Real-World Evidence to Support Regulatory Decisions for Medical Devices

The 24th AHWP Annual Meeting
14 November 2019
The Crystal Ballroom, Grand Millennium
Muscat, Oman

Bill Sutton
萨盾
International Program and Policy Analyst (Medical Devices)
国际项目和政策研究员（医疗器械）
U.S. FDA China Office 美国FDA驻华办公室
U.S. Embassy, Beijing 美国大使馆， 北京

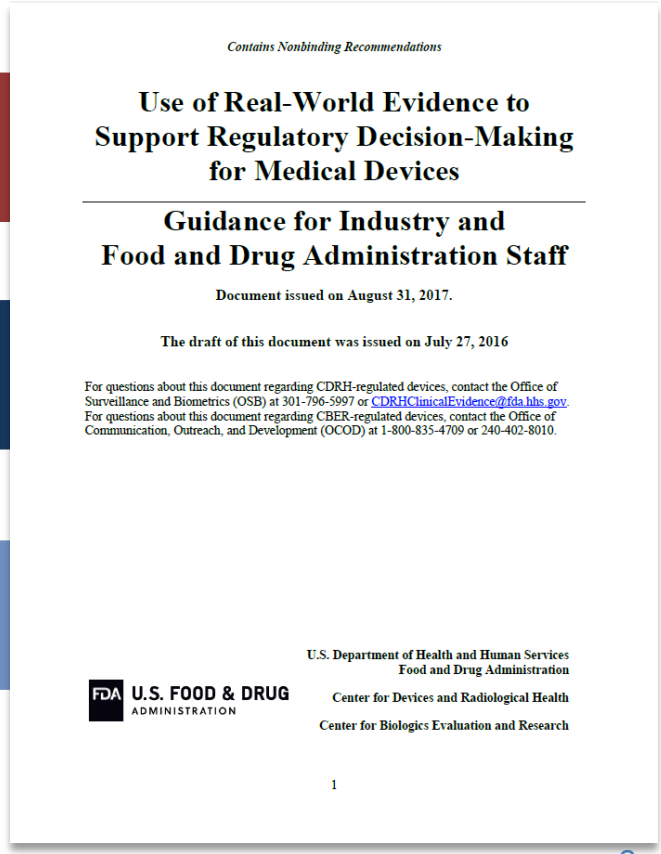
Context for RWE

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

21st Century Cures Act

National Evaluation System for health Technology (NEST)

Guidance issued to clarify how RWE may be used to support regulatory decisions



Contains Nonbinding Recommendations

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

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

1

Scope of the Guidance

- Guidance Discusses:
  - How FDA will evaluate whether RWE is of sufficient quality to inform regulatory decisions for medical devices
  - Some of the potential uses of RWD

- Outside the Scope of the Guidance:
  - Use of non-clinical data, adverse event reports, secondary use of clinical trial data, or systematic literature reviews
  - Specific methodological approaches to study design/conduct or analytical methodologies

