



The emerging role of the patient registry

Patient registries provide a mass of evidence on the performance and safety of new drugs in larger and more diverse populations than those covered in clinical trials. **Dr Richard E Gliklich** and **Michelle Bertagna** explain why their use looks set to increase as healthcare professionals and providers focus on evidence-based medicine

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Patient registries are a valuable post-approval tool, providing evidence of the real-world results of medical products, therapies, and services. While clinical trials give important data about treatment effects in controlled conditions, trial data are often not applicable to the diverse population that may receive the interventions in the post-approval setting. This results in evidence gaps that impede the ability of patients and providers to make informed treatment decisions and of payers to determine what kinds of coverage will be appropriate. Patient registries can close these evidence gaps by offering additional data, to enable decision-makers to judge whether products or procedures are safe and effective.

Registries collect data on a broad population (with few exclusion criteria) and evaluate care as it is actually provided. As a result, registry data are more representative of the real-world patient experience. Registries can also make useful data available when a clinical trial is not feasible for ethical or practical reasons (for example, pregnancy exposures or rare diseases). Although registries can support a range of objectives, most focus on one of four main areas: describing the natural history of a disease, determining clinical and cost-effectiveness, monitoring safety, or measuring quality of care. These areas are often priorities for sponsors and regulators, and registries are well suited to provide such data in a range of clinical areas and practice settings.

Natural history of disease

Registries may be established to evaluate the natural history of a disease, meaning its characteristics, management, and outcomes with or without treatment. In many cases, the natural histories of diseases are not well described. Gathering this information requires a concentrated effort, because the natural history may vary across different groups and geographic regions, and often changes over time. Furthermore, the natural history of diseases may change after the introduction of certain therapies. For instance, previously patients with a particular rare disease may not have survived to their twenties, but now they are entering their fourth and fifth decades of life, and this uncharted natural history is being first described through a registry.

Such registries provide pre-market information on background safety issues, care patterns and treatment outcomes. They can also help when planning clinical trials, or with clinical trial recruitment. After approval, the natural history can be studied as it is affected by new therapeutics.

Determining effectiveness

Multiple studies have highlighted the disparities between results obtained in clinical trials and those obtained in clinical practice. Disparities could arise from differences in the patient population, such as age, co-morbidities, or concomitant medications. For example, the average age of patients in most heart failure trials is below 60, while the average age of patients with heart failure is above 60. Similarly, clinical trials do not give information on how results

can be generalised for different practice settings. For instance, if training, case volume, or skill of the provider is a factor in effectiveness, as it can be in some device-related procedures, the trial setting provides different results to those obtained from a more representative sample of practising clinicians.

From a coverage perspective, policy determinations on payment rely on cost-effectiveness and cost-utility data, and can therefore be informed by registries as well as clinical trials. The establishment of disease-specific data registries has even been recommended to facilitate the process of technology assessment and improving patient care, particularly where it can be difficult to gather clinical-effectiveness data together with quality-of-life data in a usable format.

Monitoring safety

The ability of a registry to provide data on a broad population can be extremely valuable where safety is concerned. Patient registries can act as surveillance systems to monitor a population for any occurrence of an unexpected or harmful event. There is increasing recognition that an active surveillance approach is more useful than passive event detection for understanding rates or for monitoring products after launch. By providing a system for reporting these adverse events (outside of the current practice of spontaneous reporting) and by gathering information on the exposed population, registries can help both to quantify the risk and to properly attribute it. The US FDA has noted 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’.

There has been increasing discussion about the possibility of a two-stage approval process, where the second stage involves close monitoring of drugs for a requisite period. This conditional approval concept may not only serve as a better detection system after product release to broader populations than can be studied in clinical trials, but could shorten times to the first stage of approval and thereby decrease drug development costs significantly. This approach is receiving strong support from industry and academia, and regulators are also showing interest.

