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Opportunities and Gaps in Real-World Evidence for Medical Devices

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Meeting Summary

Purpose

Medical devices have substantially improved our ability to manage and treat a wide variety of conditions. Given the extent of their use, it is important that there be an effective system for monitoring medical device performance and the associated patient outcomes. Although significant steps have been taken to enable evaluation and safety surveillance of medical products, critical gaps remain in capturing real-world data (RWD) to evaluate medical devices before and after FDA approval. As the collection and use of RWD advances, real-world evidence (RWE) will be able to incorporate data captured throughout the total medical device lifecycle, informing and improving the next iteration of devices.[1] The recently launched National Evaluation System for health Technology Coordinating Center (NESTcc) is compiling a landscape analysis report to facilitate conversation and encourage the increased and improved use of RWD with stakeholders across the medical device ecosystem. The analysis will build on the work of FDA, the Planning Board, the Registry Taskforce, and many stakeholders and experts. The long-term goal is for the landscape analysis to become a living document and a NESTcc-maintained resource that encourages communication and collaboration. This workshop convened a broad range of experts and stakeholders to provide input on the analysis, including highlighting some of the current uses of RWD/RWE and identifying where gaps still remain.[2]

For over a decade, there have been increasing concerns that the post-market surveillance system in the United States was not fully meeting the demands of a constantly evolving medical device ecosystem. In 2010, the U.S. Food and Drug Administration (FDA) launched an initial effort to address these concerns called the Medical Device Epidemiology Network (MDEpiNet), followed in September 2012 by an FDA report titled *Strengthening Our National System for Medical Device Postmarket Surveillance*.[1] In 2013, two groups were formed to work in parallel on different aspects of the development of a national surveillance system for medical devices. The National Medical Device Postmarket Surveillance System Planning Board outlined a long-term vision of a sustainable national system and released its first report *Strengthening Patient Care: Building an Effective National Medical Device Surveillance System* in February 2015.[2] The MDEpiNet Medical Device Registries Task Force (MDRTF) focused on the objectives, operations, and architecture of a national system, and released their report *Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge Clinical Care and Research* in September 2015.[3] The consensus of both groups was that a robust and sustainable national system would need to evaluate the safety and effectiveness of medical devices throughout the total

[1] *Real-world data (RWD)* is data collected from sources outside of traditional clinical trials. *Real-world evidence(RWE)* is the evidence derived from aggregation and analysis of RWD elements. (FDA, Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices Draft Guidance, 2016)

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product life cycle. The system would also need to meet the needs of multiple stakeholders. Subsequent work by the Planning Board produced two additional reports with recommendations on implementation: *Better Evidence on Medical Devices: A Coordinating Center for a 21st Century National Medical Device Evaluation System* and *The National Evaluation System for health Technology (NEST): Priorities for Effective Early Implementation*.[4,5]

In September 2016, the Medical Device Innovation Consortium (MDIC) was awarded a grant by the FDA to create and operationalize the NESTcc. MDIC is a public-private partnership that works to advance the regulatory science of medical devices for patient benefit. MDIC is responsible for establishing NESTcc by 1) engaging stakeholders, 2) establishing organizational governance, 3) developing shared resources to facilitate stakeholder alignment and collaboration, and 4) achieving organizational sustainability.

Current Uses of Real-World Evidence Generation for Medical Devices

RWD that meet the standards of quality necessary can be used to gather evidence on the safety, effectiveness, and value of medical devices throughout all stages of development and marketing. Workshop participants listed multiple use cases for RWE beyond pre- and post-market regulatory pathways, such as population-level safety surveillance, comparative effectiveness studies, utilization and adherence analysis, and coverage and reimbursement decision-making.

International Developments in Real-World Evidence Generation

There have been novel and successful global efforts to generate RWE that can be used to inform efforts in the United States. Workshop participants emphasized work on harmonizing data standards, collection, and evaluation of medical device postmarket surveillance data that is underway, including progress by the European Union's Medical Device and In Vitro Diagnostics Regulations (MDR), which include rules to strengthen post-market surveillance and facilitate the creation of a unique device identification system.[6] Unique device identifiers (UDIs) are alphanumeric codes that encode a greater specificity of standardized medical device information in comparison to the currently fragmented regime of claims and proprietary device codes. Participants mentioned the developments within the International Consortium of Orthopaedic Registries (ICOR), a collaborative public-private partnership network of research institutions and registries that seek to close evidence gaps and develop best practices for orthopedic medical device registries.[7] Its organizational model and specific focus on topics that span the pre- and post-market space, including the 510(k) process, UDI, and longitudinal data capture, offer promising examples of collaborative RWE generation. In addition, the International Medical Device Regulators Forum (IMDRF), which grew out of the Global Harmonization Task Force (GHTF) a volunteer network of medical device regulators, includes efforts to harmonize around unique device identification, adverse event terminology, and patient registries.[8]

Mapping Real-World Evidence to the Total-Product Life Cycle

One of the goals of the MDIC landscape analysis is to identify RWE work that has not been published previously in order to integrate a wider range of examples. Other resources include academic literature and research, including MDRTF's 2015 report on strategically coordinated registry networks.[9] These RWE applications can be plotted along the successive phases of the Total Product Life Cycle (TPLC) and among distinct therapeutic designations. Trends in medical device RWE generation can be understood through inspection of general activity levels and unique characteristics recorded among various medical device therapeutic categories.

