

## Patient Registries – New Gold Standard for Real World Data

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### ABSTRACT

Patient registries have been evolving in the last few years as our quest for Real World Data (RWD) is increasing. The current global movement towards innovative and patient-centered healthcare is enabling patient registries to increasingly emerge as valuable tool not just for collecting Real World Data but also for making meaningful inferences and insights from the collected data. In the last few years, The Food and Drug Administration (FDA), European Medicines Agency (EMA) and other regulatory bodies have initiated several frameworks to highlight the importance of patient registries. In Sep, 2020 EMA has issued a draft guidance for considerations on patient registries. The paper highlights some key points from the guidance. Patient Registries are highly recommended to determine the effectiveness of the investigational product by exploring various subgroup of patients for extensive time duration. It also helps in assessing the safety or harm caused by the approved drug. Registries also prove worthy in measuring the quality of care and highlights the areas of improvement in various facets of the real world clinical practices. Registries can be designed precisely as per the research question and can serve as a significant medium to observe the real world clinical practices. Patient Registries are indeed going to be a new gold standard for real world data research.

### INTRODUCTION

In our attempt to provide drugs to the patients safely and efficiently, it is imperative to evaluate the potential use of Real World Evidence (RWE) to support the drug post approval study requirements. Patient registries are extensive source of Real World Data (RWD) that could be used to generate Real World Evidence (RWE). Patient registry is an organized system that uses observational study methods to collect clinical and other data 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. Regulatory authorities like Food and Drug Administration (FDA) and European Medicines Agency (EMA) have launched initiatives to revive the use of registries to serve as a medium to provide real world view of clinical practices, patient outcomes, safety and comparative effectiveness. The paper highlights key uses of patient registries along with the update on the programs initiated by the regulatory authorities and some key considerations on patient registries from the recent guidance published by European Medicines Agency (EMA). The paper thus intends to bring awareness on the potential of patient registries to become the new gold standard for Real World Data (RWD).

### WHY PATIENT REGISTRIES?

Patient registries are no more seen as just a tool for data collection. The data collected from patient registries however has been effectively utilized to address the purpose for which the registry is created. The lead federal agency of United States – ‘The Agency for Healthcare Research and Quality’ (AHRQ) has been extensively working on the guidance on registries for evaluating patient outcomes. Mission of AHRQ is to develop the knowledge, tools, and data needed to improve the health care system and help the citizen, health care professionals, and policymakers make informed health decisions. AHRQ’s user guide on registries has identified four primary use cases for patient registries:

1. Determining clinical effectiveness - Based on the research question in hand, registries can be developed to determine the clinical effectiveness in real world setting. Effectiveness refers to how well the investigational product performs in the real world setting in the general patient amidst the general chaos of clinical practice whereas efficacy refers to how well the investigational product performs in a setting of carefully selected patients as per the carefully designed protocol. Many registries have provided evidences for the differences between the results of clinical trials and the results from the real clinical practices. For example, underrepresentation of older patients has been reported in some heart failure and oncology trials. The patients in the real world are much older and have higher

mortality rate. With the inclusion of various subgroups of patient population, registries are effectively used to expand the labels of the products. For example, the FDA used the American Academy of Ophthalmology's intraocular lens registry to expand the label for intraocular lenses to younger patients. Due to the longer period of execution, registries have also been successfully tracking the effectiveness outcomes for a large time period like some growth hormone registries have tracked children well into adulthood.

2. Safety surveillance - As the post marketing requirements for medical product is critical so does the use of patient registries as a safety surveillance program. Registries are emerging as a resource for capturing proactive risk assessment method in the real world setting. The inclusive design of registries allows monitoring of more diverse patient population. It has potential to capture issues ranging from common and minor side effects to some fatal drug reactions which were not reported in the controlled settings. Registries provide a systematic approach of adverse events reporting as opposed to the spontaneous reporting of adverse events by physicians in the real world. The registry also provides the data on exposed population which helps to understand the incidence of the event which is not possible in the conventional clinician's reporting of adverse event. With these benefits registries have been increasingly in demand to capture and analyze the real world data for safety assessment.
3. Understanding natural history of a disease – Patient registries have the ability to enhance existing knowledge and disease characterization of specific rare diseases. Since these diseases are rare in nature only small number of patients are affected which leads to inadequate clinical knowledge and hence there is lack of knowledge on the natural history of rare diseases. Conducting controlled clinical studies with appropriate sample size is the biggest challenge for the rare disease research. This difficulty aggravates for the ultra-rare diseases. Long term follow-up required in rare diseases also poses unique challenges. Many of these challenges can be overcome via registries. Knowledge on characteristics, outcome and management of certain rare disease have changed after the introduction of certain therapies. For example, the life expectancy of patients with lysosomal storage disease has changed from 20 years to 40 or 50 years has been firstly described by a registry.
4. Evaluating and Improving Quality of Care – Registries can also be designed to measure and improve quality of care of the targeted patient population. They are extensively used to provide a deeper understanding of the epidemiologic changes in the population over time, to evaluate the associations between clinical characteristics and health outcomes. By tracking the health outcomes and care delivery process over time it is possible to identify underutilized but effective clinical practices and demonstrate other opportunities of improvement in clinical care.

