

The Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Context for RWE Guidance



2016-2017 CDRH Strategic Priorities



National Evaluation System for health Technology (NEST)



FDARA (including MDUFA IV) commitment to use of real-world evidence to support device pre/postmarket decisions



Guidance issued to clarify how RWE may be used to support regulatory decisions. Issued August 31, 2017

The NEW ENGLAND JOURNAL *of* MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D.,
and Janet Woodcock, M.D., *Editors*

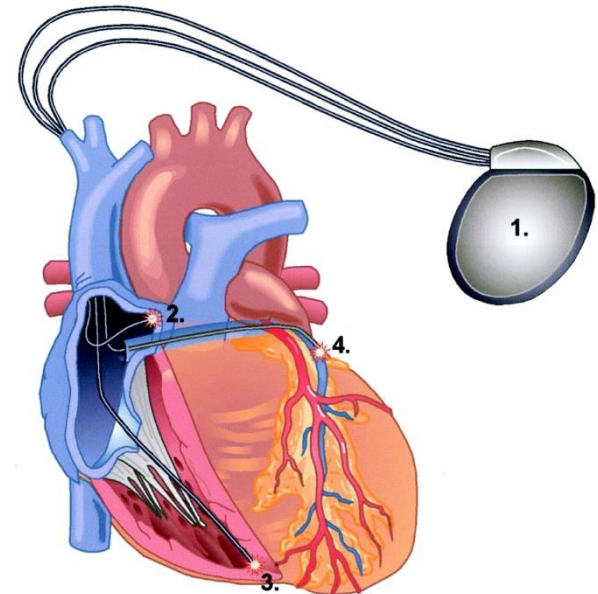
An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials

Owen Faris, Ph.D., and Jeffrey Shuren, M.D., J.D.

April 6, 2017

Devices Are Different from Drugs

- Many devices are highly dependent on clinician knowledge, experience, and skill
- Devices and techniques iteratively and rapidly improve (sometimes even during a trial)
- Gold-standard RCT often not practical



What are the opportunities?



Flexibility

- “Can’t always get what you want....”
- But if we are flexible, we can “get what we need”



Innovation

- Modeling
- Adaptive designs
- Real-world evidence



Collaborations

- NEST
- Industry groups
- Patient and clinician groups

Clinical Trial Innovation

FDA

**Patient Preference Information –
Voluntary Submission, Review in
Premarket Approval Applications,**

Breakthrough Devices Program

**Human Factors
Applicat
and Inclu**

**Use of Real-World Evidence to
Support Regulatory Decision-Making
for Medical Devices**

**Industry and
on Staff**

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**Guidan
Drug**

**Guidance for Industry and
Food and Drug Administration Staff**

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Data in
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Document issued on August 31, 2017.

