Medical Device Real-World Evidence for Beginners: A Primer

Stephen S. Johnston, MA; **Abhishek S. Chitnis, MPharm, PhD**, Johnson & Johnson, Inc, New Brunswick, NJ, USA; **Joshua J. Gagne, PharmD, ScD**, Harvard TH Chan School of Public Health, Boston, MA, USA; **Frank R. Ernst, PharmD, MS**, CTI Clinical Trial and Consulting Services, Covington, KY, USA

The future of medical devices will bring with it a massive amount of data—from not only the devices themselves but also wearable and mobile technologies to which they are connected—and will present exciting new challenges and opportunities for the medical device researcher.

WHAT IS A MEDICAL DEVICE?

Medical devices include any equipment used for therapeutic or diagnostic medical purposes[1], and therefore comprise an extremely wide array of items—from tongue depressors to orthopedic implants to magnetic resonance imaging scanners and software. Medical devices used to identify the health status of a patient are considered diagnostic, while those that are valuable to treatment or amelioration of a disease or disorder are considered therapeutic.

WHAT ARE REAL-WORLD DATA (RWD) AND REAL-WORLD EVIDENCE (RWE)?

The concepts of real-world data (RWD) and real-world evidence (RWE) have evolved over the years. In 2017 guidance, the US Food and Drug Administration (FDA) articulated formal definitions: RWD are "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources" (eg, electronic health records) and RWE is "the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD."[2]

WHAT ARE KEY USES OF RWE FOR MEDICAL DEVICES?

Key uses of RWE for medical devices include commonplace applications such as epidemiologic and safety evaluations (eg, incidence of complications after specific device-centric surgical interventions)[3], characterizations of treatment patterns and healthcare utilization trends (eg, dissemination of new technologies such as robotics)[4], and comparative-effectiveness research (eg, comparisons of 2 or more technologies)[5]. Additionally, the FDA has recently encouraged and issued guidance on the use of RWE for regulatory purposes[2]. Such uses include support of expanded indications for use, postmarket surveillance studies, establishment of historical or concurrent control groups for nonrandomized clinical studies, and using historical data to set clinical study goals (eg, to determine equivalence of a new device to a predicate device), among others[2]. Furthermore, with the enactment of the new European Medical Device Regulation, RWE will likely play a key role in satisfying proactive surveillance requirements for medical devices marketed in Europe. In summary, RWE for medical devices can be used to provide information on a wide variety of subjects. These subjects collectively affect all stakeholders: the patients for and in whom medical devices are used, the healthcare practitioners who deliver medical device-related care, those who purchase—or influence reimbursement of—medical devices (eg, hospitals, payers), and the regulators of medical devices, among others.

FROM WHAT RWD SOURCES CAN RWE FOR MEDICAL DEVICES BE GENERATED?

Registries: Prospectively collected registries have the natural benefit of providing high-quality, detailed information on medical devices and outcomes of interest, and therefore play an extremely important role in the evaluation of medical device safety and performance. In the United States, public-private partnerships—most notably the Medical Device Epidemiology Network Initiative (MDEpiNet), through which the FDA's Center for Devices and Radiological Health (CDRH), academic and medical institutions, industry, and other governmental and private organizations have partnered—have led to the development of numerous Coordinated Registry Networks from which medical device RWE will be generated. Globally, there are also many national and international registries, with organizations such as the International Medical Device Regulators Forum (IMDRF) advocating for the use of registries for regulatory decision making.[6]

Secondary data: In some cases, the cost of collecting registry-based RWD for medical devices may be prohibitive or economically unjustified, or loss-to-follow-up rates too high for long-term quality >

and effectiveness measures (eg, 10-year hip replacement revision rates). Access to existing registry data is also generally restricted and, therefore, such data may be unavailable to a given medical device researcher. Thus, traditional secondary RWD sources are also vital to RWE generation for medical devices. Among the secondary data sources available for medical device RWE studies are: administrative payer (insurance) claims data; administrative hospital data; medical record data, including charts and electronic health records (EHRs); surveys; and expert panels.