An example of a registry for monitoring safety might be a programme that collects data on the first 10,000 patients to receive a new product. In the clinical trials, the product may have been tested on only 2,000 carefully selected patients. By proactively gathering information on the product after launch, the manufacturer and regulators can quickly identify any new safety signals and build a foundation for an appropriate risk-management programme.

Registries can also be used to monitor safety for products with a known risk factor, such as clozapine or isotretinoin. In such cases, access to the drug may be linked to fulfilment of a set of obligations on the

part of the physician, pharmacist and patient. Registries can collect data and make the information accessible to both the pharmacist and the physician, so that access to the drug will be granted only under appropriate circumstances. This type of registry may also provide a valuable source of data for the manufacturer on the frequency of the adverse event.

Pregnancy exposure registries offer a similar service, with patients who are exposed to a drug during pregnancy being enrolled and followed through the pregnancy outcome. The information gathered is used to better understand the possible teratogenic properties of the drug and to improve safety information and counselling for future patients.

Improving quality

Quality of care may also be measured by a registry, and quality improvement promoted. Registries are becoming increasingly popular among providers as a tool for ensuring adherence to clinical guidelines and assessing performance. Such registries can help to identify disparities in care and areas for improvement, and they can establish differentials for payment by third parties, or provide transparency through public reporting.

From a sponsor’s perspective, it is important to recognise that the effectiveness of many healthcare

Considerations for sponsoring companies

In order to plan for, or develop, a successful registry, the pharma company must consider the following issues early in the registry development process:

- The purpose or purposes should be clearly stated. A registry must have a clear purpose that can be articulated by the sponsoring organisation
- Determine if the registry is an appropriate strategy to achieve the purpose and how the data from the registry will fit into the overall evidence programme for the sponsor’s product. Alternative evidence development approaches, including randomised trials or existing datasets, might be compared or contrasted
- Identify the stakeholders. Internal stakeholders include organisational ‘owners’ of the registry as well as other influencers. Sufficient resources should be allocated. External stakeholders should also be determined and potentially engaged
- The target population, that is the population for which the registry results should be applicable, should be defined
- The scope of the registry, which is usually driven by the primary and secondary objectives, should be clear, and appropriate funding should be available
- If there are issues of feasibility, from concept to specifics of data collection, these should be assessed
- A plan for using the data, from internal purposes to publications to regulatory reporting, should be clear before the data is collected. This includes creating an analysis plan
- If the programme is primarily for safety monitoring, it should be clear how the data will be reported (for example, periodic safety update report)
- The adverse event reporting requirements – generally driven by whether or not the registry has direct patient contact and when the sponsor ‘becomes aware’ – should be clear and understood by everyone involved in the programme



products is influenced by how they are delivered, whether competence in a procedure is concerned, or appropriate education in support of medication compliance. Furthermore, as providers find that their reimbursement is increasingly tied to 'performance', they will become more interested in the relative effectiveness of various products in their own practice, because this may directly affect their livelihoods.

Many examples of quality improvement registries exist in a range of disease areas and practice settings. A large quality improvement registry programme in the US is the 'Get with the guidelines' initiative, which focuses on improving in-hospital care for patients with coronary artery disease, heart failure and stroke. The programme uses a continuous quality improvement cycle to help hospitals implement and study the results of quality initiatives. The registry component of the programme plays a key role in this cycle, by providing a real-time source of data feedback and reporting, to enable hospitals to identify areas for improvement and analyse the success of quality initiatives.

Design and implementation considerations

In order to collect data in real-world situations efficiently, registries must be structured differently from clinical trials. Because registries are typically in the post-approval phase, non-monetary incentives play a larger role in encouraging sites and investigators to participate. This is because excessive payments for work performed (data collection) can be viewed as an 'inducement'. Key considerations in generating interest and incentives include the relevance of the registry to the physician's practice, its scientific credibility, non-monetary incentives such as reports, and ease of participation. In short, balancing the burden of participation with incentives (both monetary and non-monetary) is a key factor for the success of a registry.

