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Nationwide Registries Associated with Cardiovascular Medical Devices in Japan

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Abstract

Background: Nationwide medical device registries have the potential to provide real world data for regulatory purposes. The objective of this article is to assess how to develop and manage Nationwide Registries Associated with Cardiovascular Medical Devices (NRACMD).

Methods: A questionnaire comprising of 43 items was designed to clarify the quality, characteristics, utility and sustainability of existing NRACMD in Japan. It was then sent to various organizing bodies.

Findings: Eight organizations responded to the questionnaire. Three NRACMD were device-specific registries in which the patient was registered when a device was used. The others were procedure-specific registries. Six registries covered more than 95% of target population and two covered 80-95%. Five registries were associated with specialty board certification systems or with physician qualification for using priority devices. No NRACMD was linked to medical re-imbursement. All NRACMD were used for academic purposes related to scientific papers. Two registries were currently in use for all case surveillance under the provision of the Japanese PMD-ACT. One registry provided a historical control group for a device in clinical trial for pre-market application. The analytical output was provided to participating institutions in all registries and to manufacturers in five registries. In terms of registry management sustainability, different funding sources including public funding, funding from institutions or from physicians and manufacturers were used for NRACMD. Accuracy of registered data was verified by institutional site visit and collation of extracted sample data.

Interpretation: Japan currently has eight NRACMD are in operation. Although mainly used for academic purposes, there are several examples where data have been used for regulatory purposes and shared with the manufacturers. Cooperation between the academic sector, industry and regulatory bodies is essential for efficient use of NRACMD data.

Keywords: Registry; Cardiovascular device; Pharmaceutical and medical device act; Post-marketing surveillance; Regulatory application

Introduction

The accumulation of real world data associated with medical devices, or a "Medical Device Registry", plays an important role in promoting the development of medical devices [1,2]. It is desirable to utilize registry data for pre-approval review as well as post-marketing safety measures. However, data has often been collected without compliance with a Good Clinical Practice. Furthermore, the registry may not include all data elements required for demonstrating the effectiveness and safety of medical devices. As such, it may not meet the regulatory requirements for pre-market review. Despite these limitations, there are many national registries, such as orthopaedic total hip joint registries in multiple countries, that have successfully detected the increased revision rate of metal on metal hip implant [3,4]. In addition, there are several national registries in the European Union, US and Japan that include registries for artificial heart placement [5,6], trans-catheter aortic valve replacement [7,8] and devices for peripheral arterial diseases [9]. The current issues of registry management include ensuring a wide patient coverage, involvement of regulatory authority, implementing rules of data utilization by the manufacturer, regulators and the academic sector, and obtaining sustainable funding for registry management. In the present article, we focus on the eight existing Nationwide Registries Associated with Cardiovascular Medical Devices (NRACMD) in Japan and discuss their characteristics including data quality, data utilization and financial sustainability.

Materials and Methods

A Medline search was conducted using the term "((Registry or Database) and (Japan or Japanese)) and Medical device and (Surgery or Intervention) and Cardiovascular". Out of the 155 articles in the results, foreign registries, clinical studies not associated with registries and regional registries in Japan were excluded. Consequently, four

NRACMDs managed by Japanese academic bodies were identified. In addition, six NRACMD which Pharmaceuticals and Medical Device Agency (PMDA), Japan has communication with, were included in the study. Accordingly, a questionnaire consisting of 43 items was sent out to the 10 organizing bodies of NRACMDs. We received eight responses. The questions are detailed in the appendix.

Results

The names of the eight NRACMDs are shown in Table 1. Three were device-specific registries where patients were registered when the device was used. The others were procedure-specific registries. Three NRACMDs had made the registry protocol publicly available on their Website (Table 1). The characteristics of NRACMD are detailed in Tables 2-5. Six NRACMDs cover more than 95% of the target population and two covered 80-95% (Table 2). The Primary endpoint of NRACMD included death in 4 NRACMDs, procedure success in 2, and amputation-free survival in the registry for critical limb ischemia. The endpoint of Japan Mechanically Assisted Circulatory Support (J-MACS) registry was a combined endpoint of transplant, death and recovery. PMDA participated in the management of three NRACMDs.

