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When Clinical Trials Aren't Enough

Effectiveness and real-world data underlie the global need for more patient registries and standards.

Patient registries have been gaining attention in recent years as health care providers, payers, and regulators have realized they can produce real-world data that more accurately depict the safety, quality, performance, and effectiveness of drugs and devices. There has been a growing movement to raise the quality of observational research, including patient registries, so that it can be used for more purposes—from labeling and advertising to regulatory submissions and reimbursement decisions.

Recent efforts by several groups have brought forth important guidelines and principles to develop or evaluate observational study data. While in clinical trials, the CONSORT statement¹ criteria have set the bar and standardized practice. However, for observational research there is not a single definitive document, but rather a series of publications and consensus efforts that build on each other. These have included publications such as:

- Guidelines for Good Pharmacoepidemiology Practices²
- Quality of Reporting of Observational Longitudinal Research³
- Government guidance documents such as Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment,⁴ Guidance for Industry: Establishing Pregnancy Exposure Registries⁵, and consensus statements from various working groups.

In May 2007, the U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality released a handbook entitled *Registries for Evaluating Patient*

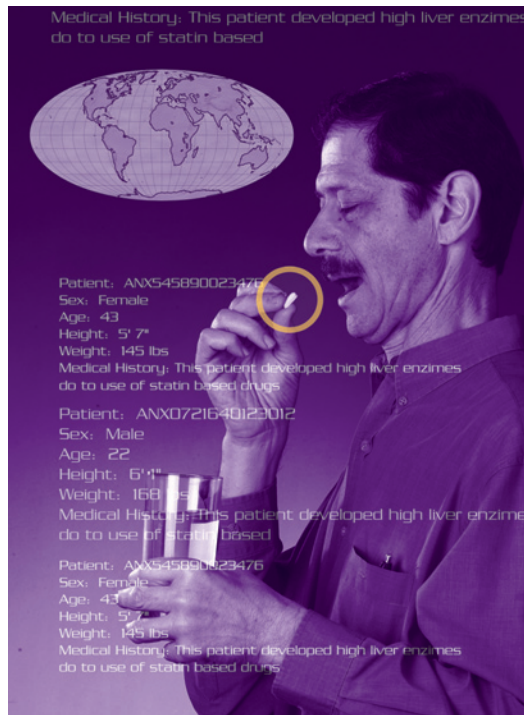
Outcomes: A User's Guide,⁶ to help guide registry design and evaluation.

With these new principles of good practice, registries in both pre- and postmarketing areas will have more potential to provide data to support decision making. Paralleling these efforts, so-called evidence hierarchies are also being reconsidered, and the role of rigorous, high-quality observational data for clinical and policy decision making is clearly changing. This article focuses on the impact of this process on unleashing the power of one type of observational program: the patient registry.

Multiple purposes

A patient registry is “an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves a predetermined scientific, clinical or policy purpose(s). The registry database is the file (or files) derived from the registry.”⁶

As this definition notes, registries are observational, meaning they collect data as patients present for care, without prescribing treatments or tests. This is the primary difference between a registry and a clinical trial. In a registry, treatment decisions, visit schedules, and any tests/measurements are generally left to the discretion of the provider; the registry simply observes as patients present for care. Registries also use broad inclusion and exclusion criteria to produce data that is generalizable to a wider population than trial data. In contrast,



clinical trials are controlled experiments designed to test a focused clinical hypothesis. They have strict inclusion and exclusion criteria that create homogenous patient groups, and treatment decisions are generally dictated by the protocol and randomization rather than by the practitioner.

The design of clinical trials gives them strong internal validity, meaning that the data collected accurately reflects the truth about the population under study. In contrast, registry data have strong external validity, or generalizability. Practitioners and payers, and even some regulatory agencies, are beginning to view real-world data from registries favorably because the limited inclusion/exclusion criteria mean that the patients are more representative of usual practice and because estimates of the impact of treatment are more realistic.

Since registries are observing patients and not dictating treatment, they can fulfill a wide variety of purposes. They can be used to conduct a prospective study of people who share a

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certain characteristic, such as product use or a procedure. Examples include registries of patients who receive intravenous thrombolytics for heart attack or particular antiplatelet therapies after similar events. Registries can also focus on diseases. They can be particularly useful for tracking long-term progression of chronic diseases, such as heart failure and cancer, and rare diseases like Pompe disease and cystic fibrosis.