Registry planning generally begins with a planning group that explores the purpose, objectives, and feasibility of the proposed study. Once the decision has been made to proceed, a governance structure is assembled to oversee the registry design and handle questions throughout the life of the registry. Patient registries should be designed with their primary objectives in mind, as these will guide the level of rigour that is necessary. For example, a registry that

is focused on improving quality will have different concerns about data quality from those of a registry that is aimed at monitoring safety. Some key points to consider in registry design include choosing a study design, selecting data sources, identifying the target population and assessing and addressing possible sources of bias. After the registry launch, a data coordinating centre generally manages the day-to-day operations, such as site recruitment and data management. The scope of the design, implementation and operation of a registry can vary widely, depending on its size. Successful registries can range from a handful of sites to thousands of sites, depending on the registry's objectives.

Regulatory and other considerations

Privacy is a critical issue when designing and operating a registry, and registries in general should use a 'minimum necessary' approach with respect to the individually identifiable information they collect. While privacy laws differ by country, in the EU or the US three basic elements of the registry generally determine whether it is meeting the appropriate privacy requirements in each applicable country or state. These are the purpose of the registry (for example, effectiveness research versus quality operations); the type and movement of the data (for example, limited data set versus de-identified data, tracking the data from the data collectors to data processors to data users); and the relevant authorisations (for example, informed consent, institutional review board authorisation).

Another regulatory consideration relates to the collection and reporting of adverse events (AEs) in registries. Decisions as to whether or not the registry should use a case report form to collect AEs should be based on the scientific importance of the information for evaluating the specified outcomes of interest. Regardless of whether AEs constitute outcomes for the registry, it is important to develop a plan for detecting, processing and reporting AEs for any registry that has direct patient contact. In the US, if the registry receives sponsorship, in whole or in part, from a regulated industry (for drugs or devices), the sponsor has mandated reporting requirements and the process for detecting and reporting AEs should be established and investigators trained on how to identify AEs and to whom they should be reported.


As registry data are used to fulfil more purposes, there is a growing need for registries to conform to scientific standards. While no one standard currently exists, significant attempts have been made to define 'quality' in both the scientific process and results for such registries. A multi-stakeholder effort to create a handbook on patient registries is currently under way in the US, sponsored by the Agency for Healthcare Research and Quality and contracted to the Outcome DEcIDE Center (see (<http://effective-healthcare.ahrq.gov/decide/>)). Such projects will play an increasing part in enabling patients, providers and payers to determine the quality of registry data.

Conclusions

Patient registries can provide data to help decision-makers better understand the potential effect of a product or procedure in a varied patient population. Registry data can support studies of effectiveness and value, help manufacturers and regulators monitor safety, and measure and promote quality improvement. Because of their flexibility in terms of size and scope, registries can fulfil the need for long-term data on a small set of patients with a rare disease, or quickly gather data on thousands of patients taking a new product.

While registries provide valuable data, it should be noted that registry data analysis requires special tools to account for the potential for bias in observational research. Registries also operate with varying levels of rigour in regard to data management and quality assurance, and this must be taken into account when analysing data from a registry. As registries become more widely used for post-approval research, particularly for research that affects coverage and payment policies, more attention will need to be paid to developing standards for their design, operation and evaluation.

Over the next few years, registries may increasingly be used for post-approval research. Recognition that the clinical effectiveness and safety of a product can only be determined in the real world may lead to changes in the clinical

development and approval process, resulting in more registries for post-approval research. Large payers, such as the Centers for Medicare and Medicaid in the US, may also drive the creation of registries, as they demand data to support the effectiveness of new treatments and procedures in their population, which is generally older and has more co-morbidities than the clinical trial population. Lastly, the increasing focus on quality in healthcare, coupled with rising interest in pay-for-performance initiatives, may lead to the creation of more registries focused on quality improvement. These trends are likely to support the continued growth of registries as one of the most important post-approval tools. 

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