STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies

Chapter 12. Registries

This article is the 12th part of a 15-part series from STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies by Hugo Stephenson, MD, President, Strategic Research & Safety, Quintiles.

Often described as “looking over a doctor’s shoulder,” a registry, technically speaking, is a prospective open-label observational study. A registry includes a naturalistic record of patient characteristics, treatment decisions, and clinical outcomes that can be used to identify important trends through a variety of data mining techniques. Registries are passive, non-experimental data collection exercises that do not influence or dictate treatment decisions. They are a special type of an observational study that does not require particular investigations or a strict follow-up schedule since the very process of doing so might influence clinical behavior.

Registries broadly fall into the following three categories, each of which has different research objectives: product registries, disease registries, and exposure registries. Even though they are not retrospective studies themselves, registries frequently involve collection of retrospective data at baseline, like product use history, disease history, or exposure history, before the collection of prospective data begins.

Types of Registries

Product Registries

In general, product registries lead to data that can be used to generate product guidelines. Product registries enroll patients receiving a particular treatment, and they often restrict participation to patients with certain demographic and medical characteristics. Product registries commonly address questions relating to the “best practice” use of a product and are generally conducted when market uptake is limited by lack of knowledge or confidence in the product. For example, market adoption of a new, more potent protease inhibitor for the treatment of HIV may be delayed if physicians do not feel comfortable switching patients from an older drug to the new agent.

Product registries can be used to help define patient characteristics that positively and negatively predict for treatment success with a drug.

Evaluating Safety in Pregnancy

Conducting clinical trials with pregnant or breastfeeding women is usually considered unethical, but characterizing the relative safety of drugs in pregnancy remains very important. This is particularly true for drugs that cannot be justifiably discontinued even for short periods of time, such as treatments for epilepsy, schizophrenia, cardiac arrhythmias, and asthma. Registries remain the most common way that manufacturers can assess the safety of their products in pregnancy. Sponsors invite doctors to enroll pregnant patients who are receiving treatment despite the relative contraindication of pregnancy. GlaxoSmithKline (GSK) initiated its International Lamotrigine Pregnancy Registry in 1992 to monitor pregnancies exposed to lamotrigine (LTG), an anti-epileptic, for the occurrence of major birth defects. By March 2004, GSK was able to analyze data from 414 patients exposed to lamotrigine monotherapy during their first trimester and demonstrate that the risk of all major birth defects was similar to that in the general population.1


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particular product. They can also assist in defining treatment expectations and health outcomes for prescribers and patients, establishing product dosing and optimal duration of treatment, identifying additional properties of a drug, and monitoring a product’s safety profile in a broader population as part of a risk management plan.

**Disease Registries**

Disease registries generate data that can be used to better establish disease treatment guidelines. Disease registries involve enrollment of patients who have been diagnosed with a particular disease, often restricting participation to patients with certain demographic and clinical characteristics. Disease registries are commonly performed when the market is unsure of a treatment’s place in the management of a disease. When should patients undergoing knee surgery be offered treatment with a new anticoagulant approved for the prevention of deep venous thrombosis in an orthopedic setting? At what age does the benefit of treating patients with high cholesterol outweigh the risks? Should product X be used first or second line, and what are the criteria for diagnosing first-line treatment failure?

Investigators often initiate disease registries, sometimes as informal programs conducted at individual practices. Such registries are common in fast-evolving therapeutic areas, such as oncology, neurology, and rheumatology, where there is no gold standard treatment. Disease registries also target diseases associated with large variations in clinical outcomes or very small patient numbers, such as HIV, cystic fibrosis, and Tay-Sachs disease.

Disease registries can be powerful in establishing or defining new disease states that were previously unrecognized as coincidental collections of unrelated symptoms or different variants of normal. Such registries enroll patients exhibiting a particular set of clinical characteristics, and they track progress over time to see if there is a collective association with unfavorable patient outcomes over the long term. Short concentration span and behavioral difficulties in children may not be considered medical problems in themselves, but demonstrating an association between these characteristics and long-term patient outcomes that clearly fall outside the normal range can establish this constellation of symptoms as a disease with a rationale for treatment.

**Exposure Registries**

Exposure registries lead to data that can be used to prove association (but not causality) between an exposure and a health outcome. Exposure registries enroll patients who have been exposed to a particular product, place or thing, and attempt to capture data over time to demonstrate association between exposure and risk of different clinical outcomes.
September 11th Registry

Following the September 11th attack on the World Trade Center (WTC), many New Yorkers were naturally concerned about the long-term effects of the disaster on their physical and mental well-being. The WTC Registry enrolled over 71,000 people who were either located near the site at the time of the disaster or involved in rescue or clean-up activities in the aftermath. Consisting of a telephone interview and periodical follow-up calls, the registry is designed to track and investigate possible trends in illness and recovery, and to help create guidelines that can save lives and reduce injuries in future disaster settings.3

Exposure registries frequently mix retrospective and prospective components. The registries collect a large amount of retrospective data at baseline about the exposure (which frequently has occurred months or years in the past). Some exposure registries collect follow-up data over time to determine if a temporal relationship exists between exposure and a given health outcome—as was found to be the case with asbestos exposure and mesothelioma.

