

Designing and Assessing Registries to Evaluate the Safety of Medical Products

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Traditionally, the safety of medical products has been assessed through spontaneous reports of serious adverse events, secondary analyses of administrative data collected for other purposes, and clinical trials and meta-analyses of clinical trials. Recent product recalls and warnings have raised questions about whether these strategies provide enough information about rare clinical events that may occur during conditions of real-world use and whether they are reliable enough to guide decisions on removing products from the market. As the limitations of the current adverse event detection methods have been noted, there has been a call for more attention to be paid to developing robust, proactive strategies for monitoring product safety. A good understanding of registries will help support a culture of safety that requires timely, clinically relevant information about the risks and benefits of medical products once they have been approved for general use.

Registries are increasingly used to support postmarketing evaluations of safety and effectiveness. In the context of evaluating patient outcomes, the term “patient registry” refers to 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).

Registries are classified according to how populations are defined. For example, product registries include patients who have used biopharmaceutical products or medical devices. Health services registries consist of patients who have had a common procedure, clinical encounter, or hospitalization. Disease or condition registries are defined by patients with the same diagnosis, such as cystic fibrosis or heart failure.

Registries investigate outcomes using observational study methods that do not specify treatments (although a specific treatment may be an inclusion criterion). These observational methods differ from clinical trials in which a randomization procedure is used to assign treatments to evaluate an active intervention intended to change a human subject’s outcome. In registries, patients are typically observed as they present for care and the data collected reflect whatever tests and measurements a provider customarily uses. Unlike trials, registries generally have few inclusion and exclusion criteria, making the results more generalizable. Patient registries therefore have the potential to serve as a monitor for the safety of a product or service in real-world practice.

In contrast to the established guidelines that exist for conducting clinical trials (e.g., good clinical practices^{1,2} and the CONSORT guidelines for reporting³), relatively little is available to guide the design, analysis, execution, and reporting of registry studies. (See www.strobe-statement.org for information about a checklist under development for use in observational studies.) Although some practices are transferable from one domain to the other, by and large the

essential differences between registries and clinical trials make clinical trial guidelines less applicable to registries than one might initially expect. Rather than reflect a flaw in registries compared with clinical trials, the lack of accepted guidelines for registry conduct simply demonstrates the relative youth of the field.

Safety Registries

Registries can be quite potent tools for evaluating safety. In some situations, they are more informative and clinically relevant than trials. Registries usually collect data on broad populations and can include children and pregnant women, as well as people with multiple co-morbidities. They are often larger, cover a broader range of prescribing physicians, and have longer duration of follow-up than trials, thus affording the possibility of detecting delayed health effects in a variety of subjects with many different risk factors. Their limited inclusion and exclusion criteria result in studies that afford a more realistic view of the patients who use products, and the many ways in which physicians administer these products. The real information yield, then, is an assessment of for whom the product works and when, and if it appears to be dangerous, then for whom and under what conditions. Any interpretation of registry data, like all observational studies, must be tempered by thoughtful consideration of how potential sources of bias would affect any causal inferences drawn from the study.

Because registries often serve more than one purpose, they are cost-efficient. For example, the National ICD Registry in the U.S. is collecting data on patients receiving implantable cardioverter defibrillators (ICDs) to study whether ICDs are as safe and effective in patients who are older than those patients studied in the clinical trials. The median age of patients included in the clinical trials was 60 years, whereas the median age of Medicare beneficiaries is 70 to 75. This registry not only serves a safety purpose, but the data will also be used to guide a national coverage policy for the procedure. The registry sponsors (manufacturers, in this example) decided to use

the registry not only to observe practice and outcomes, but also to implement national training programs and quality improvement efforts to demonstrate the feasibility of achieving favorable outcomes on a large scale. Nearly 1,500 hospital sites are participating, and this registry annually records data on more than 100,000 patients. This example highlights many of the differences between registries and most randomized clinical trials—the registry is multipurpose, large, and includes older patients, presumably many of whom have significant co-morbidities and use many medications.

This is only one example of a registry that is proving useful to patients, physicians, manufacturers, and regulatory agencies. If we accept that registries can fill a useful niche in the evidence hierarchy, then the focus shifts from “Why conduct an observational study like a registry?” to “How should a registry be designed and conducted to produce information of high enough quality to support decision-making?” and “How can I distinguish high-quality registries?”