Other registries provide a comparison of cases and controls to understand what differentiates them. These studies can be used to evaluate safety, characterize adherence, and describe off-label use. Finally, registries provide a means of gathering data in areas where experimental research is impractical or not feasible, such as in studies of compliance and adherence; long-term follow-up studies; studies in special patient subgroups (e.g., pregnant women, the elderly, and children); and when randomization to certain treatments is not ethical.

Efficacy and effectiveness

The flexibility of registry design and the wide number of purposes that registries can serve has led to their growing popularity. Interest in registries has also increased as the focus in evidence-based medicine has shifted from efficacy to effectiveness. Efficacy is the extent to which medical interventions achieve health improvements under ideal circumstances—essentially, does the intervention work? Effectiveness, on the other hand, is the extent to which medical interventions achieve health improvements in real practice settings.

Effectiveness adds an additional hurdle for interventions: They must work in the real world, where providers must prescribe them correctly and patients must comply with therapy

(and patients often have more comorbidities and concomitant medicines than those included in the controlled setting of a clinical trial). While clinical trials are the best measure of efficacy, registries provide strong evidence for effectiveness by observing typical practice and including a broad patient population.

While registries can serve many purposes and provide strong effectiveness data, decision-makers need to be able to evaluate a registry in terms of the quality of the research and evidence. The recent efforts described earlier have culminated in a far better understanding of what constitutes good registry practices, such as confidence that the design, conduct, and analysis of the registry protect against systematic errors and errors in inference. Promoting consistent standards for registry design and evaluation will encourage the use of patient registries as a way to provide evidence to support decision making. Widespread use of patient registries as a complement to clinical trials will provide benefits to patients, health care providers, companies, payers, and even regulators.

Patient and physician benefits

Registries can provide data on real world treatment choices and outcomes for all types of patients. Clinical trial data may only provide limited evidence for treating patients with multiple or complex conditions or patients who are part of a sensitive subgroup, such as pregnant women, children or the elderly. A registry can gather data on a broad patient population and provide evidence to support treatment decisions for many types of patients. Registries often include long-term follow-up data, which can be particularly useful for patients with chronic conditions and for insight into long-term medication use. In some disease areas, particularly rare diseases, patient advocacy groups also promote participation in a registry as a means of increasing knowledge about the disease and promoting greater communication between patients and providers.

Health care providers similarly benefit from additional evidence on effectiveness and safety that is broadly applicable to their patient populations. Registry data can provide practical information on how to treat a wide variety of patients, including the sensitive subgroups rarely studied in clinical trials. Registries also generate data to help characterize rare diseases and can promote information sharing among providers treating patients with such diseases. Additionally, in cases where a provider has only one or two patients with a particular condition, a registry can provide a way to learn more about the disease and connect with other providers with similar patients.

By collecting data on treatment patterns and long-term outcomes, registries can also provide evidence to support the development of treatment guidelines.

A company perspective

Registries offer companies a way to achieve clinical and marketing goals, meet regulatory needs, and support other data needs. Clinical goals of company-sponsored registries include studying the effects of products designated for long-term use; examining unanticipated beneficial effects that may lead to new

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indications or side effects that lead to labeling changes; and identifying best practices to achieve optimal outcomes.

A registry can support marketing goals, such as assisting in market penetration; understanding utilization patterns and special patient subpopulations; further documenting safety or effectiveness; repositioning the product through different outcomes (e.g., quality of life and cost effectiveness) and developing relationships with providers. Data on cost effectiveness and comparative effectiveness can be useful in advocating for national or private payer changes in coverage determinations. Registries can also offer data for understanding a particular market by answering questions on what kind of patients use a product, what other treatments they use, how often and why they switch therapies, and what other co-morbidities they have.

Companies also turn to registries to meet regulatory needs. Registries can collect additional data for products

approved under an accelerated review process and fulfill post-marketing commitments. Some registries are required to further study premarket safety signals or answer additional questions from the regulatory agency. In some cases, companies develop rollover safety registries as a way to continue to monitor a population from a clinical trial for any long-term safety signals. The ability to provide long-term data to support safety during real-world use is a strong benefit of registries and one that is encouraging some companies to implement registries for new products as a proactive approach to risk management in the current environment of heightened concerns.

Payers and insurers are also beginning to appreciate the benefits of registry data. These groups can use the practical comparative information on clinical effectiveness and safety from registries to help them make better formulary and reimbursement decisions, including understanding the needs of sensitive subgroups. In some cases, payers have even requested registry data to better evaluate the use of a new product or procedure in populations similar to their covered population.

