

Patient Registries in Malaysia and the Role of the Clinical Research Centre of the Ministry of Health

M S Pillay*, A Noor Hisham**, M Z Zaki Morad***, T O Lim****, H Jamaiah****, S P Jaya Purany****

*Pejabat Timbalan Ketua Pengarah (Sokongan Teknikal), Kementerian Kesihatan Malaysia, Aras 12, Blok E7, Parcel E, Pusat Pentadbiran Kerajaan Persekutuan, 62590 Putrajaya, **Pejabat Timbalan Ketua Pengarah (Perubatan), Kementerian Kesihatan Malaysia, Aras 7, Blok E7, Parcel E, Pusat Pentadbiran Kerajaan Persekutuan, 62590 Putrajaya, ***International Medical University, No 126, Jalan 19/155B, Bukit Jalil, 57000 Kuala Lumpur, ****Clinical Research Centre, Tingkat 3, Blok Dermatologi, Hospital Kuala Lumpur, 50586 Kuala Lumpur, Malaysia

INTRODUCTION

A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and others) to evaluate specified outcomes for a population defined by a particular disease or therapy (target disease or therapy), and that serves one or more predetermined scientific, clinical, or policy purposes¹. The resulting clinical database describes a file (or files) derived from the registry.

Patient registries have four common objectives. These are to:

1. Describe the natural history of the target disease.
2. Determine clinical and cost effectiveness of treatments for the target disease.
3. Monitor safety and harm of therapeutic products and services for target disease.
4. Evaluate access to and quality of healthcare for the target disease.

Natural history of the target disease

Patient registry data from real-world clinical setting is ideally suited to describe the characteristics of patients, the healthcare they had received, and the resulting long term patient survival and quality of life outcomes. The data are also useful for describing the variation in patient care and outcomes across different patient groups, clinical practices, healthcare sectors or geographic regions, and the secular trend over time of such variations in Malaysia.

Clinical and cost effectiveness of treatments for the target disease

Patient registry data from real-world clinical practices in Malaysia is also useful for determining the clinical and cost effectiveness of treatments provided. Multiple studies^{2,3} have demonstrated disparities between the results of clinical trials and results in actual clinical practice. Furthermore, efficacy in a clinical trial for a well-defined population may not be generalizable to the Malaysian population. The registry is also particularly useful for tracking effectiveness outcomes for a longer time period than is typically feasible with clinical trials.

Beyond clinical effectiveness, registry may also be designed to collect resource use and cost data for the same patients to be used in modeling cost effectiveness. Cost effectiveness refers to a means to describe the comparative value of a health care

product or service in terms of its ability to achieve a desired outcome for a given unit of resources⁴.

Monitoring the safety and harm of therapeutic products and services for the target disease.

Patient registry can serve as an active surveillance system for the occurrence of unexpected or harmful events for products and services. Patient registries offer several advantages for active surveillance. First, the current practice of spontaneous reporting of adverse events relies on a nonsystematic recognition of an adverse event by a clinician and the active effort by the clinician to make a report to manufacturers and health authorities. Second, these events are generally reported without a denominator (i.e., the exposed population), and therefore an incidence level is difficult to determine. Because patient registries can provide systematic data on adverse events and the incidence of these events, they are being used with increasing frequency in the areas of health care products and services⁵.

Evaluating access to and quality of healthcare for the target disease.

Patient registry data can be used to assess differences between providers or patient populations based on performance measures that compare treatments provided or outcomes achieved with "gold standards" (e.g., evidence-based guidelines) or comparative benchmarks for specific health outcomes (e.g., risk-adjusted survival rates). Such programs may be used to identify disparities in access to care, demonstrate opportunities for improvement, establish differentials for payment by third parties, or provide transparency through public reporting.

Patient registry is clearly a powerful tool to observe the course of disease; to understand variations in treatment and outcomes; to examine factors that influence prognosis and quality of life; to describe care patterns, including appropriateness of care, access to treatments and disparities in delivery of care; to assess effectiveness; to monitor safety; and to change behavior through feedback of data.

Its benefits are evident from several perspectives:

- For clinicians, registries can collect data about disease presentation and outcomes on large numbers of patients

rapidly, thereby producing a real-world picture of disease. This establishes the evidence base to underpin clinicians' demand for more resources to better treat their patients.