Adapt

Device Clinical Studies

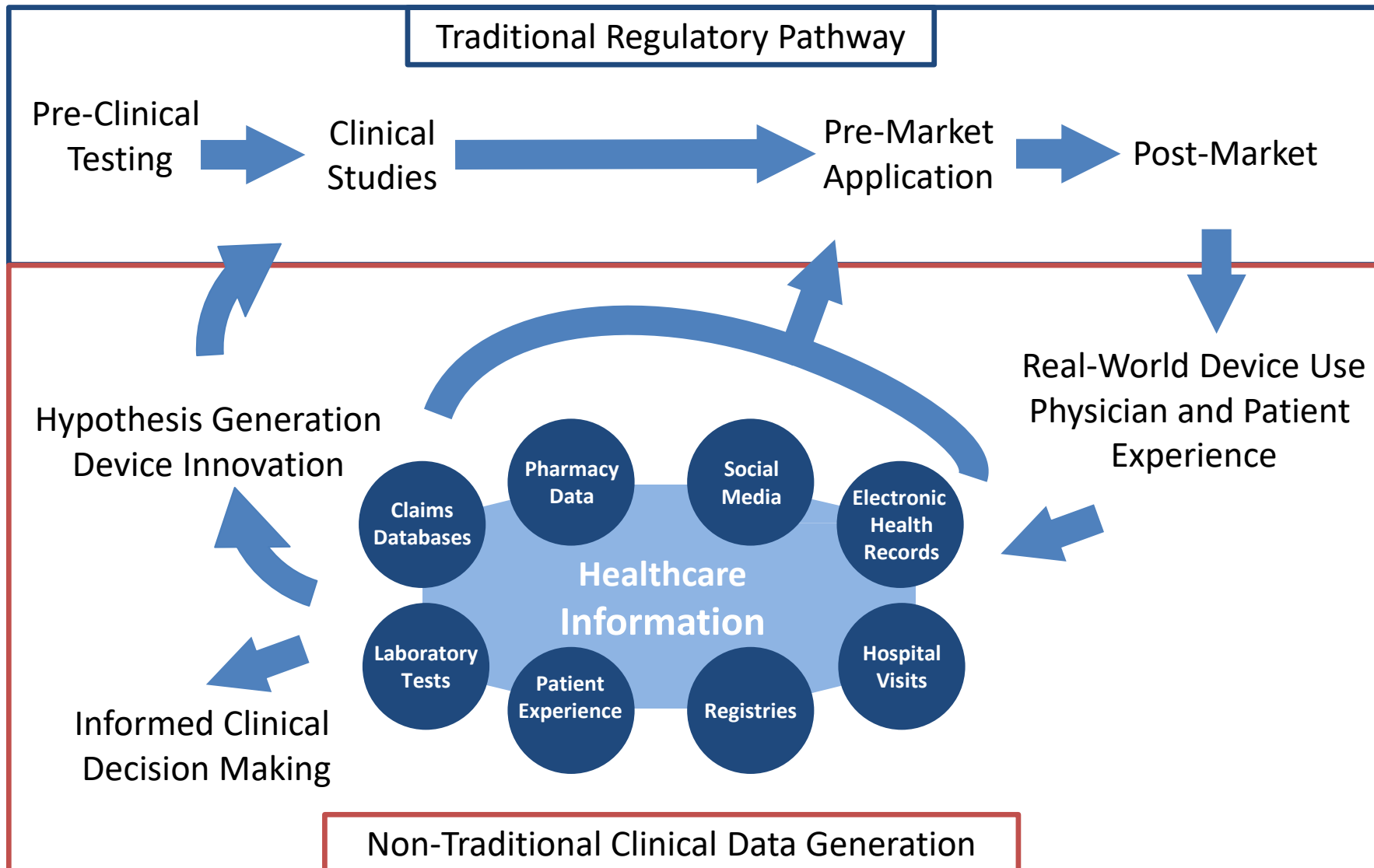
**Guidance for Industry and Food
and Drug Administration Staff**

Document issued on July 27, 2016.

**Guidance for Industry and
Food and Drug Administration Staff**

Document issued on September 12, 2017.

Evidence in Regulatory Decisions



Data Quality

'Fit for Purpose'

Data should be assessed for completeness, consistency, accuracy, and whether it contains all critical data elements needed to evaluate a medical device and its claims.

Relevant & Reliable

Benefit



Risk

Practice of Medicine

- Section 1006 of the FD&C act gives latitude to health care practitioners in the use of legally marketed devices within a legitimate health care practitioner-patient relationship.
- Practice of Medicine may include off-label use of legally marketed devices.
- If found to be of sufficient quality, these data may be used to support regulatory decisions.

IDE and Patient Protections

- The FDA regulations 21 CFR 50, 56, and 812 apply to all clinical investigations of devices to determine safety and effectiveness, with limited exceptions.
- If the approved or cleared device is used in the normal course of medical practice, an IDE would likely not be required.
- An IDE may be required when RWD collection that is intended to determine safety and effectiveness of a medical device influences patient treatment decisions.