JACVSD	Japan Adult Cardiovascular Surgery Database	http://www.jacvsd.umin.jp/
JCCVSD	Japan Congenital Cardiovascular Surgery Database	http://jccvsd.umin.jp/
J-PCI	Japan Percutaneous Cardiovascular Intervention Registry	http://www.cvit.jp/registry/ncd.html
J-PIC	Japan Pediatric Interventional Cardiology Registry	http://www.jpic-meeting.org/
J-MACS	Japan Mechanically Assisted Circulatory Support Registry	http://www.mhlw.go.jp/file.jsp?id=147446&name=0000013474.pdf
JCSM Registry	Japanese Committee of Stent-graft Management Registry	http://stentgraft.jp/pro/registration/
TAVR Registry	Trans-Catheter Aortic Valve Replacement Registry	http://j-tavr.com/
JCLIMB Registry	Japan Critical Limb Ischemia Database	http://www.jsvs.org/ja/file/info/2012/2012-12-05_gaiyou.pdf
Registry Protocol Released by Steering Committee		
J-PCI	Japan Percutaneous Cardiovascular Intervention Registry	http://www.cvit.jp/registry/jpci_definition.pdf
J-PIC	Japan Paediatric Interventional Cardiology Registry	http://www.jpic-meeting.org/aboutdb/index.shtml#01
JCLIMB Registry	Japan Critical Limb Ischemia Database	http://www.jsvs.org/ja/file/info/2012/2012-12-05_protocol.pdf

Table 1: Names of registries associated with cardiovascular medical devices.

	Target population	**Coverage**	**Endpoint**	**Participation of PMDA**	**Data utilization for academic purpose**	**Data utilization for post-marketing surveillance**	**Data utilization by manufacture**
JACVSD	Adult cardiac surgery	>95%	Death within 30 days	✕	○	✕	○*
JCCVSD	Congenital cardiac surgery	>95%	Death within 30 days	✕	○	✕	○*
J-PCI	Interventional cardiology	80-95%	Procedural success	✕	○	✕	✕
J-PIC	Paediatric interventional cardiology	80-95%	Procedural success	✕	○	✕	✕
J-MACS	Left ventricular assist device	>95%	Death, Transplant or recovery	○	○	○	○**
J-TAVR	Trans-Catheter Aortic Valve Replacement	>95%	Death within 5 years	○	○	○	○**
JCMS	Endovascular aneurysm repair	>95%	Death within 10 years	○	○	✕	○*
JCLIMB	Critical Limb Ischemia	>95%	Amputation free survival within 5 years	✕	○	✕	✕

RACMD: Registry Associated with Cardiovascular Medical Device, PMDA: Pharmaceuticals and Medical Devices Agency, ○*: Steering committee need to approve, ○**: Data is provided to manufacture by pre-arrangement for post-marketing surveillance of PMD-ACT, PMD-ACT: Pharmaceuticals and Medical Devices Act in Japan

Table 2: Characteristics of eight NRACMD.

All NRACMD aimed to use registry data for academic purposes. Japan Adult Cardiovascular Surgery Database (JACVSD) had previously provided data of surgical thoracic aneurysm repair as a historical control for the clinical trial of a stent graft designed for aneurysm repair. This data was used for pre-approval review (Table 2).

	Device identification	SC meeting	Adverse event adjudication committee	Patient participation	Release of members of SC	Linkage with specialty board	Regular Report of analysis
JACVSD	Product name	Regularly held	✕	✕	✕	○	○
JCCVSD	Product name	Regularly held	✕	✕	✕	○	○
J-PCI	A group of product	Regularly held	✕	✕	○	✕	○
J-PIC	A group of product	Regularly held	✕	✕	○	✕	○
J-MACS	Lot and Serial numbers	Regularly held	○	✕	✕	○	○
J-TAVR	device model identification codes	Regularly held	✕	✕	✕	○	○*
JCMS	Product name	Regularly held	✕	✕	✕	○	○
JCLIMB	A group of product	Regularly held	✕	✕	○	○	○

RACMD: Registry Associated with Cardiovascular Medical Device, SC: Steering Committee, *: The result of analysis in J-TAVR was disclosed in the annual meeting of Japanese Trans-Catheter Valve Therapeutics

Table 3: Device identification, transparency and other features of eight NRACMV.

The analytical output of registered data was provided to academic bodies in all registries and to the manufacturers in 5 registries. Two registries were currently used for all case surveillance under the provision of PMD-ACT in Japan.

The information on device identification that NRACMD collects, management of steering committee and other characteristics are shown in Table 3. J-MACS Registry records the lot and serial number of each device, and Trans-catheter Aortic Valve Replacement (J-TAVR) registry records the device model identification codes to accurately identify the device generation including minor modifications. Three NRACMDs are identified by product name and two by the product group name. Four NRACMD are associated with the specialty board certification for physicians, while two are linked to qualifications for using the priority device (Table 3). No NRACMD was linked with medical re-imbursements.

	Informed consent	Data utilization of regulatory review	Reliability assurance: Site visit	Reliability assurance: Collation of the extracted data	Reliability assurance: Regular monitoring
JACVSD	Opt out	○	○	○	✕
JCCVSD	Opt out	✕	○	○	✕
J-PCI	Opt out	✕	○	✕	✕
J-PIC	Opt out	✕	○	✕	✕
J-MACS	Opt in	✕	○	○	✕
J-TAVR	Opt out	✕	○	○	✕
JCMS	Opt out	✕	○	✕	✕
JCLIMB	Opt out	✕	○	✕	✕

RACMD: Registry Associated with Cardiovascular Medical Device

Table 4: Privacy protection and reliability assurance of eight NRACMD.