- For academic organization or medical association, a registry might assess the degree to which clinicians are managing a disease in accordance with evidence-based guidelines, focus attention on specific aspects of a particular disease that might otherwise be overlooked, or provide data for clinicians to compare themselves with their peers.
- From policy-makers and payers' perspective, registries can provide detailed information from large numbers of patients on how procedures, devices, or pharmaceuticals are actually used and on their effectiveness in different populations. This information may be useful to drive resource allocation for under served therapeutic groups and for determining coverage or reimbursement policies.
- For a drug or device manufacturer, a registry might demonstrate the performance of a product in the real world, meet a post-marketing study commitment, develop hypotheses, or identify patient populations that will be useful for product development, clinical trials design, and patient recruitment. The U.S. Food and Drug Administration (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."⁵

Setting up a patient registry in Malaysia

It takes much to set up and operate a patient registry. Key success factors are:

1. An able leadership, typically the well respected key-opinion leaders in the relevant clinical discipline, to galvanize the commitment of all stakeholders.
2. Source Data Providers (SDP) buy-in are obviously crucial. SDPs are the individual clinicians or clinical departments who report the required data to the registry. Patient registries however also receive data from other sources such as other clinical databases and, particularly important, data from the National Registration Department (Jabatan Pendaftaran Negara) to ascertain or verify mortality outcomes of registered patients.
3. Skilled organization, which will typically include the sponsors to provide funding, a Governance Board with broad oversight responsibility, a Steering Committee to direct the registry operations, and a Registry Coordinating centre for day-to-day operations.
4. Skilled human resource in a multi-disciplinary team, including the all important dedicated and obsessive administrative personnel and other supporting staff to operate the registry day-to-day.
5. Competent clinical epidemiological, biostatistical and data processing capability, and a sophisticated IT infrastructure to underpin that.

And of course the financial resources to pay for much of the above

Ethical and legal considerations

Several ethical and legal issues require critical considerations in the design and operations of any patient registry. Participation in patient registry in Malaysia is entirely voluntary; there is no legal provision to compel any individual or institution to report data to a registry. Hence, to secure and maintain SDP buy-in, any registry must conduct itself in accordance with the highest ethical standards and applicable regulations in the country. In particular, we expect registries in Malaysia to comply with the ethical principles as stated in the Declaration of Helsinki, CIOMS's International Guidelines for Ethical Review of Epidemiological Studies⁶, Good Pharmaco-epidemiological Practice⁷ as well as applicable local research guideline such as those of our National Institute of Health (NIH)⁸.

Patient registry resembles observational research that involves the participation of human subjects. In compliance with current NIH research guideline⁸, the registry protocol must be reviewed and approved by a properly constituted Independent Ethics Committee (IEC). Moreover, patient registry typically also operates under a waiver from the requirement to obtain individual informed consent from the patients whose data are reported to the registry by participating clinical sites. This requires explicit justifications and approval by IEC. Usual justifications of such waiver, in accordance with current ethical guidelines^{7,9} are:

1. Registry is an observational research and involves no physical risk to the subjects.
2. The waiver will not adversely affect the rights and welfare of the subjects.
3. The requirement of individual informed consent would make the conduct of the registry impracticable and unscientific. In particular, observational research (unlike randomized trial) needs to avoid selection bias that the requirement for informed consent would inevitably introduce. A waiver permits the registry to include all patients who are eligible, rather than those who consent.
4. The registry cannot be practically be conducted without access to patients' health information.
5. An adequate policies and procedures will be implemented by the registry to protect patients' data and prevent improper use or disclosure. No individual information will ever be disclosed; only aggregate statistical results will be published by the registry.
6. Patients will not actually be enrolled since the registry is based entirely on review of medical record. The registry does not collect data that is not already routinely available.
7. The registry is carried out under the public health authority residing with the Ministry of Health, the primary sponsor of most registries in Malaysia.

In addition, in view of the confidential medical information, often identifiable, that are collected and stored by registry, a registry must institute stringent information security policies and procedures, supported by state of the art data protection technology, which will be in accord with the requirements regarding personal data protection in applicable local guideline¹⁰, and for us in Malaysia, often with applicable US and European standards too^{11,12,13}, until such time the much anticipated Malaysian Data Protection regulation are enforced.