Some Regulatory Uses for RWE

**Control arm for
pivotal clinical
study**

**New indications
for approved
devices**

**Studying new
improvements
to devices**

**Replacing post
approval study**

**Adverse event
reporting**

**Shifts to pre-
postmarket
balance**

Some Non-Regulatory Uses for RWE

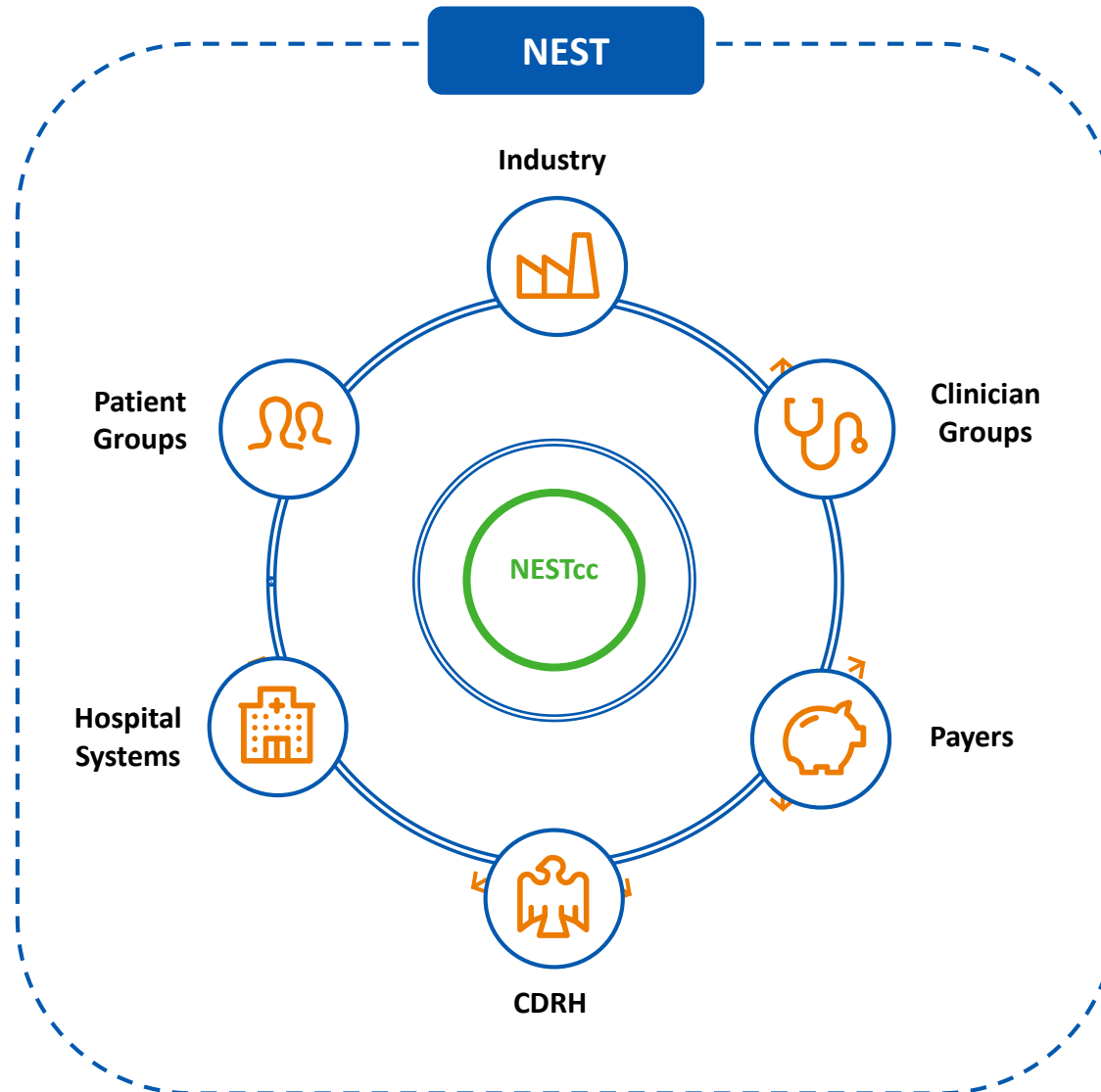
**Informing the
community on
optimal care**

