it easy for far-flung, research-naïve sites to participate Studies of rare conditions often mean sponsors must conduct global studies to assemble enough patients. This introduces such issues as multi-national patient protection rules, different patterns of care driven by varying forms of healthcare delivery, and the need to assemble information from providers who don't share a common language.

To make matters more complicated, companies may have to work with sites that don't

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have experience conducting clinical research. That's why it's important for companies to use data collection tools that are easy to teach and user-friendly. In this way, electronic data capture (EDC) is gaining favor because it is easy for research-naïve sites to collect large volumes of data at relatively low cost. Data can be screened as they are entered, which makes the data cleaner and allows sponsors to more quickly identify errors—as well as pertinent safety issues. The EDC programs are available through Web portals, which can also host materials (e.g., consent forms and patient information) and reduce the technology burden on sites. EDC tools can also track, log, and identify genetic samples, which is helpful in streamlining the research program.

It is also important to include some “give-backs” to sites to enhance their motivation to participate, such as physician education and practice-enhancement tools, such as notes that can be printed and added to patients' charts. These types of items can be made available as part of the research program.

Value-Added Research

In addition to the very basics of proving clinical and cost effectiveness, and long-term safety, observational studies can help advance understanding about the natural history of disease and treatment practices. The reward is increased visibility in a disease area, which can reinforce corporate image in terms of promoting disease recognition and appropriate management.

Information gleaned from these studies can also feed broader disease registries, which may help to generate additional goodwill among doctors. Disease registries provide a tremendous amount of information and help unite physicians from around the world on the best science and cutting-edge therapies, and offer continuing information that the drug's label doesn't provide. For example, although Cerezyme was approved based on data from relatively few patients, Genzyme has created a registry for Gaucher disease that includes more than 3,000 patients, and allows physicians to learn about a patients' experiences from around the world.

These types of post-approval studies can also direct future efforts because they provide a window into how physicians

BIOLOGY OF AN INFORMED CONSENT FORM

Because of the many issues surrounding use of genetic information, companies are often required to create special informed consent forms. The consent form must address potential interpretations of outcomes on a patient's health—specifically, the likelihood that the research will not benefit them directly. Researchers also need to disclose arrangements regarding the potential for developing products with commercial applications.

Consent forms should also note:

- » who owns the genetic material used for the study
- » whether it can be reused for future (as yet, unspecified) studies
- » whether the results will be communicated to study subjects—especially in light of situations in which no effective prevention or treatment exists, but also in the context of finding information that, at this point in time, has no clear implication
- » whether it could become available in such a manner as to jeopardize future employment and/or health insurance coverage
- » whether genetic counseling will be part of the study.




For more information about issues sponsors should consider when conducting population-based genetic studies, see <http://www.cdc.gov/genomics/population/publications/consentarticle.htm>

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think about and prescribe the drug. Based on the results, companies may find that physicians need more information and medical education to prescribe the product appropriately. Or, the pharma company may learn about how doctors are prescribing the drug for off-label conditions, which may offer clues to companies about potential new indications.

Finally, these resources can provide a wealth of data for a steady stream of publications and presentations at scientific meetings.

The use of practical, streamlined tools, tailored to real-world situations, will help control costs for the small markets and lower budgets associated with developing personalized medicines—and ensure that companies have viable commercial claims for their products. Moreover, by better understanding how their product is used in real-world settings, companies can start asking the next set of questions that will not only ensure that these drugs become a mainstay of modern medicine, but also lead the way toward a more cost-effective healthcare system. 

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