Table I: Patient registers currently supported by CRC

	Clinical Database or Disease Registry	Since	Owners
1	National Renal Registry (NRR) http://www.msn.org.my/nrr	1993	MOH Nephrology & Malaysian Society of Nephrology (MSN)
2	National Neonatal Registry (MNRR) http://www.acrm.org.my/mnrr	2003	MOH Pediatric Dept & Perinatal Society of Malaysia
3	National Transplant Registry (NTR)- Kidney, Bone Marrow, Heart and Lung, Liver, Corneal, Bone, Tissue and Heart valve http://www.mst.org.my/ntrSite/index.htm	2004	MOH Transplant & Malaysian Society of Transplantation (MST)
4	Malaysian Liver Registry Website not ready	2004	MOH Hepatology
5	National Medicines Use Survey (NMUS) http://www.crc.gov.my/nmus	2004	MOH Pharmaceutical Services & CRC, HKL
6	National Mental Health Registry (NMHR): Schizophrenia Registry http://www.nmhr.gov.my	2004	MOH Psychiatry Services
7	Malaysian Registry of Renal Biopsy (MRRB) https://www.macr.org.my/emrrb	2005	MOH Nephrology & Malaysian Society Nephrology (MSN)
8	National Eye Database (NED) http://www.acrm.org.my/ned	2006	MOH Ophthalmology
9	National Cardiovascular Disease Database (NCVD)- Acute Coronary Syndrome (ACS) & Percutaneous Coronary Intervention (PCI) http://www.acrm.org.my/ncvd	2006	MOH Cardiac & Medical Services, UM, HUKM & IJN
10	National Trauma Database (NTRD)- Major Trauma Outcome & Traumatic Brain Injury database http://www.acrm.org.my/ntrd	2006	MOH Trauma & MOH Neurology
11	Diabetes in Children and Adolescent Registry (DiCARE) http://www.acrm.org.my/dicare	2006	CRC, MOH Pediatric Dept, HUKM & UMMC
12	National Suicide Registry (NSRM) http://www.nsr.gov.my	2007	Psychiatry and Mental Health Services, Forensic Medicine Services, Mental Health Registry Unit, MOH & CRC HKL
13	National Cancer Patient Registry (NCPR) https://app.acrm.org.my/ncpr	2007	CRC MOH
14	NCPR: Colorectal Cancer https://app.acrm.org.my/CCD/	2007	MOH Gastro, Surgery, Pathology
15	NCPR: Nasopharyngeal Carcinoma Cancer (NPC) https://app.acrm.org.my/npc/	2007	MOH ENT, Pathology, Radiotherapy & Oncology, UMMC, CARIF, IMR & CRC
16	NCPR: Cervical Cancer Website not ready	2007	MOH Oncology
17	NCPR: Hematology Malignancy https://app.acrm.org.my/hema/	2007	MOH Hematology & CRC
18	Malaysian Psoriasis Registry (MPR) https://www.macr.org.my/empr	2007	MOH Dermatology
19	National Endoscopy Registry (NER) https://www.macr.org.my/ener/	2007	MOH Gastro
20	NCPR: Breast Cancer https://app.acrm.org.my/breast	2008	MOH Surgery
21	National Inflammatory Arthritis Registry (NIAR) Website not ready	2008	MOH Rheumatology & Arthritis Foundation
22	National Orthopaedic Registry: Hip Fracture Register (NOHFD) https://www.macr.org.my/enorm	2008	MOH Orthopaedic
23	National Orthopaedic Registry: Diabetic Hand & Foot Disorder Register (NODFD) https://www.macr.org.my/enorm	2008	MOH Orthopaedic
24	An Audit of Diabetes Control & Management (ADCM) https://app.acrm.org.my/ADCM	2008	CRC HKL, MOH Medical Dept, Disease Control Dept & Medical Development Dept
25	Malaysian Cardiothoracic Registry (MyCaRe) Website not ready	2008	CRC HKL

Since most registries in Malaysia are funded largely by public funds disbursed through the CRC MOH, it is desirable that the operations of patient registries be transparent. That means, making information about the registry operations public and readily accessible to anyone who is interested. Transparency in registry operations is desirable because it helps to realize the potential benefits of the registry; educates the public and other stakeholders about the scientific process; contributes to public and professional confidence in the scientific integrity and validity of the registry processes, and thus its findings; and finally transparency increases scientific utility of the registry data by promoting inquiries from interested scientists.