**Identifying
needs and gaps**

Market analysis

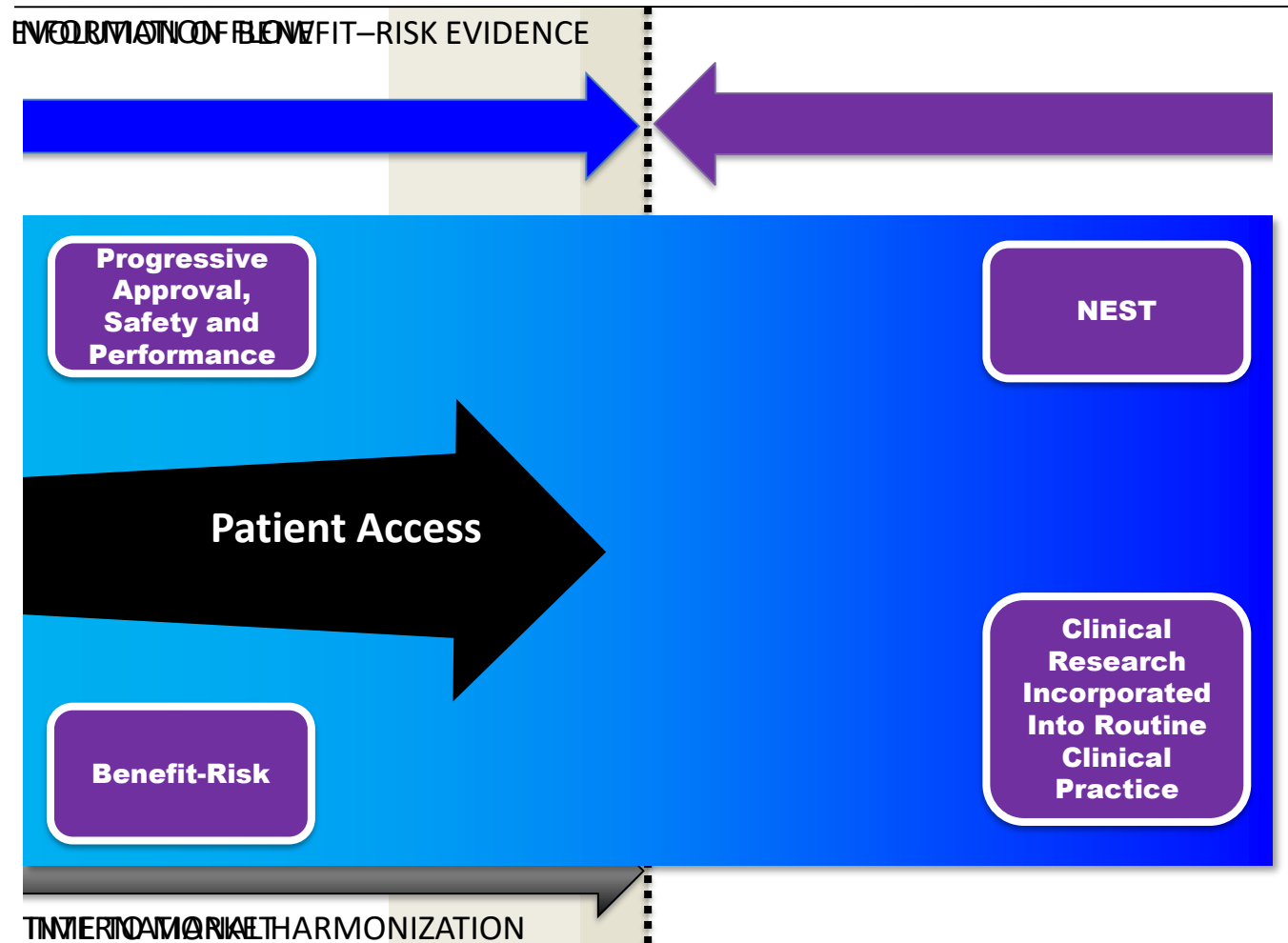
**Assessing
quality of care**

National Evaluation System for health Technologies (NEST)