Steering committees were held regularly in all NRACMD. The method of obtaining permission to register and utilize patient data was via "opt in" in J-MACS only and via "opt out" in seven (Table 4). With respect to the reliability of data, registered data are verified by institutional site visits in six NRACMD and by collation of the extracted data in Table 3. However, regular monitoring was not performed in any NRACMD (Table 4).

In terms of sustainability of registry management, different sources of funding were utilized for development and maintenance of NRACMD (Table 5). There is only one example of merging the registered data internationally. J-MACS registry has begun merging the data with Inter-agency Mechanically Assisted Circulatory Support (Inter-MACS) registry.

	Public fund	Manufacture	Participating institutions	Academic society	Countermeasure for computer virus	Prevention of improper access	Regular maintenance of system vulnerability	Anonimization of registered data
JACVSD	○	○	○	○	○	○	○	○
JCCVSD	○	○	○	○	○	○	○	○
J-PCI	×	×	×	○	○	○	○	○
J-PIC	×	×	○	○	○	○	○	○
J-MACS	○	○	×	×	○	○	○	○
J-TAVR	×	○	○*	×	○	○	○	○
JCMS	×	○	×	○	○	○	○	○
JCLIMB	×	×	×	○	○	○	○	○

RACMD: Registry Associated with Cardiovascular Medical Device, *: J-TAVR earns fee for qualification of institution which requirement of Trans-Catheter Aortic Valve Replacement

Table 5: Funding source and security of eight NRACMD.

Discussion

The results of the present investigation disclose the current characteristics, management, and utility of NRACMD in Japan. The data of NRACMD have been mainly used for academic purposes and not for pre-approval review, except for one example from JACVSD. There were two accounts of registry data being used for legal post-market surveillance.

When discussing the nationwide registry of medical devices, it is essential to clarify the level of unique device identification and patient level data collection including long term outcome data. In addition, the following issues are important for the management of registry: how to obtain patients' consent for data registration and data use, the method of data access, how to achieve high level of coverage, how to maintain data quality including its accuracy, security, and governance and transparency.

Unique device identification

NRACMDs have different levels of unique device identification from the lot and serial numbers or device model identification codes that enable identification of the device generation to that registry contains limited information including only the general name of the product. The level of device information is important in assessing device performance and safety profile. The solution is most likely to use the Unique Device Identifier (UDI), which is required in the United States by the Food and Drug Administration (FDA) [10]. The FDA aimed to use UDI in combination with registries to accumulate safety information of the medical devices. In Japan, Supply, Processing and Distribution services are compliant with an international standard of GS1 code system in healthcare. The supply chain and patient health records in most medical institutions are managed with a Barcode reader system as well. However, there is no obligation for healthcare manufacturers to register such device identification codes to the Japanese regulatory authority. The dialogue to develop the UDI system in Japan was just started by the cooperation of the Ministry of Health, Labour and Welfare (MHLW), PMDA and The Japan Federation of Medical Devices Associations.

Patient level data collection and data repository

One major issue in patient data collection is that the electric health records in the hospital is not accessible outside the hospital because of confidentiality issues associated with individual electric health information. Therefore, the collection of patient level data requires some degree of manual input into the institutional data storage by physicians or other healthcare professionals. Potentially, it could be possible to use a data sheet template for registries using the electric health records that connects with laboratory data. Unfortunately, there are some differences in data formatting between several vendors at present preventing such electric data capture. The integration of different data formats can be achieved by the CDISC format [11]. As CDISC was introduced to drug applications to PMDA this year, it is anticipated that the extension of CDISC format into the area of medical devices would facilitate the integration of the stored data between medical institutions for registries.

Privacy protection and informed consent

In Japanese NRACMDs, the data stored in the institutional data centre are uploaded into data repositories such as the National Clinical Database (NCD). NCD, which is a consortium of surgical specialty databases, provides the infrastructure of data repository for seven of the eight NRACMDs mentioned earlier [12]. The stored data are anonymized in the NCD, but the information for those cases is identifiable at the institution if required. It is ideal that data is collected and used for secondary evaluation after the initial project of registries without the need to obtain informed consent again. Out of the eight NRACMDs, seven collected data via "opt out" system. Therefore, the data was analyzed internally and only the analytic output was provided

to those conducting the studies. One NRACMD, J-MACS, did this by "opt in" system from individual patients at the time when the device was used for treatment, making it possible to use stored data for secondary utilization and to provide it to the manufacturer. With respect to data linkage with other electric health information, Japanese NRACMDs have not yet been successful in connecting with the payers' information from the national insurance system.

