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Review article

THE PATIENT REGISTRY: A HIGH IMPACT TOOL FOR REAL WORLD EVIDENCE

*BarickUttam[1], MohantyRituraj[2], GowdaArun[3]

[1]Clinical Research Consultant, [2]Associate Project Manager, [3]Director, focus scientific research centre, Part of phamax Market Access Pvt. Ltd.,KMJ Ascend,19,1st Cross, 17th C Main, Fifth Block, Koramangala, Bangalore, Karnataka, India

*Corresponding author email:uttam.barick@fs-researchcenter.com

ABSTRACT

Background: In this world of seemingly infinite data across domains, one strives to acquire better tools and methodologies to fully exploit available data. This process begins with meticulous planning to gather relevant information and continues until there is an output in the form of credible evidence. The ability to generate real-world evidence would take such a process to new level: the factors that influence these processes under real-world conditions are varied, unpredictable, and unregulated. Results obtained in highly regulated or controlled conditions are universally accepted and sought after for regulatory approvals, but performance indicators in the real world will set the tone for the future. Hence, the demands for very reliant and robust tools and mechanisms for gathering evidence are all the more prominent and necessary. Patient registries fill this gap and stand tall among the various tools that could deliver the desired end results with acceptable accuracy. Over the years, pharmaceutical companies, along with policymakers and other stakeholders, have been actively involved in the development of such registries. **Aims:** Here we provide an overview of the usefulness of registries for the various stakeholders in healthcare in terms of conduct, approach, and barriers to initiating such studies. **Conclusion:** One of the impediments for the wider appeal and utility of registries is low awareness among the public and policymakers. Incorporating them as a part of the standard global healthcare system would involve setting up a regulatory framework.

Keywords: Patient registry, Real world evidence, Stakeholders, Classical randomized clinical trials, Health economics

INTRODUCTION

Healthcare stakeholders the world over- from decision makers to sponsors to physicians are increasingly recognizing the need for more-credible, real-world information that will allow a better understanding of disease and its treatment beyond the traditional randomized clinical trial (RCT). In particular, there is a huge demand for credible evidence on the safety and efficacy of a product once it is already on the market, that is, the so-called post-marketing studies.[1]Regulators, for example, are demanding observational studies to substantiate claims of efficacy and safety in a broader range of patients following approval.[2]Moreover, patient groups have focused their efforts toward ensuring outcome-informed therapy rather than having patients simply submit to any treatment available. However, this is not possible without first collecting reliable data. Unfortunately, such real-world data must be collected in line with rigorous clinical practices but outside the controls and constraints of traditional RCTs. Over the years, post-marketing studies have significantly evolved in terms of both their objectives

and scope and are thus gaining rapid acceptance. Of particular interest is a type of observational post-marketing study called a *"patient registry"*. The need of the hour is to understand the complete impact of a product, especially its safety profile, under real-world conditions for which they are actually used. Thus, such studies could provide the real-world observational data so strongly demanded by healthcare stakeholders[2]. However, registries represent an emerging area that has not quite received the attention it deserves from stakeholders the world over. In particular, while the need for patient registries is well understood in a general sense, few stakeholders are aware of how such a study should be conducted, when a registry becomes necessary, and what the results of a registry can and cannot be used for. Thus, the present article attempts to present a review of the current state of the art as regards patient registries. In what follows, we first define patient registries as they are understood today and list the different types of such studies. Next, we briefly describe the usefulness of registries to various stakeholders and identify the key stakeholder for such studies. Subsequently, we define the most appropriate time for registry to be conducted in terms of realizing the maximum impact.Finally,we provide guidance on how stakeholders can approach the problem of conducting a registry and also enumerate the barriers to initiating such a study.

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The Agency for Healthcare Research and Quality (a part of the U.S. Department for Health and Human Services) defines a patient registry as 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 one or more predetermined scientific, clinical, or policy purposes."[3]There are, basically, three categories of patient registries:

1. Product registry : Patient is exposed to a drug or a device
2. Health services registry: Patient is exposed to a particular healthcare service
3. Disease or condition registry: Patient suffering from a particular disease or condition

As registries are defined by a limited set of exclusion criteria, they collect data from a broader range of the population (e.g., children, elderly, pregnant women, different racial and ethnic groups, and those with multiple co-morbidities). More over, the data are obtained in a more realistic setting, hence better representing the *real-world* patient experience. A patient registry can assess a product's effectiveness over time and is therefore particularly useful in understanding the safety and efficacy profile of a product in populations and conditions that are not generally studied in traditional RCTs. In addition to the clinical and safety evidence, patient registries have proven very useful in initiatives focused on health-related quality of life (HRQoL) and health economics/outcomes research (HE/OR).[4]Indeed, registries can often offer more comprehensive data otherwise inaccessible from classical RCTs or other data sources, including:

1. Health outcomes
2. Patient-reported outcomes
3. Burden of diseases
4. Effectiveness of a product
5. Safety surveillance data
6. Treatment compliance
7. Reimbursement and impact of reimbursement policy

In sum, there are four key benefits that serve as the typical goals of real-world evidence, which can be organized under the convenient mnemonic ***TEAM***:

- **T**rack the natural history of disease
- **E**valuate clinical or comparative effectiveness of a product
- **A**llow stakeholders to have evidence based data
- **M**easure or Monitor the safety profile of a product

What is at stake for different stakeholders?

A properly designed patient registry has the ability to address objectives of all stakeholders, as shown in Fig 1.The stakeholders and their objectives could be summarized as follows:

Pharmaceutical companies

- Gain market access
- Maintain formulary status
- Encourage product use
- Challenge a therapy combination
- Uncover safety concerns
- Understand Risk Evaluation and Mitigation Strategy (REMS)[3,5]

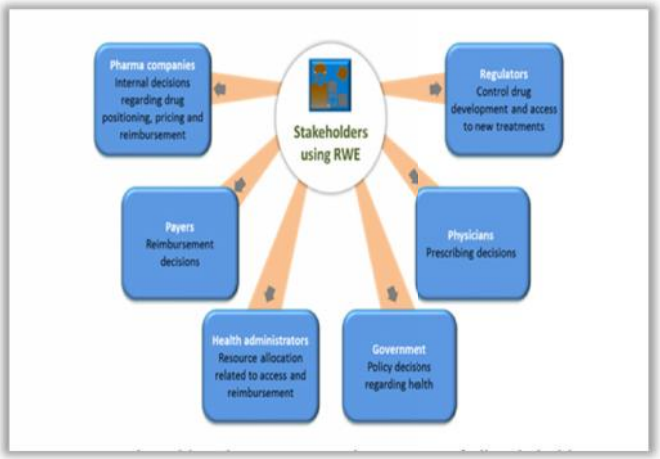

Fig1. Real world evidence caters to the interests of all stakeholders

Payers

(Patient registries have the most relevance from the payer's perspective)

- Understand cost-effective healthcare systems
- Evaluate large numbers of patients/consumers
- Expand the role of the study sponsor as thought partner in medical specialties[6,7]

Health administrators

- Heighten disease awareness
- Evaluate and assist in improving quality of care[7]

Policymakers and regulators

- Cost-effective healthcare system
- Better understand the effects of a particular intervention or sets of interventions on a disease process[3]
- Track long-term safety outcomes, mitigate risk, and monitor off-label use
- Support research and scientific inquiry
- Obtain evidence on health coverage and healthcare decisions[3]

Physicians

- Track the natural history of the disease of interest as well as the impact of therapeutic interventions[3]
- Track practice patterns and outcomes for quality-improvement initiatives
- Assist in recruitment for clinical trials
- Better understand treatment selection and affordability

Who are the most influential pharmaceutical stakeholders?

The influence of payers is rising substantially in the pharmaceutical marketplace (Fig 2). Owing to the rise in healthcare costs, there is crowding in therapeutic categories and little to differentiate one product from its competitors. In this scenario, payers have gained considerable influence and now seek to engender robust strategic relationships with pharmaceutical companies to achieve superior cost-effective patient outcomes. This is where real-world data comes into play and aids in fulfilling the objectives of different stakeholders.[8]

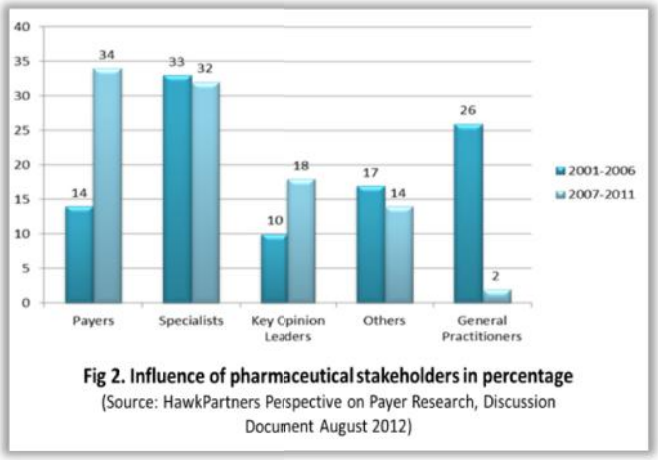

Fig 2: Influence of pharmaceutical stakeholders in percentage

Product/health services registry or disease registry?