Registries can be designed and executed to serve more than one of the above purposes. Due to the long duration of registries, their purpose can be changed with time as per the changes in research and clinical practices. However, the main design and execution of the registry is guided by the primary purpose of the registry and a careful planning is required to assess results for other purposes.

## REGULATORY AGENCIES AND EVOLUTION OF REGISTRIES

In December, 2018, The Food and Drug Administration (FDA) has created a framework for Real-World Evidence program. This framework is created to evaluate the potential use of Real World Evidence (RWE) to help support the approval of a new indication for already approved drug or to help support or satisfy drug post approval study requirements. FDA will collaborate with various stakeholders to understand how RWE can best be used to enhance the efficiency of clinical research and provide answer to the questions that were unanswered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval. For the purpose of this framework, FDA has recognized patient registries as one of the sources of Real World Data (RWD) that could be extensively used to generate RWE. Through this framework FDA aims to develop guidance documents to help sponsors interested in using RWE to support their work.

More recently, the newly formed Patient-Centered Outcomes Research Institute (PCORI) has identified registries as an important potential source of data to support patient-centered outcomes research

(PCOR). Their mandate is to improve the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy makers make better-informed health decisions. To achieve this, they work with those healthcare stakeholders to identify critical research questions and answer them through comparative Clinical Effectiveness Research, or CER, focusing on outcomes important to patients. They also disseminate the results in ways that members of the healthcare community will find useful. Registries are expected to play an important role in this new area of research because of their ability to provide information on ‘real-world’ settings and broad patient populations.

European Medicines Agency (EMA) had this belief that Patient registries are greatly underused in regulatory assessments. To revive the use of registries, in 2015, EMA established a ‘Patient Registries Initiative’ to support a systematic and standardized approach for registry contribution to medicines assessment, especially for post-authorization safety studies (PASS) and post-authorization effectiveness studies (PAES). The initiative aims to create a registry framework with collaboration between registry coordinators, including healthcare professionals’ and patients’ associations, academic institutions and national agencies responsible for overseeing healthcare services, and potential users of registry data, such as medicines regulators, reimbursement bodies, and pharmaceutical companies. Key elements of its strategy include facilitating the use of existing patient registries within the current legal and regulatory framework for medicinal products and providing methodological support for the establishment of new registries.

## CONSIDERATIONS FOR PATIENT REGISTRIES

With the increasing need of standardizing the registry implementation in the real world setting, European Medicines Agency (EMA) has provided many factors of good regulatory practice in the establishment and ongoing management of patient registries. Following are some points of considerations as per the recent draft guidance launched by European Medicines Agency (EMA).

### REGISTRY POPULATION

The data generated from a patient registry should be representative of the target population of the product. Ideally, the registry should cover a broad patient population covering all disease aspects and patient characteristics. The following steps can be considered prior to the enrolment of a registry population:

- To clearly define the purpose of the registry and the corresponding target population
- Translate the target population definition into a detailed description of when, where and how patients will be enrolled in practice
- To establish processes allowing for enrolment of all eligible patients fulfilling the description of the target population definition
- To create a system that best minimizes loss to follow-up and maximizes the completeness and accuracy of key information collected on each enrolled patient. Completeness of follow-up should be monitored and reported, and deviations from expectations explained

### DATA ELEMENTS

Data elements should be identified and routinely collected. The definitions of data elements should be in line with existing general and disease-specific guidelines. Core and optional data elements should also be well categorized. “Core” data elements are those that are considered essential for the purpose of the registry or the coordinated registry network. They should be collected from all patients in all concerned registries and are those on which greater amounts of resources should be allocated to ensure data quality. “Optional” data elements are those considered of interest and useful to some stakeholders, but not essential to all. The dataset should ideally contain all the core data elements like – administrative information – name of centre, informed consent availability, registry entry and exit date etc. patient data – birthdate, gender, lifestyle factors, disease – diagnosis, stage, grade/severity of disease, genomic

information if important and other relevant milestones in disease monitoring, comorbidities, disease related treatments, relevant concomitant therapies, safety recording and reporting, pregnancies, patient related outcomes and any other additional core data elements defined in disease specific regulatory guidelines.