Learning Medical Device Ecosystem

Total Product Life Cycle (TPLC) Framework



Challenges of Using Real-World Evidence and FDA's Opportunities in the Field

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Challenges Using Real-World Evidence

“The more widespread use of [real-world evidence] can make our medical product development process more efficient, and help lower the cost of development. More importantly, it can help make sure doctors and patients are better informed about the clinical use of new products, enabling them to make more effective, efficient medical choices.” – FDA Commissioner Scott Gottlieb

- Leading challenges for FDA and Industry:
 - Patient privacy and anonymization of data
 - Secondary-source data and missing information
 - Bias and lack of standardization
 - Interoperability between proprietary systems
 - Lack of regulatory framework for interpretation and use

Patient Privacy and Anonymization of Data

- Anonymization of data is perhaps the biggest challenge of using real-world data
- Utilizing data from clinical studies and self-reported sources involves use of data from patients who have not consented
- The patients are undefined and difficult to adequately regulate — are they patients, participants, or something else entirely?

Secondary-Source Data and Missing Information

- Because the data is collected for a primary purpose other than research, it may not have all the necessary data points, and it may not tell the whole story
- For example, electronic health records might not contain all of the data that researchers want, so they should either be expanded to include all desired information or, instead, missing information could be collected with simple data collection tools to supplement the records

Bias and Lack of Standardization

- Potential bias may skew results depending on where the data comes from
 - For example, claims datasets are often more complete because payment serves as the incentive to enter data, but more expensive things are more likely to be captured there
- Lack of standardization between diagnoses and conditions can lead to mismatch between the data
 - For example, one study found 120 different definitions of myocardial infarction, which can disrupt effective findings

Interoperability Between Proprietary Systems

- Scientific work is needed to validate results from wearables and define wearable-oriented endpoints that will support regulatory approval
- Several technology companies are getting involved in real-world evidence (“RWE”):
 - **CancerLinQ LLC**, the American Society of Clinical Oncology’s bag data initiative, partnered with the FDA to “harness cancer patient information and big data analytics to examine the real-world use of emerging and newly approved cancer therapies”
 - **Apple** is investing in its wearables technology, ResearchKit, an open-source framework for the creation of mobile applications that support medical researchers by gathering “robust and meaningful data”
 - **Qualcomm** is a “global digital health collaborator” for Novartis’s “Trials of the Future” program, which hopes to serve as a global connectivity platform for collecting and aggregating medical device data during clinical trials
 - **Amazon** is providing technologies such as Amazon S3 and Amazon Elasticsearch Service to create “data lakes”—huge aggregations of data—and an architecture with which to search it
- Each company is taking its own approach to RWE, which could mean that the data, even if aggregated, could not be accurately compared

Lack of Framework for Data Interpretation and Use

- FDA has yet to define the context for using RWE
 - RWE can be used to monitor patients for adverse events, and can be regulated and used as such
 - Alternatively, it can be used in a way more similar to post-marketing studies, which would subject the data to an entirely different regulatory regime
- Without a defined regulatory structure, the data can become meaningless
 - For example, a common problem with massive quantities of unstructured data is “data dredging” – where multiple analyses are conducted until one gives the hoped-for result

Areas of Focus for the FDA

- It is critical that FDA take a leadership role in addressing these issues
- FDA's immediate focus in real-world evidence should include:
 - Ensuring patient safety and engagement
 - Regulating consumer-reported data
 - Creating a weighting framework for data
 - Developing a standardized information database
 - Constructing a regulatory framework