However, identification of devices in secondary RWD sources can be challenging. Unlike pharmaceuticals, which (with some exceptions) are reimbursed directly by payers and generate a specific prescription claim with documentation of the product's National Drug Code (NCD) and other useful information for research, medical devices tend to be purchased directly by healthcare providers (hospitals and other facilities/practices, key consumers of medical device RWE) and paid under what equates to a bundled payment; reimbursement for a specific procedure will not necessarily correlate with the provider's underlying expenditure on the medical devices used therein. Although Unique Device Identifiers (UDIs)—a medical device-specific analogue to the NDC—exist, healthcare claim forms currently do not contain a field in which to record UDIs, and the documentation of standardized device identifiers is not ubiquitous in most traditional secondary RWD sources (although some healthcare systems can access UDIs from supply chain databases and link these to EHR data). Thus, medical device identification is often dependent on the device possessing a specific billing code (eg, a Healthcare Common Procedure Coding System code, which is uncommon), or mining unstructured data fields such as hospital charge master data or physician notes, which can introduce various forms of measurement error. These data sources can also lack information on important device-specific outcomes, such as device failures—which may necessitate the use of failure proxies (eg, reoperative/revisional surgery).

Table 1. Example of RWD Sources to Support RWE for Medical Devices

ADMINISTRATIVE DATABASES

Examples*:
- **Publicly Available**
  - Healthcare Cost and Utilization Project (HCUP) (eg, Nationwide Inpatient Sample)
  - Medicare/Medicaid Standard Analytic Files
  - National Hospital Discharge Survey
  - Surveillance, Epidemiology, and End Results (SEER)—Medicare
- **Payer-sourced Data**
  - Optum
  - HealthCore/Anthem, Inc
  - Blue Health Intelligence
  - Korean Health Insurance Review and Assessment
- **Hospital/Group Purchasing Organization**
  - Premier Hospital Database
  - Vizient (formerly MedAssets) Database
  - MedMining/Geisinger
  - Japanese Medical Data Vision
- **Multisource Data Consolidations**
  - IBM Watson Health/Truven/MarketScan
  - IQVIA Pharmetrics
  - Japanese Medical Data Center (Japan)
  - Orizon (Brazil)

Key Considerations:
- Relatively inexpensive and rich in data elements like diagnoses, procedures, medications, and healthcare costs/expenditures
- Typically comprise data from millions of patients and therefore are considered to have good generalizability
- Medical device identification is often dependent on the device possessing a specific billing code (eg, a Healthcare Common Procedure Coding System code), or mining unstructured data fields, such as hospital charge master data or physician notes, which can introduce measurement error
- Cannot usually answer questions such as why a provider chose one therapeutic approach over another (eg, surgery versus medication)
- Can lack information on important device-specific outcomes, such as device failures

ELECTRONIC HEALTH RECORDS

Examples*:
- Hospitals/academic medical centers
- Community practice sites
- Flatiron Health Oncology
- Cerner Health Facts
- Optum/Humedica
- US Oncology
- Practice Fusion
- GE Healthcare Centricity
- Clinical Practice Research Datalink (UK)
- IBM Watson Health Explorys

Key Considerations:
- Limited longitudinal follow-up, sometimes unable to track patients across sites of care
- Typically have same medical device identification challenges as administrative databases
- With proper design, researchers may be able to evaluate "why" events happen during treatment or treatment decision rationales
- Can lack information on important device-specific outcomes, such as device failures

SURVEYS & REGISTRIES

Examples*:
- Society of Thoracic Surgeons (STS) National Database
- Vascular Quality Initiative
- Japan PCI (Japan)
- US Cath-PCI Registry
- National Cardiovascular Data Registry's Implantable Cardiac Device Registry
- National Joint Replacement Registry (Australia)
- Kaiser Permanente National Total Joint Replacement Registry
- National Joint Registry (GB, Wales, N-IRL)
- Canadian Joint Replacement Registry
- Kaiser Permanente National Implant Registries
- European Database for Medical Devices (anticipated launch in 2020)

Key Considerations:
- Can collect and yield medical device satisfaction information directly from patients
- Provider surveys and expert panels can provide insights into clinical perspectives on drivers of treatment choice and product prescribing preferences
- Direct-to-subject study designs are often patient-centered and can capture subjective information unavailable via claims data or medical records
- Limited longitudinal follow-up; ability to link to other longitudinal data sources is inconsistent
- Information specific to the purpose of the registry design or to the remit of the expert panel is included, but they are otherwise limited in scope

** Not intended to be comprehensive; sources are US-based unless otherwise noted.*

WHAT IS THE STATUS OF RWE FOR MEDICAL DEVICES OUTSIDE OF THE UNITED STATES?