Workshop participants were asked to assess this framework and include suggestions for additional analysis. Participants noted the need for more information on the present and future areas of valuable RWE that are generally considered to exist outside the TPLC such as coverage and reimbursement and

supply chain management. In addition, participants noted that companies in more mature, larger, and/or more profitable therapeutic areas may have better capability (i.e., greater resources and experience) to generate more RWE. It was suggested to extend the analysis by mapping capability, resources, and incentives to the different therapeutic areas to better understand any gaps. It was also noted that a better understanding of how variation in physician community engagement and communication of research value affects participation in RWE generation. One example is the observed higher incidence of RWE studies in cardiology in contrast to the more tepid embrace of these studies in the surgical disciplines. The ability to control for differences in capability and physician engagement would be needed to better understand which therapeutic areas are outperforming RWE benchmarks to help identify best practices and important developments.

Participants urged label expansion be added as a category in the framework given the importance of labels to patient access, device utilization, and physician practice. Participants noted the use of the Society for Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry to provide evidence for label expansions.[10] It was also suggested to include activities within the venture capital and startup community that support RWD for decision making. Investments and efforts initiated by this stakeholder group can be a leading indicator of downstream use cases for patients and industry. Additional suggestions for development phases include market assessments and segmentation, clinical trial management, patient recruitment, and methods disclosure.

Technical Considerations

In order to ensure the long-term sustainability of NEST, it is critical to understand and find innovative solutions to address the needs of various stakeholders. Participants agreed th e landscape analysis should address specific technical challenges and opportunities that affect the generation and use of RWE. These include UDI adoption, analytical methods, governance and privacy concerns, as well as data quality, representativeness, validation, accuracy, purpose, and cost.

UDI and Automatic Identification and Data Capture

UDI, in combination with innovative patient reporting technologies and RWD systems such as PCORnet and the Sentinel System, may help FDA better understand true adverse event rates. By 2020, all medical devices that are legally required to include UDI will do so, as mandated by the Food and Drug Administration Amendments Act of 2007.[11] More information on UDI adoption and trends is needed to inform the usability of this new identifier. In particular, it was felt that examples of how UDI is being integrated into coverage and reimbursement data would be helpful.

Providers are at the front line of administering care to patients and collecting data on the safety and performance of medical devices critical to patient care. Physicians and hospitals are under intense resource and time burdens as they seek to provide high-quality personalized medical care while allowing maximum value to be extracted from the resulting clinical data. Participants felt that it is important to understand how trends in automatic identification and data capture (AIDC) technology adoption are proceeding and how tightly they are integrating with existing electronic health record (EHR) implementations. An international example is the United Kingdom's National Health Service Scan for Safety project in hospitals which uses AIDC technology to match clinical events to a specific location, patient, service or device.[12]

Patient-centered technology

The national move towards patient-centered health care has importantly put patient-consumers at the nexus of treatment, data collection, monitoring, and engagement. It was expressed that patients needa better system for handling adverse event reports and product complaints to improve transparency and reduce harm. Open application programming interfaces and patient-centered aggregation platforms could allow patients better access to their own health and medical device data. Participants emphasized that more knowledge is needed on current attempts to provide patients with greater access, transparency, and tools for real-time feedback concerning the medical devices they use.

Enhancing claims data

In comparison to electronic health care data, administrative or claims data are often viewed as cleaner and more comprehensive records of longitudinal patient care. The impact of UDI adoption into CMS systems, given recent support from Medicare Payment Advisory Commission and ASC X12, needs to be assessed.[13] Participants suggested that it would be useful for researchers if the landscape provided information on standards or best practices that may exist for claims-based data sources and registries to be used as observational control groups. In addition, detailed information on efforts to linkpatientsacross payers and providers systems would be helpful. More information is also needed on effortstousemedical device RWE to manage value-based payment, addressing challenges such as identification of devicesfor attribution and managing practice variation.

Registries

Participants noted that more information regarding the relationship between medical device manufacturers, researchers, and registries would be helpful. It was asked if industry participation in registry development changes based on governance principles and/or transparency of data collection. Industry sponsors have previously noted their desire for faster access to the data in registries. Some participants suggested looking for pilots to include in the landscape document that involve novel access to RWE pathways that could make access and utilization more predictable. Such a system might also improve the quality of adverse event reports and product complaints, while simultaneously decreasing the effort needed to report those events.