Data elements collected from patients should ideally be harmonized to international standards across all centers participating in a registry and all registries participating in a coordinated registry network. Such harmonization supports implementation of a common data quality system (e.g. automated data entry control and check for data consistency), data exchange, identical data analysis with the same programming codes, pooling of data and interpretation of results.

## **QUALITY MANAGEMENT**

Uncertainties about the quality of the data collected in registries may undermine the confidence in the validity and reliability of the evidence generated from registry data in registry-based studies. Measurable quality requirements can be achieved by proper quality planning, quality assurance and control and quality improvement. These quality management activities should be done in a continuous manner throughout the lifetime of the registry and they should be regularly assessed. In this context, data quality may include four components – consistency, completeness, accuracy and timeliness.

## **GOVERNANCE**

Registries generally operate under governance principles that may be influenced by their purpose, operating procedures, legal environment or funding sources. Different parties may potentially also have divergent priorities, such as scientific independence, fulfilment of regulatory commitments, transparency or intellectual property rights. Clear governance principles supporting effective collaborations between all parties for regulatory use of registries, including data sharing, are therefore useful. Registry holders should follow the guidance from the appropriate Code of Conduct to ensure best use and sustainability of their registry.

## **DATA SHARING OUTSIDE THE CONTEXT OF REGISTRY BASED STUDIES**

There may be situations where registry data can be shared in the format of counts, aggregated data or statistical reports with regulators, or other parties for clinical development planning or the evaluation or monitoring of medicinal products. This information may require capacity for analysis within the registry or, if allowed by the registry governance, transfer of an anonymized dataset with selected variables to the requester or a third-party performing the analysis on behalf of the registry or the requester. Data sharing may require a contractual agreement between the registry coordinated network and the other concerned parties.

With the launch of this latest guidance we are a step closer to standardize the conduct of registries.

## **CONCLUSION**

Patient registries offer great potential to address many types of research questions. Studies derived from well-designed and well-performed patient registries can provide a real-world view of clinical practice, patient outcomes, safety assessment, clinical effectiveness, and can serve a number of evidence development and decision-making purposes. It is the need of the hour to have a thorough regulatory guidance to help registries operate in the best effective way. With the various initiatives launched by regulatory authorities, we are hopeful to overcome the current challenges faced in the registry operations like ensuring collection of quality data, standardizing data elements for multinational registries, differences in ethical and legal environments. Registries have been shown to be widely useful and is gaining acceptance from the research community. Once a clear regulatory framework is in place, patient registries are definitely going to be the new gold standard for Real World Data (RWD).

## REFERENCES

- Gliklich RE, Dreyer NA, editors. "Registries for Evaluating Patient Outcomes: A User's Guide." 2nd edition. Rockville (MD): Agency for Healthcare Research and Quality (US). 2010 Sep. <https://www.ncbi.nlm.nih.gov/books/NBK49448>.
- Boulanger, V., Schlemmer, M., Rossov, S. et al. "Establishing Patient Registries for Rare Diseases: Rationale and Challenges." *Pharm Med* 34, 185–190 (2020). <https://doi.org/10.1007/s40290-020-00332-1>.
- US Food and Drug Administration. "Framework for FDA's Real-World Evidence Program." December 2018. <https://www.fda.gov/media/120060/download>.
- European Medicines Agency. "Guideline on registry based studies Draft." 24 September 2020. Available [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf).
- Agency for Healthcare Research and Quality: A Profile. March 2018. Agency for Healthcare Research and Quality, Rockville, MD. <https://www.ahrq.gov/cpi/about/profile/index.html>
- Multinational Registries: Challenges and Opportunities, Addendum to Registries for evaluating Patient Outcomes: A User's Guide. February 2018. [https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/multinational-registries-guide-3rd-ed-addendum\\_white-paper-2018-1.pdf](https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/multinational-registries-guide-3rd-ed-addendum_white-paper-2018-1.pdf)

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