Use of Real-World Evidence to Support Regulatory Decision Making

Turning Data into Evidence

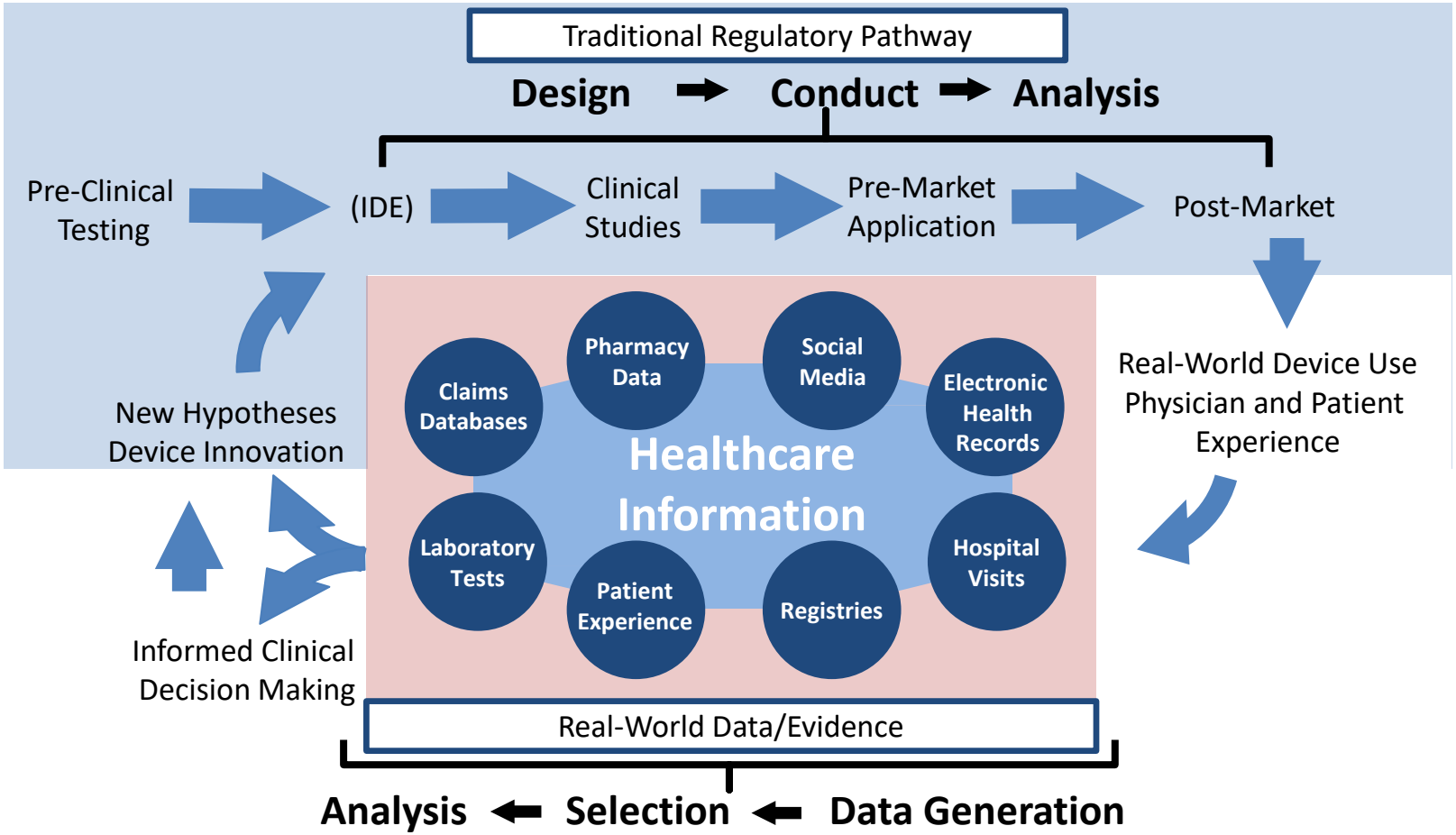
Real-World Data (RWD)
Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-World Evidence (RWE)
Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