The recent implementation of the coverage under evidence development⁷ program by the Centers for Medicare and Medicaid Services (CMS) is an example of how registries may be used to determine reimbursement policies. In the case of implantable cardioverter defibrillators (ICDs), when CMS was asked to reconsider its prior coverage decision in 2004, the agency determined that the new clinical trial evidence was not useful for determining the appropriateness of the procedure for an elderly population. The median age in the trial population was 60, but the median age of Medicare patients is 70 to 75. CMS also noted concerns about the expanding group of physician specialists inserting ICDs.

To gather data on these questions, CMS made an ICD registry a condition of coverage for Medicare beneficiaries and the results have been dramatic, with nearly 1500 hospitals participating. Full participation in a registry as a requirement for coverage for pharmaceutical and biologic products seems unlikely in the foreseeable future. However, the interest and value placed on such observational data by decision makers is not, and more and more data of this type will be increasingly requested in reimbursement determinations.

More recently, regulatory groups have begun to consider registry data in safety evaluations. Registries can meet regulatory requirements for risk management plans and postmarketing commitments. Some regulatory agencies have even begun including observational data in their assessments of requests for supplementary indication approval. The use of registry data is likely to increase as more registries can provide data that meet the requirements for decision making.

In addition, the current debate over products with safety issues that were not detected until the product was being widely used could result in an increase in the use of patient registries to study real-world product use. In the United States, a September 2006 report by the Institute of Medicine called for widespread changes in the way medications are monitored and marketed after approval. Recommendations

Canada, EU Exchange Safety Info

A new agreement between Canada and the European Union will allow their respective regulatory experts to share confidential information, such as safety and authorization issues regarding products on the market or in development. The European Commission (EC) and the European Medicines Agency (EMA) struck this deal with the Health Products and Food Branch of Health Canada at their bilateral meeting on December 7 in Brussels, Belgium. The confidentiality arrangements will enable earlier availability of information, helping authorities to better protect public health by improving the safety and performance of medicines and allowing speedier patient access to new treatments.

Since Canada and the EU have a history of working together in the regulatory environment, this new collaboration will further previous efforts by encouraging the exchange of information, which includes position papers and regulatory guidance documents, scientific advice on product development, assessments of marketing authorization applications, and safety information on marketed medicines.

To view the letters from Health Canada and the EC and EMA concerning the confidentiality arrangements, visit www.emea.europa.eu/pdfs/general/direct/pr/confidentiality_canada.pdf and www.emea.europa.eu/pdfs/general/direct/pr/confidentiality_EU_EMA.pdf. — *Samantha Etkin*

included changing labeling and marketing rules for new products and reevaluating safety and effectiveness data of new products within five years of approval.⁸

Japan is already studying real world drug use through observational studies called drug use investigations. These studies monitor real-world product use for several years after the product is approved and can be used to estimate the incidence of an adverse event or identify new safety signals. Final drug approval is contingent upon submission of drug use investigation plans. As more regulatory agencies develop postmarketing data requirements, companies can implement patient registries to gather long-term data from a heterogeneous population to further document the safety of their products.

Growing interest

The need for patient registries is clearly global. In many European countries, long-term registries are being used to meet both pharmacovigilance and reimbursement needs. Registries are being recommended or used increasingly for risk minimization plans.⁹ Growth in patient registries is also occurring from a public health perspective. In the United Kingdom, for example, in late 2006, the Cooksey Report specifically highlighted the need for the development of a series of national disease registries. The availability of international good practice principles is one enabler, as are new technologies that provide infrastructure for deploying multinational programs—even with regional differences—in a cost-effective manner.¹⁰

Although clinical trials have been the gold standard for evidence for some time now, observational data from a well-designed study can provide strong, trustworthy evidence in a variety of situations.¹¹ Observational data from registries is gaining favor for its ability to provide generalizable data on effectiveness, safety, and real-world treatment patterns. The growing movement for good practice principles for registry data is an indication of this interest. As researchers turn to registries to fulfill more data needs, they will likely incorporate the handbook principles as a way to ensure that the evidence that they produce is strong enough to support decision making.

A 2006 report by the Institute of Medicine calls for changes in the way drugs are monitored after approval.

The resulting increase in registry data will help patients and health care providers make more informed treatment decisions, enable payers to better determine coverage policies, and help companies better understand and market their products.

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