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# Collecting Health Information: Disease Registry, Product Registry, or Neither ?

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## Background

Health registries refer to collections of health information on a set of identifiable participants [1]. Health registries exist in a variety of formats and are instituted for investigations in clinical research, public health, and pharmacovigilance [2]. The National Committee on Vital and Health Statistics has defined medical and public health registries as "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects [3]. Although different definitions of health registries exist, there is agreement that undertaking a health registry is a complex and expensive task, and defining who should be included in the registry is an essential decision for registry success and quality [1].

## **Disease and Product Registries**

Health registries can be designed specifically, focusing on a particular population, or more generally, allowing for a broader investigation of populations or outcomes. For example, product and disease registries are often implemented before, or as a component of regulatory commitments during, the approval process of pharmaceutical products [4]. Product registries restrict participation to those who have been exposed to the product of interest, whereas disease registries extend participation to all with the indicated medical condition or disease.

Disease registries are useful when the primary objective is to obtain observational data regarding the disease and the impact of the disease. Data obtained from disease registries often include duration of the condition, treatments used (including those that are off-label), comorbid conditions, satisfaction with treatments, quality of life measures, and other measurements on function and disease status. Product registries, on the other hand, are intended to elucidate the use and impact of a product in a "real world" setting. Product registries provide manufacturers and regulatory agencies with information on product performance and safety outside of the controlled environment of the clinical trial [5]. Participants in product registries typically provide detailed information on product usage, concomitant medications, and safety. Quality of life and treatment satisfaction may also be collected in a product registry.

Both types of registries have benefits and limitations. Disease registries offer data on therapy and healthcare utilization for a particular medical condition, as well as a diverse group of patients in terms of severity and duration of disease. Disease registries are analyzed and mined to identify potential subsets and groups for ad-hoc comparisons of health outcomes; these analyses may be identified in the design of the registry, throughout the life of the registry, or both. Given the potential diversity of patients, these registries are typically quite large. In fact, unless the disease registry is substantial in size and/ or follow-up, some comparison groups will not be available; registries investigating rare conditions could require considerable time to enroll enough participants. Product registries aim to provide a more comprehensive understanding of the safety and effectiveness of a specific product. Since clinical trials are often too short and too limited to investigate safety concerns or signals, many times product registries are implemented to obtain better estimates of the incidences of targeted adverse events [6]. Even though comparator groups may arise from a product registry, comparisons made using such registry data are restricted to participants with some level of exposure to the product.

#### **Making Comparisons**

Inevitably, comparisons between groups will be made with both types of registries. While control comparator groups may be identifiable in a disease registry, product registries have such specific inclusion criteria that a control group is typically unavailable.

#### **Disease registries**

One of the primary advantages of a disease registry is its diversity and the resulting ample opportunities to make comparisons between groups. However, the diversity of registry participants often complicates determining group memberships. Moreover, when registries are longitudinal and designed to capture changes in patients or disease status, creating groups with time-varying conditions is even more complicated, requiring significant efforts in data management to accurately capture comparison groups [7]. Even when these groups are identified, the observational nature of health registries limits the usefulness of simple comparisons, given the potential for multiple variable confounding and effect modification. Perhaps most problematic is the potential for sparse comparison groups. For registries, where it is expected that some comparison groups will naturally emerge, comparisons may only be possible after a significant amount of time has allowed for a sufficient enrollment of participants in a particular group.

#### **Product registries**

Even when the focus of a registry is specific, enrolling only participants exposed to a particular pharmaceutical product, for example, comparisons are still of interest. Like comparison groups that emerge in disease registries, comparison groups may also become available within a product registry. For example, comparisons based on level of exposure, adverse event experience, or responder status may be of interest within those who have been exposed to the product.

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However, a product registry is limited in participation to those exposed to a product and does not include an unexposed control group for comparisons. When it is of interest to compare estimates obtained from a product registry, external or historical controls may be used. External controls provide comparator groups that exist outside the registry. External controls are most often used when control groups are not available, are unethical to include, or are impractical. Data for external controls can be obtained from previously conducted trials, populationbased studies, or other registries [8].