A product/health services registry provides a deeper understanding of the utilization and outcomes of a specific drug, device, or healthcare service. This kind of registry can only be initiated after the drug/device has been launched in the market or the service is in place.

Disease registries, by contrast, assess the natural history of a particular disease and shed light on its management and outcomes. This kind of registry can be initiated well before the launch of a drug or a device. It is a proactive approach that allows a pharmaceutical company to collect valuable information prior to the launch of a product. In other words, these registries help companies assess all possible parameters and outcomes in order to ensure smooth entry into relevant markets.

The question is "When?"

A registry can be initiated at any time by the sponsor; however, it may be most appropriate if the registry is initiated at or before the launch of initial marketing, when a new indication is approved, or when there is a

specific need to evaluate nonclinical data. Concerning the specific needs that would necessitate a registry, the U.S. Food and Drug Administration (FDA) recommends that a sponsor consider the following factors when deciding to establish a registry: [9]

- The types of additional risk information desired
- The attainability of that information through other methods; and
- The feasibility of establishing the registry

Furthermore, a registry mandates the development of protocols that provide:

- Objectives for the registry
- A review of the literature, and
- A summary of relevant animal and human data

The FDA also suggests that protocols also contain detailed descriptions of the following:

- Plans for systematic patient recruitment and follow-up
- Methods for data collection, management, and analysis, and
- Conditions under which the registry will be terminated

A registry-based monitoring system should involve precise data collection forms that ensure data quality and integrity, with validation of registry findings through medical record sampling or health care provider interviews.[9]

Rare diseases patient registries

Data pertaining to rare diseases is valuable and of high interest to researchers, industrial partners, healthcare professionals, patients and patient organizations, and, ultimately, for the community. However, databases are expensive to establish and maintain as they require extensive collaboration among many healthcare providers and meticulous management. Thus, for rare diseases, patient registries have some specific additional features beyond the benefits listed above:

- Due to small number of cases worldwide and the complex nature of these diseases, collection of data becomes difficult owing to a need for a large geographical coverage, usually trans-national.
- It becomes important and desirable to trace family-related cases as most of rare diseases are genetic in origin.

Even though the cost of establishing and maintaining a rare disease patient registry is almost at par with any other patient registry, the budgets are more difficult to obtain for the former.[10]

How to conduct a registry?

The "real world" itself is an inherently and constantly changing system. Therefore, it seems obvious that conducting a real-world observational study requires considerable expertise. Although, in many ways, registries are identical to traditional RCTs, and they cannot be designed or managed on similar lines. Indeed, designing a patient registry to meet the objectives of different stakeholders is a significant challenge. What is needed is a robust understanding of the disease scenario, a strong background in observational research, and niche expertise (to understand the scope and requirements from a stakeholder's perspective) that might not be demonstrated by traditional clinical research organizations (CROs).The right partner should demonstrate the following key strengths:

- Strong scientific background
- Dedicated project management team
- Technical and site management competence
- Global experience in real world studies

Educating stakeholders about the purpose and benefits of registries is also an important role that a partner plays throughout the process. Furthermore, a properly designed patient registry can bring a wealth of valuable data that can significantly impact decision making for various stakeholders. Thus, registries often prove to be worthwhile in terms of the actual return on the project's investment. Hence, from an organizational point of view, selecting the right partner is the key to the ultimate success of the project.[1]

DISCUSSION

A significant gap in understanding has been observed to exist regarding the concept and importance of patient registries *vis-à-vis* conventional RCTs. The most significant barrier at present is the stakeholders 'lack of understanding of the impact and the benefits of real-world evidence. Furthermore, this large gap in understanding is also reflected in lagging regulations at the national or regional level. Indeed, most countries have no specific guidelines to govern the conduct of registries. Nevertheless, regulatory guidance on conducting this type of study is evolving. According to the U.S. FDA, "through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other

sources, and the factors that affect the risk of adverse outcomes such as dose, timing of exposure, or patient characteristics".[9] Hence, presently, there is no way to conduct such studies without the regulatory or ethics committee's approval/notification. All stakeholders bear equal social responsibility to set standards that ensure registry studies are properly understood and conducted in order to produce significant/reliable evidence in support of the objectives of all the stakeholders.

CONCLUSION

Registries have been shown to be widely useful and have now gained acceptance from the research community.However, the low awareness of the need for and utility of registries among the public and policymakers hinders widespread adoption. Regardless, once a clear regulatory framework is in place, registries will become a standard part of the global healthcare system.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interests regarding the publication of this paper.

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