Numerous international, regional, and country-specific registries and secondary databases have been used to generate RWE for medical devices (for examples, see Table 1). Although the influence of medical device RWE varies widely by country, RWE is receiving increasingly more attention in regions such as Europe (due to the new European Medical Device Regulation) and Asia.[7] As noted above, IMDRF is one international group that is actively advocating for the use of registries for regulatory decision making related to medical devices. In 2016, the IMDRF issued a report on this subject titled, Principles of International System of Registries Linked to Other Data Sources and Tools.[6] Opportunities to be involved in RWE for medical devices outside of the United States also exist through the Observational Health Data Sciences and Informatics collaborative (https://www.ohdsi.org/), which is an open multi-stakeholder group that collectively maintains a disseminated international network of healthcare databases stored in a common data model.

WHAT KEY SOURCES OF BIAS ARE PRESENT IN MEDICAL DEVICE RESEARCH?

Studies of medical devices, particularly those that involve invasive procedures, are especially susceptible to biases. These are due to confounding by indication and difficulty in identifying appropriate comparison groups, as well as difficulties separating out the effects of a device versus the procedure.

Confounding by indication: Individuals who receive a particular device may be different from those that receive no device or a different device. In an observational study comparing outcomes of bare-metal versus drug-eluting stents, James et al found that within the first 6 months following implantation, patients who received drug-eluting stents were nearly 30% less likely to experience heart attack or death as compared to those who received bare-metal stents.[5] Most of the difference occurred in the first few days following implantation even though the benefits of preventing restenosis are not realized so quickly. Using a landmark design, in which the investigators started following patients 6 months after implantation, the cumulative risk of death or myocardial infarction was comparable between patients who received bare-metal versus drug-eluting stents, suggesting that confounding by indication biased the initial result, a limitation addressed by thoughtful design. Thus, careful control for confounding by indication is essential for RWE studies of medical devices.

As greater focus is put on RWE for medical devices, particular attention is needed to the design of real-world studies that can distinguish the effects of a device from differences in patient characteristics, medical practice, and operator.

Historical control groups: Appropriate comparator selection is perhaps the most effective strategy for addressing biases in observational studies. In a review of high-risk cardiovascular devices, Chen et al found that most studies that support device approval do not use a parallel active control group.[8] Because of the highly iterative nature of medical device development, historical control groups, comprising patients who received a different device or a different version of the device of interest, represent an attractive alternative. However, historically controlled studies require special considerations to address confounding and misclassification. For example, if medical practice and outcomes have evolved over time, there can be intractable confounding between historical and contemporary groups. Such studies are also limited to the outcomes and covariates measured in the historical cohort. Ensuring similarity in medical practice, surveillance, and measurement between periods is essential.

Provider effects: Finally, when studying medical devices, one must be clear about whether the exposure of interest is the device itself or the combination of the device plus the hospital's processes for the procedure in which the device was used and the surgical team's proficiency in conducting the procedure, as outcomes can vary based on operator experience and the process for the procedure.[9] As greater focus is put on RWE for medical devices, particular attention is needed to the design of real-world studies that can distinguish the effects of a device from differences in patient characteristics, medical practice, and operator.

WHAT IS THE FUTURE OF RWE FOR MEDICAL DEVICES?