To this end, a registry is expected to achieve transparency by publishing a regular report on its findings at least annually and disseminating the report free of charge to anyone who is interested through its official website; and by providing information on the registry's objectives; governance, policy and organization; methods, operations and data sources available to anyone who is interested through its official website

Finally, concerning registry data ownership, in theory, it is likely that the health information compiled by the registry will satisfy the statutory definition of a compilation, and thus copyright law may provide a legal basis for claims of ownership and legal restrictions on access to and use of the registry data by other parties. In practice, however, given the large number of parties involved in the creation of a registry, from funders, participating clinical sites and individual specialists involved in its design, it is uncertain how any claims of property rights in the registry data may be distributed and legally constituted. Further, the health information in the registry are information concerning individual patients, it is also uncertain how patients would respond, favorably or adversely, to any such claims of data ownership.

As a practical matter, since "ownership" implies operational control of the registry data and publication rights, a funding agency such CRC, should agree to cede control of the registry operations and publication rights to the Steering Committee, the membership of which shall be appointed after due consultation with participating SDPs and individual subject matter experts involved in the creation of the registry.

Role of CRC and currently supported registries in Malaysia

In working towards accomplishing our stated mission, which is "To improve patients' outcomes through quality clinical research", the CRC has an important role in promoting and supporting the establishment and operations of patient registries in Malaysia. Table I below show all the patient registers currently supported by the CRC.

In such collaborative efforts, the CRC's role is to provide:

1. Funding through a Special Registry Grant generously set aside by the office of the Deputy Director General (Research & Technical Support) Ministry of Health Malaysia.

2. Technical resources for the registers; in particular the requisite expertise in registry sciences (clinical epidemiology, clinical economics, biostatistics, medical informatics etc).
3. Oversight to ensure that all registries produce the promised results and operationally comply with applicable regulations, ethical guidelines and best practices concerning operational transparency, information security, access to data for research and so on.

In other words, we assist medical professionals to establish patient registries in their therapeutic areas. However, we expect each clinical group to be committed to owning and operating its own registries to ensure continuing funding and support by CRC.

CONCLUSION

Any serious effort to advance healthcare in Malaysia requires hard information on its availability and distribution, and its effect on our population health outcomes. The availability of such information is currently very limited for most diseases in our country. There is a cogent need to establish more high quality patient registers in Malaysia to bridge the information gap. We urge all stakeholders in healthcare, whether as policy-makers, funders or providers to support this mission critical national endeavor.

ACKNOWLEDGEMENT

We would like to acknowledge all the staff at CRC especially Ms Harnani Tamat, Editor of MJM and the staff of MMA especially Ms Matilda and Ms Norazlin for all their effort in making this supplement possible.

REFERENCES

1. Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. AHRQ Publication No. 07-EHC001-1. Rockville, MD: Agency for Healthcare Research and Quality. April 2007.
2. Wennberg DE, Lucas FL, Birkmeyer JD *et al.* Variation in carotid endarterectomy mortality in the Medicare population. *JAMA* 1998; 279: 1278-81.
3. MacIntyre K, Capewell S, Stewart S *et al.* Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. *Circulation* 2000; 102: 1126-31.
4. Eichler HG, Kong SX, Gerth WC *et al.* Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value in Health* 2004; 7: 518-28.
5. U.S. Food and Drug Administration. FDA Guidance for Industry. Good pharmacovigilance and pharmacoepidemiologic assessment. March 2005.
6. Council for International Organizations of Medical Sciences: 1991 International Guidelines for Ethical Review of Epidemiological Studies. Available at: <http://www.cioms.ch/>
7. Epstein M. Guidelines for Good Pharmacoepidemiology practice. ISPE commentary. *Pharmacoepidemiol Drug Safety* 2005; 14: 589-95.
8. National Institute of Health Ministry of Health Malaysia. NIH Guidelines for conducting research at MOH Institutes and facilities. Available at: <http://www.nmrr.gov.my>
9. Code of Federal Regulations. Title 45-Department of Health and Human Services; Part 46-Protection of Human subjects. Updated 1 Oct 1997. Available at: www4.law.cornell.edu/cfr
10. Malaysian Public sector management of ICT Security handbook. MAMPU 2001.
11. Directive 94/EC and 95/EC Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data. 1995. Implementation 2000.
12. European Network of Cancer Registries. Guidelines on Confidentiality in population-based Cancer Registration in the EU. Feb 2002.
13. US Health Insurance Portability and Accountability Act 1996 (HIPAA).