Utilization of registry data

The organizing body of steering committees in eight NRACMDs hold meetings regularly for governance of registry management and assessment of appropriate data utilization for academic purposes. It also releases the results of statistical analyses about the registered data to the public on a regular basis. These activities provide useful clinical information regarding priority medical devices to the user, manufacturer and patient. The steering committee also assesses whether proposed clinical studies are suitable for patients or for academic activities. It is anticipated that data accumulated in the registry can be utilized for regulatory purposes such as legal Post-Marketing Surveillance (PMS) with re-assessment of approved priority devices under the provision of the PMD-ACT [13]. J-MACS and J-TAVR registry were designed for utilizing stored data for PMS. In these two cases, regulatory bodies and the manufacturers were involved in the early stage of registry development so that appropriate data elements were selected for regulatory re-assessment of the devices. The manufacturers of these devices can obtain raw data when they report PMS results to PMDA.

Data coverage and data assurance

As mentioned previously, six NRACMDs claimed more than 95% of data coverage and two between 80-95%. The incentive of data entry is associated with specialty board certification and its renewal and/or qualification of the physicians to perform the procedure using the priority medical device. Although Japanese NRACMD is not linked to reimbursement by the national insurance system, physicians and healthcare professionals have a strong incentive to input data to the registry [12]. The physician collects the follow-up data as well from outpatient records.

In order to achieve a reliable and robust dataset in clinical trials, several methods are defined in the Good Clinical Practice such as regular monitoring and audit. Although regular monitoring is not performed, site visit and coalition of extracted data assure the data quality in most NRACMD.

Sustainability

Sustainability is a key element in maintaining the registry for long term. There are a variety of funding sources for NRACMDs in Japan. J-MACS were established with public funding from PMDA in combination with expenses from four manufacturers, where the left ventricular assist device is on the market. The funding source for J-MACS is slowly shifting from public funds to funding from manufacturers and medical institutions where the device is used. In the case of J-TAVR registry, it was developed and managed with funding from manufacturers only. The registry of Japanese Committee for Stent-Graft Management (JCSM) for the devices of endovascular aneurysm repair receives revenue from the fee certifying the qualified or instructive physician to perform endovascular aneurysm repair using pertinent devices. In other NRACMDs, the academic sector provides the expenses from their budget for developing and maintaining the registry. Multiple funding sources are thus used for maintaining NRACMDs.

International collaboration

International collaboration of registries in multiple countries has strengthened the evidence generation. The success of such effort is reflected by the International Consortium of Orthopaedic Registry (ICOR) [14] and International Consortium of Vascular Registry (ICVR) [15]. Multiple national registries in European and Oceania countries have successfully detected the increased rate of device failure in metal on metal hip joint prosthesis [3,4]. In this example, the analytical results of each registry consistently support the interpretation that an increased revision rate was observed in metal on metal hip implants. In Japan, two NRACMDs have the potential to achieve international collaboration, one being the J-MACS registry. As a data format, data elements and definitions were referred to the Inter-MACS. The data of J-MACS has already started to merge with that of the Inter-MACS in the US. The other example where close international collaboration is possible is the J-TAVR registry in which data elements and definitions aligned with Trans-catheter Valve Therapeutics (TVT) registry managed by the National Cardiovascular Data Registry founded by Society of Thoracic Surgeons and American College of Cardiology.

Examples of efficient utilization of registry data in Japan

In Japan, the first procedure-specific registry of Japan Adult Cardiovascular Database (JACVSD) was launched in 2000, which referred to the Society of Thoracic Surgeons database. Although JACVSD is a procedure-specific registry, it has collected device information as well that has been utilized to assess the quality of medical practices associated with cardiovascular surgery [16]. The accumulated surgical outcome of thoracic aneurysm repair in JACVSD was used as a control group of a clinical trial in comparison with the results of thoracic endovascular aneurysm repair. This is the only example so far that has used registry data for pre-market review. The other example of efficient utilization of registry data is signal detection. In J-MACS Registry, the driveline that provided power source for the left ventricular assist device was impaired in certain devices due to patient body movement. This failure was detected in the early phase based on the registry data. Early detection prevented further health damage to the patient [17].

Conclusion

Characteristics, management, utility, and sustainability of eight existing NRACMDs in Japan were investigated and reviewed in this article. Some of them were utilized for regulatory purposes. Early participation of regulators for developing NRACMD and a system that assures accuracy of data seems to be a key element for their regulatory applications based on Japanese PMD-ACT. The cooperation between the academic sector, industry and regulatory bodies is essential for utilizing NRACMD data efficiently.

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