Evaluation of data quality

Critical to the assessment of available RWD is whether such data meets a standard of quality and appropriateness for the type of analysis being conducted, also called fit-for-purpose. Standardsofquality may include acceptable levels of missing data, validity to some clinical standard, reliability,andspecificity. Participants were interested in examples of and the practical implication and stakeholder valueregarding a minimum data set on patient characteristics, consent, device characteristics, and the institutional setting. Other participants noted that a minimum core data set may prove difficult given changes in essential data across device classes. A dynamic minimum data set was suggested as a possible compromise, retaining core elements of a minimum data set while adapting to changes in device characteristics. Information on how provider systems are developing best practices for integrating, cleaning, and processing clinical data into RWD pipelines would be beneficial. Studies using machine learning techniques such as natural language processing to review and digitize clinical notes should also be explored.

Participants believed it would be helpful to gather evidence on the value of RWD management and use, starting at the provider system supply chain and demonstrating progressive economic value as information flows through hospitals and physician offices. Participants noted that while creating a high-quality standard for data is a noble target, in practice the paradigm for data quality shouldn't be rigid or

unrealistic. A differential risk classification of different data types may be more helpful so that data can be mapped to its suited purposes.

Legal Considerations

The successful integration of RWD sources, particularly those involving multiple parties, requires legal frameworks to allow for the collection, sharing, and use of sensitive patient data. Participants discussed several pertinent legal issues that could require additional insight to inform the landscape analysis.

Consent and data governance

Strategies for broadening the use of patient informed consent could allow RWD to used faster and more often while decreasing the need to use public health authority or to qualify as quality improvement activities. Participants noted that key developments at the intersection of technology, patient comprehension, and protections regarding patient data and privacy need further clarity.

Intellectual property protection

Participants were interested in examples of best practices for protection of intellectual property and trade secrets while still promoting industry cooperation and transparency. It was suggested that intimate strategic forums where industry would be able to discuss best practices and failures would be helpful (e.g. the FDA advisory forum model).

Distinctions with Common Rule and Public Health Authority

Participants noted that clarification is needed to determine when analysis of data collected in an observational study requires FDA and Office for Human Research Protections (OHRP) oversight. A review of the practical delineations between the updated Common Rule and exempted public health authority research would, therefore, be beneficial. Operating under FDA's public health authority may reduce administrative overhead and lead time for studies. However, some participants felt that questions remain as to whether this pathway is sustainable in comparison to the broader and more robust patient consent which is needed for efficient and repeated use of their data. It was also noted that differences between significant and non-significant devices affect the ability of FDA to waive certain PHA requirements.

High-value opportunities for National Evaluation System for health Technology Coordinating Center

A central goal of the landscape analysis is to clearly illustrate where high-value opportunities exist for closing gaps in RWE infrastructure, methodology, and policy. Participants noted that fostering partnerships between various stakeholder groups to share data and resources for generating better evidence on medical devices will remain an important goal for NESTcc throughout its development. Clinical researchers and analytics professionals will need platforms that readily provide standardized, fit-for-purpose data as well as rigorous and fast methods for data linkages, especially for longitudinal tracking. This includes more accessible resources for data sharing including APIs and patient health information aggregators. Participants suggested that efforts to establish informed consent and data sharing best practices should inform the development of innovative patient-facing systems that permit secure data collection, data sharing, and observational research. Such system might also allow for greater patient-directed monitoring, crowdsourcing of medical device adverse events, and predictive analytics.

In the short term, participants felt that clear opportunities exist for using data from well-characterized patient populations, such as data from Medicare, Optum, and WellCore, to gather RWE on medical devices. Participants suggested finding ways to link mortality data to existing claims data as well as exploring the viability of a minimum dataset for longitudinal tracking of patient experiences. Transparency in protocols for data collection and analysis will be critical as evolving methodologies are incorporated

into the growing health information technology ecosystem and patient information becomes more plentiful and precise.

Acronym List

AIDC	Automatic identification and data capture
EHR	Electronic health record
FDA	U.S. Food and Drug Administration
GHTF	Global Harmonization Task Force
ICOR	International Consortium of Orthopaedic Registries
IMDRF	International Medical Device Regulators Forum
MDEpiNet	Medical Device Epidemiology Network
MDIC	Medical Device Innovation Consortium
MDR	European Union's Medical Device and In Vitro Diagnostics Regulations
MDRTF	MDEpiNet Medical Device Registries Task Force
NEST	National Evaluation System for health Technology
NESTcc	National Evaluation System for health Technology Coordinating Center
OHRP	Office for Human Research Protections
RWD	Real World Data
RWE	Real World Evidence
TPLC	Total Product Life Cycle
TVT	Transcatheter Valve Therapy
UDI	Unique device identifiers

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