The primary disadvantage to using external or historical controls is that the comparator or control group does not exist concurrently with the registry participants. Medical advances or health changes over time are primary issues that affect controls not collected concurrently. Advances in screening, healthcare, and introduction of new products could lessen the relevance of historical controls. When using external controls from clinical trials, there are additional implications. To better demonstrate efficacy, controlled trials often use restrictive inclusion/ exclusion criteria, and subjects used for external controls may be very different from registry participants [5]. Furthermore, since controlled trials are typically shorter in duration than registries, product exposures will not be equivalent. Using published values as estimated incidences for controls may not offer a better alternative since many of these are obtained from clinical trials. Since manufacturers are required to report safety outcomes to regulatory agencies (e.g. FDA and EMEA), it is recommended that, when possible, results be obtained from these agencies as such results are generally complete and comprehensive [8].

## **Registry Planning and Study Design**

Especially in the case of regulatory commitments and pharmacovigilance, disease and product registries are often proposed using traditional study design concepts. When comparison groups are identified, disease registries are planned as prospective cohort studies, and the size of the registry is suggested by anticipated effect sizes for comparisons of interest, power, and significance levels. For product registries, where concurrent comparison groups are not collected, the design process is similar except that the size of the planned registry is determined using comparisons to external controls. When planned in this way, product registries result in smaller required sample sizes than disease registries. For this reason, when the primary outcome is a rare event, the sample sizes needed for comparative groups make disease registries infeasible and product registries more attractive.

While health registries should be planned and comparisons made only when there are sufficiently many participants, a health registry is not just a large observational cohort study. Health registries are distinctive in that they are open-ended, exploratory and not confirmatory, often focusing on identification and estimation. They do not naturally conform to statistical analysis plans and controlled trial protocols. Given that health registries serve the purpose of generating rather than testing hypotheses, it is not recommended to design health registries using the traditional constructs of power, planned comparisons, and hypothesis testing. Health registries are better suited for planning strategies that include metrics and goals. For example, designing a registry that will recruit a given number of patients each year and requiring, for longitudinal registries, metrics on follow-up participation is preferred to designing the registry with a priori limitations on number of participants or length of study. For this reason, deciding between product and disease registries cannot simply be a matter of sample size.

# Conclusions

Health registries provide an opportunity to better understand medical conditions and exposures when more traditional designs fail, but they require a different perspective in planning, data collection, and analysis.

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#### Applications of a disease registry

Understanding the product market and epidemiology are two reasons to implement a disease registry. Pre-approval trials do not provide information on how a product performs in conjunction or competition with other products. Disease registries offer the opportunity to provide information on treatment satisfaction, responder status, and changes in disease status in a real-world setting for a specific product and for competitor products. For epidemiological investigations, disease registries can provide information on disease progression, disease management, and quality of life. Disease registries allow for direct group comparisons on health outcomes.

#### Applications of a product registry

If the primary purpose of the registry is to investigate safety, a product registry allows for a more focused investigation of the impacts of product exposure. While direct comparisons to an unexposed group would be desirable, this typically cannot be done within the constructs of a product registry. The observational nature of the registry makes an unexposed control group difficult to define. Furthermore, many safety outcomes are rare, requiring that exposed subjects be followed for a significant amount of time. The expense of following subjects for long periods of time may make a less-focused disease registry impractical.

## When registries do not apply

Before deciding whom to enroll in a health registry, it is necessary to first decide whether implementing a registry is even the best approach. Large observational studies, when designed appropriately, may be more effective for short-term investigations and planned comparisons. The primary benefit of a health registry is that it provides a long-term catalog of health concerns and conditions. Health registries tend to be dynamic, flexible, and open-ended, but they are only successful after they have had the time to mature. Health registries created for shortterm comparisons often are incomplete and resemble poorly designed observational studies. A registry can be a valuable tool for better understanding public health, health delivery, exposures, and trends in provider and patient behavior. Implementing a registry, however, is costly. Therefore, determining whom to enroll is secondary to first identifying the purpose, feasibility, and the long-term commitment to realize the full benefits of a health registry.

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