In an effort to promote the quality of registries, the U.S. Agency for Healthcare Research and Quality (AHRQ) used its DEcIDE Network (Developing Evidence to Inform Decisions about Effectiveness) in its Effective Health Care Program to commission a reference for establishing, maintaining, and evaluating registries created to collect data about patient outcomes. A user’s guide for registries for evaluating patient outcomes⁴ was developed as a collaborative effort with relatively equal representation of individuals from academia, government (predominantly U.S. as well as from the National Institute for Clinical Excellence in the United Kingdom), and the private sector. In all, 39 contributors and 35 individual reviewers participated. In addition, several agencies provided more in-depth reviews of the document. A draft was posted for public comment on the AHRQ website and received substantial review from a diverse audience. The handbook describes in full the basics of registry design, operation, and evaluation, and this report highlights many of its key points.

Planning

The key steps in planning a patient registry include articulating the purpose of the registry; determining whether a registry is an appropriate means for addressing the research question; identifying stakeholders; defining the scope and target population; assessing feasibility; and securing funding. The term “governance” refers to a structure that is used for high-level decision-making and oversight. Such a committee (or group of committees) should be charged not only with overall direction of the registry, but also with guiding decisions relating to operations, scientific content, ethics, safety, data access, publications, and change management. Having these mechanisms for decision-making in place at the outset of a registry can help avoid problems that may develop due to the nature of the findings from the registry. For example, if a safety problem is uncovered, how, when, and to whom will the results be released? It is also useful to plan for the entire lifespan of a registry, including how and when the registry will end and what will be done with the data that have been collected.

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Design

A patient registry should be designed with respect to its major purpose, with the understanding that the level of rigor required for safety registries is greater than for registries that primarily are intended to provide descriptive information, such as natural history studies. The key points to consider include formulating a research question, choosing a study design, translating questions of clinical interest into measurable exposures and outcomes, choosing patients for study, and deciding whether a comparison group is needed, where data can be found, and how many patients need to be studied for how long.

Data Elements

The selection of data elements requires balancing such factors as their importance for the integrity of the registry and for the analysis of primary outcomes, their reliability, their contribution to the overall burden for respondents, and the incremental costs associated with their collection. Selection begins with identifying relevant domains. Specific data elements are then identified with consideration for established clinical data standards, common data definitions, and the use of patient identifiers. It is important to determine which elements are absolutely necessary and which are desirable, but not essential. In choosing measurement scales for assessing patient-reported outcomes, it is preferable to use scales that have been appropriately validated when such exist. Once data elements have been selected, a data map should be created, and the data collection tools should be pilot tested. Testing allows assessment of respondent burden, accuracy, and completeness of questions, and potential areas for missing data. Overall, choice of data elements should be guided by parsimony, validity, and a focus on achieving the registry's purpose.

Data Sources

A single registry may integrate data from various sources, including active data collection (primary data collection for the direct purpose of the registry) and sec-

ondary data collection. Secondary data are comprised of information that has been collected for purposes other than the registry, and they may not be uniformly structured or validated with the same rigor as primary data. Sufficient patient identifiers are necessary to guarantee an accurate match between secondary sources and registry patients. Furthermore, a solid understanding of the original purpose of the secondary data and how they were collected is advised, because knowing how those data were collected and verified or validated will help shape their use. Common secondary sources of data linked to registries include medical records systems, institutional or organizational databases, administrative health insurance claims data, birth and death records, census databases, and related existing registry databases.

Ethics, Data Ownership, and Privacy

Critical ethical and legal considerations should guide the development and use of patient registries. The research purpose of a registry, the type of entity that is responsible for developing the registry, and the extent to which data are individually identifiable largely determine applicable regulatory requirements. Other important ethical and legal concerns include transparency of activities, oversight, and data ownership. Rules and regulations differ from country to country; even within countries, institutions may have unique interpretations of these rules. It is essential to check with all institutions and local authorities at the outset of any registry.