Initial Steps

- FDA recently announced that it is sponsoring a RWE demonstration project
 - The 21st Century Cures Act and FDA Reauthorization Act require FDA to conduct pilot studies or demonstration projects for use of RWE in decision-making
 - Harvard Medical School, Brigham & Women's Hospital and Aetion will attempt to replicate the results of 30 randomized clinical trials (RCTs) using claims databases
 - Eventually, the group hopes to attempt to replicate ongoing RCTs where results are not yet known
- The group believes the project has the potential to validate the use of RWEs instead of RCTs as part of a drug development strategy

Ensuring Patient Safety and Engagement

- Patients can be a source of important data not routinely collected for purposes of care — socioeconomic, cultural, and educational background factors — that significantly affect treatment outcomes
 - Nigam Shah, Associate Professor of Medicine at Stanford University, says that a culture of data sharing needs to be promoted to advance the public's understanding that to benefit from a learning health system, patients need to contribute their data
- The application of informed consent should be clarified
 - ADVAMed, in a comment to the FDA, noted: “Clearly distinguishing the use of a test article, where consideration of informed consent is appropriate, from approved or cleared devices used in clinical practice will benefit FDA staff and industry in the application and understanding of RWE.”
- Similarly, safeguards such as study registration must be utilized to discourage alteration of patient care plans in order to gather RWE

Regulating Consumer-Reported Data

- Mobile and Personal Health Devices are an important and growing source of real-world data
 - Finding a way to access and use this data would give the FDA the ability to capture data from the 99% of patient and consumer activity that occurs outside the health care setting
 - These devices can be used to compare pre- and post-event or intervention data at the individual level as well as population-level outcome measures.
 - For example, these can be used to measure recovery of mobility following surgery
 - In the context of clinical trials, distribution of digital health devices across large and diverse populations can enable virtual study recruitment, creating potential to increase efficiency of clinical trials and reach subpopulations that might not be reached through traditional recruitment practices

Creating a Weighting Framework

- Some data sources are more useful and unbiased — regulation may be used to make data as effective and clear as possible
- A scoring or weighting framework can be used to standardize data and prevent information from being too subjective in nature to be used effectively by the FDA and industry

Creating a Standardized Database

- FDA can make information easy to use by creating a universal database or consistent form through which compatible and standardized data can be gleaned
 - For example, the Patient-Centered Clinical Research Network (PCORnet) is advancing real-world evidence research by leveraging existing electronic health data sources to support national comparative effectiveness studies and pragmatic clinical trials
 - In addition to its 20 patient-powered research networks, PCORnet consists of 13 clinical data research networks (CDRNs) representing more than 100 health care systems and organizations across the country
- Reporters adding data to the database should be required to use standardized definitions of symptoms and other medical issues, which will further standardize the data

Developing a Regulatory Framework

- FDA must create a system capable of streamlining and making efficient “data exhaust”—the term given to taking full advantage of data gathered
 - This ensures that data is used in as many contexts as possible to provide support for various studies at once
- However, the framework must require studies to be clearly defined, to prevent data dredging
- Similarly, the framework should regulate data differently depending on its use—whether it be for post-marketing studies, adverse event reporting, or something else



Navigating the Use of Real-World Evidence in Promotion

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RWE Promotion and FDA Guidance

- Promotion contemplated by Medical Product Communications Draft Guidance
 - e.g., Post-marketing info about types/rates of AE occurrence “that have been observed in practice”
- Promotion contemplated by Payor Draft Guidance
 - e.g., HCEI relating to persistence can be based on estimates from drug utilization database
- *Use of RWE to Support Regulatory Decision-Making for Medical Devices*

Considerations for Use in Promotion

- Characteristics of RWD/RWE
 - Relevance
 - Reliability
 - Design
- Audience
- Evidentiary landscape



Considerations for Presentation in Promotion

- Design
- Disclosures
- Characterization



Implications for Review Process

- Inclusion of SMEs
- Training
- Updating