Investigators commonly perform exposure registries when trying to understand the etiology of a particular disease, and epidemiologists frequently use them to identify any particular characteristics of an exposure that modify patient risk. Are Gulf War veterans or World Trade Center survivors at increased risk for developing particular diseases? If so, what characteristics of their exposure place them at increased risk? Do children of mothers who took a particular product prior to or during pregnancy have an increased risk of developing certain pathologies? Is the measles, mumps and rubella vaccine related to an increased risk of autism?

Analytical Opportunities

By passively collecting data, often over long periods of time, registries can produce excellent data sets to support quantitative and descriptive analyses that aim to identify hypothetical trends. Registries can often generate strong empirical evidence of association through retrospective case-control analyses and are routinely used to influence product-safety label changes. Registries frequently lead to excellent and ongoing publication opportunities in scientific journals. Beginning with a cross-sectional analysis of baseline data, analytic teams can support a range of communication activities across the lifecycle of the research project.

Improving Transplant Outcomes

The International Pancreas Transplant Registry (IPTR), supported by grants from the National Institutes of Health and Roche, is one of the longest running registries. Established in 1980, the registry has worked closely with pancreatic transplant institutions around the world to record almost all pancreatic transplants performed since the first in 1969. The registry now has records of over 24,000 patients. The IPTR has been influential in better understanding the changing approaches to surgical treatment of diabetes mellitus and in identifying best practices to improve treatment outcomes and patient survival. Data from the IPTR has supported the development of simultaneous pancreas and kidney transplants, improvements in the management of immunosuppression, and identification of donor and recipient risk factors for treatment failure.2
Investigator Dynamics

How can you motivate investigators to do registry work? By definition, registries do not influence treatment, investigations or follow-up. As a result, it is impossible to provide free drug, free tests, or additional services as part of a registry, diminishing any potential patient benefit associated with participation in the study. Registries frequently require many thousands of patients in order to produce a large enough data set for analysis. This limits the amount of payment that can realistically be made to physicians for data collection.

With patient benefits and financial rewards diminished as possible investigator motivators, study designers need to rely on scientific immediacy to compensate for study workload. Reducing this study workload to the extreme is a critical part of the registry design process as well. Even simple registries can experience slow patient enrollment because workload still places too much burden on sites.

Scientific immediacy can be maximized by clearly establishing the objectives of a registry in a market-relevant context, providing examples of questions that the registry hopes to address, and committing to a timeline for communication of results. Obviously, this immediacy is further increased through a strategic selection of investigators most interested in the scientific objectives of the study.

Investigators can limit the burden to sites by streamlining site registration activities through simplified documentation and centralized ethics/IRB approval. Other approaches include supporting the process of patient consent by providing enrollment brochures that describe the scientific value of the study, and applying workflow-sensitive follow-up designs that may involve creative methods of data collection. It is sometimes possible for an ethics committee to waive the need for informed patient consent when the registry has no impact on medical treatment. By wrapping a registry in appropriate medical and lay public relations activity, which focuses on the market-relevant questions that the study intends to answer, one can both increase the scientific immediacy of the study and generate positive attention in support of a brand.

Pitfalls

Registries have gained popularity within the industry as a generic, commercially attractive Phase IV study because they are associated with small payments to investigators and have no requirement to provide study drug. Some companies calculate their return on investment from a registry on the basis of “number of patients times number of scripts,” in possible violation of the Anti-Kickback Statute (see the appendix) and completely miss the enormous value that market-relevant research findings may have on product sales. Other companies can damage sales force relationships by assigning negatively perceived administrative tasks, such as collecting forms, to sales representatives as an excuse for increased clinical contact. It would be better to provide them with tools to facilitate communication of study results back to investigators.

Many companies conduct “catch all” registries that have no clear research goals and market-relevant objectives. Sometimes an armful of objectives are lumped together to avoid the cost of conducting multiple studies. These registries rarely generate useful scientific data.

A registry that lacks scientific immediacy is often marked by a good start followed by poor ongoing performance. Before the launch of the study, internal brand team excitement fuels expectations. Site enrollment proceeds to plan, but within the first 8 to 12 weeks it becomes clear that patient recruitment is not making the expected numbers. Repeated contact with sites to increase patient enrollment begins to strain investigator relationships, and the sales team begins to receive negative feedback. Confronted with this situation, companies
attempt to recover by increasing investigator fees without considering the key drivers of investigator motivation: patient benefit and scientific immediacy. Instead of focusing on these motivators, companies significantly increase study costs without dramatically improving site performance. In contrast, academically driven registries with well-established, market-relevant scientific objectives can easily attract 50,000-plus patients without offering any payment, by applying these key principles too often forgotten in industry registries.

**Regulatory Issues**

Since registries are vehicles for passive data collection that have no influence on patient care, ethical issues associated with registries are normally limited to the data collection process and relevant privacy considerations. Many countries do not require ethics approval for registries; those that do typically use the process to ensure that the study is limited to passive data collection only.

Because the conduct of a registry does not place patient safety at risk, monitoring to ensure protocol compliance is unnecessary. Monitoring is only necessary to ensure data quality and completeness, and to protect against malicious activity. Infrequent monitoring is the rule, and “for cause” on-site visits are reserved for cases of suspected fraud. In many registries, particularly disease and exposure registries, the only monitoring done is remote “for cause” monitoring, initiated when outlying data points need confirmation to ensure accuracy.

**References**


* Note: All citations to websites listed in this book were verified in May of 2005.