Patient and Provider Recruitment and Management

Recruitment and retention of providers (as registry sites) and patients are essential to the success of a registry. Recruitment typically occurs at several levels, including facilities (hospital, practice, and/or pharmacy), providers, and patients. Because provider and patient recruitment and retention can affect how well a registry accurately represents the target population, well-planned strategies for enrollment and retention are

critical. Factors that motivate participation include the perceived relevance, importance, or scientific credibility of the registry, as well as the risks and burdens of participation and any incentives for participation. Goals for recruitment, retention, and follow-up should be explicitly laid out in the registry planning phase, and deviations during the conduct of the registry should be continuously evaluated for their risk of introducing bias.

Data Collection and Quality Assurance

The integrated system for collecting, cleaning, storing, monitoring, reviewing, and reporting on registry data determines the utility of those data for meeting the registry's goals. Critical factors in the ultimate quality of the data include how data elements are structured and defined, how personnel are trained, and how data problems are handled (e.g., missing, out of range, or logically inconsistent values). Quality assurance (QA) aims to affirm that the data were, in fact, collected in accordance with established procedures and that they meet the requisite standards of quality to accomplish the registry's intended purposes and the intended use of the data. Because certain requirements may have significant cost implications, a risk-based approach to developing a QA plan is recommended, based on the sources of error or potential lapses in procedures that may impact the quality of the registry.

Adverse Event Detection, Processing, and Reporting

Governing bodies in the U.S. and European Union require that serious and unexpected events that have a reasonable probability of being related to drug exposure be reported to them in a timely manner. Collection of adverse event (AE) data falls into two categories: those events that are intentionally solicited (i.e., data that are part of the uniform collection of information in the registry) and those that are volunteered or noted in an unsolicited manner. It is important to develop a plan for detection, process-

ing, and reporting AEs for any registry that has direct patient interaction, including how reports will be handled, both for the main product of interest as well as for AEs that may be identified for comparator products.

Sponsors are encouraged to hold discussions with health authorities about the most appropriate process for serious AE reporting for registries designed specifically to meet requirements for surveillance of drug or device safety. The process for detecting and reporting AEs should be established and registry personnel trained on how to identify AEs and to whom they should be reported. Consideration of registry funding will help determine the process and timing for reporting AEs for the main products of interest, but there is substantial variation in how AEs are handled for comparative products.

Analysis and Interpretation

Analysis and interpretation of registry data begin with answering a series of core questions: Who was studied? How were the data collected, edited, and verified? How were missing data handled? How were the analyses performed? How representative is the actual population studied when compared with the target population of interest?

Analysis of registry outcomes first requires an analysis of the completeness of data collection and data quality. Analyses should provide descriptive information on the characteristics of the patient population, the exposures of interest, and the endpoints, as well as quantitative descriptions of the magnitude and precision of the effects of treatment characteristics on safety outcomes of interest. Interpretation of registry data should be provided so that the conclusions can be understood in the appropriate context, and so that any lessons from the registry may be applied to the target population and used to improve patient care and outcomes.

Evaluating Registries

There are levels of rigor that enhance validity and make the information from

some registries more useful for guiding decisions than others. The term “quality” can be applied to registries to describe the confidence that the design, conduct, and analysis of the registry can be shown to protect against bias and errors in inference, that is, erroneous conclusions drawn from a registry. We designed a quality component analysis⁴ to evaluate high-level factors that may affect results. We differentiated between research quality (which pertains to the scientific process) and evidence quality (which pertains to the data/findings emanating from the research process). Quality components are classified as either basic elements of good registry practice, which can be viewed as a basic checklist that should be considered for all patient registries, or as potential enhancements to good practice that strengthen the information value. The results of such an evaluation should be considered in the context of the disease area(s), the type of registry, and the purpose of the registry, and should also take into account feasibility and affordability.

Conclusion

Registries offer a unique means to view the benefits and risks of medical products in real-world conditions. They generally have few inclusion and exclusion criteria and leave choices of medical therapy to medical judgment, thereby more accurately reflecting conditions of actual product use. Registries also provide a numerator of events along with a denominator of exposures (such as the re-stenosis rate among a population receiving vascular stents). As such, they can provide more precise information on benefit and risk than achievable with current voluntary reporting systems for AEs. Full utilization of patient registries for the evaluation of safety of medical products requires a clear understanding of how stakeholders can evaluate the quality of data from a safety registry.

Additional Reading

We encourage readers to refer to the AHRQ handbook⁵ in its entirety. It is

available in machine-readable form on the internet at www.effectivehealthcare.ahrq.gov. Print copies are also available upon request from AHRQ.

References

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