One ongoing development in RWE for medical devices is the National Evaluation System for Health Technology (NEST), an FDA CDRH-led collaborative national evaluation system aimed at efficient and improved RWE generation for medical device evaluation and regulatory decision making. NEST will use distributed data networks to link data from clinical registries and administrative sources, with the objective to inform treatment decisions, ensure safety, and foster device innovation and patient access. NEST and its associated collaborators are currently conducting and soliciting test cases to gain insights into the practical implementation of the NEST approach to evidence generation within the medical device ecosystem.[10]

Technological innovations will also drive substantial changes. The amalgamation of advanced data analytics (eg, machine learning) and medical device engineering will create an opportunity to develop smart, intelligent, and automated devices. Mobile health apps built with data analytics could be used to automate drug delivery or simply give patients day-to-day guidance on their medical care. For example, a sensor connected to an inhaler records where, when, and why a patient takes medication, which in turn provides patients and physicians a view to better understand usage and medication adherence. Additionally, a smart medical device could collect and analyze data from disparate sources like wearables, weather reports, medical records, diagnostic results, diet-tracking apps, and more to make real-time treatment recommendations.[11,12] Medical sensors and predictive analytics could be used to circumvent adverse outcomes before they occur, for example, to help sensors learn to recognize early warning signs of serious conditions (eg, abnormal values) and trigger automatic alerts to healthcare providers.[12] >

Over the coming decade, the medical device sector is likely to see the entry of new players from other industries who can collect and analyze RWD from smart devices. Leveraging data and making investments in intelligent technology such as wearables, smart device applications, cloud-based data and analytics, and the Internet of Things will be an essential part of the new device value proposition. With the widespread dissemination of such technologies and the massive amounts of data generated from them, medical device researchers will face exciting new challenges and opportunities.

REFERENCES

1. Ackerman SJ, et al, Eds. (2011) Therapeutic and Diagnostic Device Outcomes Research. International Society for Pharmacoeconomics and Outcomes Research. Lawrenceville, NJ, USA.

2. US Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Guidance for Industry and Food and Drug Administration Staff. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf. Accessed: August 15, 2018.

3. Ranasinghe I, Parzynski CS, Freeman JV, et al. Long-term risk for device-related complications and reoperations after implantable cardioverter-defibrillator implantation: An observational cohort study. Ann Intern Med. 2016 May 3. doi: 10.7326/M15-2732.

4. Wright JD, Tergas AI, Hou JY, et al. Effect of regional hospital competition and hospital financial status on the use of robotic-assisted surgery. JAMA Surg. 2016 Jul 1;151(7):612-620. doi: 10.1001/jamasurg.2015.5508.

5. James SK, Stenestrand U, Lindbäck J, et al. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med. 2009;360:1933-1945.

6. International Medical Device Regulators Forum Patient Registries Working Group. Principles of International System of Registries Linked to Other Data Sources and Tools. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-160930-principles-system-registries.pdf. Accessed August 15, 2018.

7. Milne CP, Smith PZ. Use of Real World Evidence Increasing Throughout Asia. Available at: https://www.pharmafocusasia.com/clinical-trials/use-real-world-evidence. Accessed October 23rd, 2018.

8. Chen CE, Dhruva SS, Redberg RF. Inclusion of comparative effectiveness data in high-risk cardiovascular device studies at the time of premarket approval. JAMA. 2012;308:1740-1742.

9. Kumamaru H, Jalbert JJ, Nguyen LL, et al. Surgeon case volume and 30-day mortality after carotid endarterectomy among contemporary Medicare beneficiaries: before and after national coverage determination for carotid artery stenting. Stroke. 2015;46:1288-1294.

10. https://nestcc.org/opportunities/

11. Bruce RI. Creating smart and adaptive medical devices: device data and analytics. J Bioengineer Biomedical Sci. 2017;7:234.

12. Kute S. Big Data, Big Difference: Building Smarter Devices with Data Analytics. https://www.mdtmag.com/article/2015/06/big-data-big-difference-building-smarter-devices-data-analytics. Accessed: August 21, 2018.

ADDITIONAL INFORMATION

The preceeding article is based on a workshop give at ISPOR 2018. For more on ISPOR's Medical Devices Special Interest Group, go to https://www.ispor.org/member-groups/special-interest-groups/medical-devices-and-diagnostics.