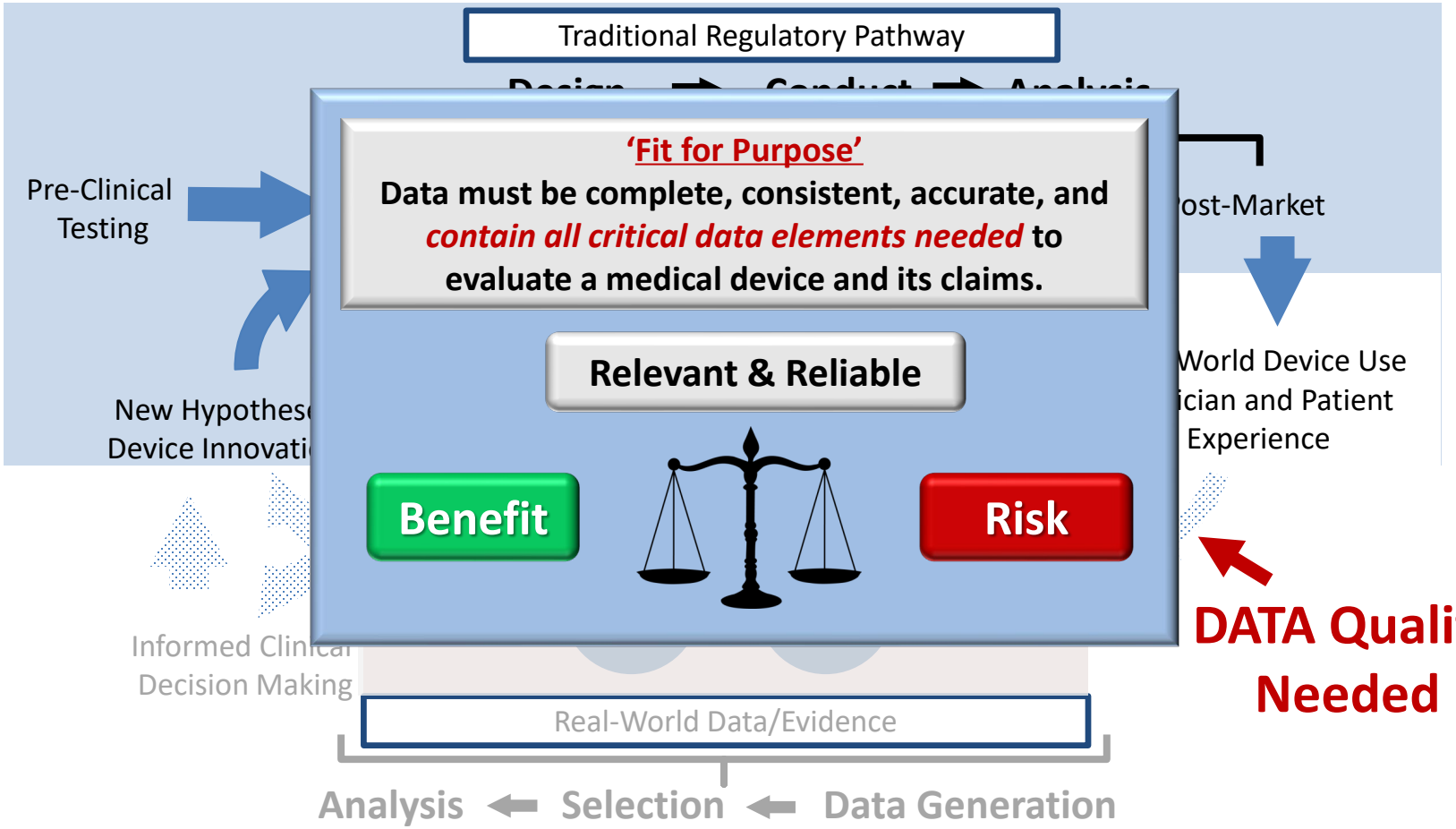
Guidance addresses issues related processes of:

- Generation and collection of RWD
- Analysis of RWD
- When results might be considered valid scientific evidence

TPLC – Prospective/Retrospective



Data Quality



What is 'Fit for Purpose'?

Valid Scientific Evidence

Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. *[21CFR 860.7(c)(1)]*

Demonstrating

Safety

…probable from use of the device *benefits to health outweigh any probable risks* *[21 CFR 860.7(d)(1)]*

Effectiveness

…use of the device in the *target population* will provide *clinically significant results* *[21 CFR 860.7(e)(1)]*

Valid Scientific Evidence

Acceptable

Valid scientific evidence is evidence from:

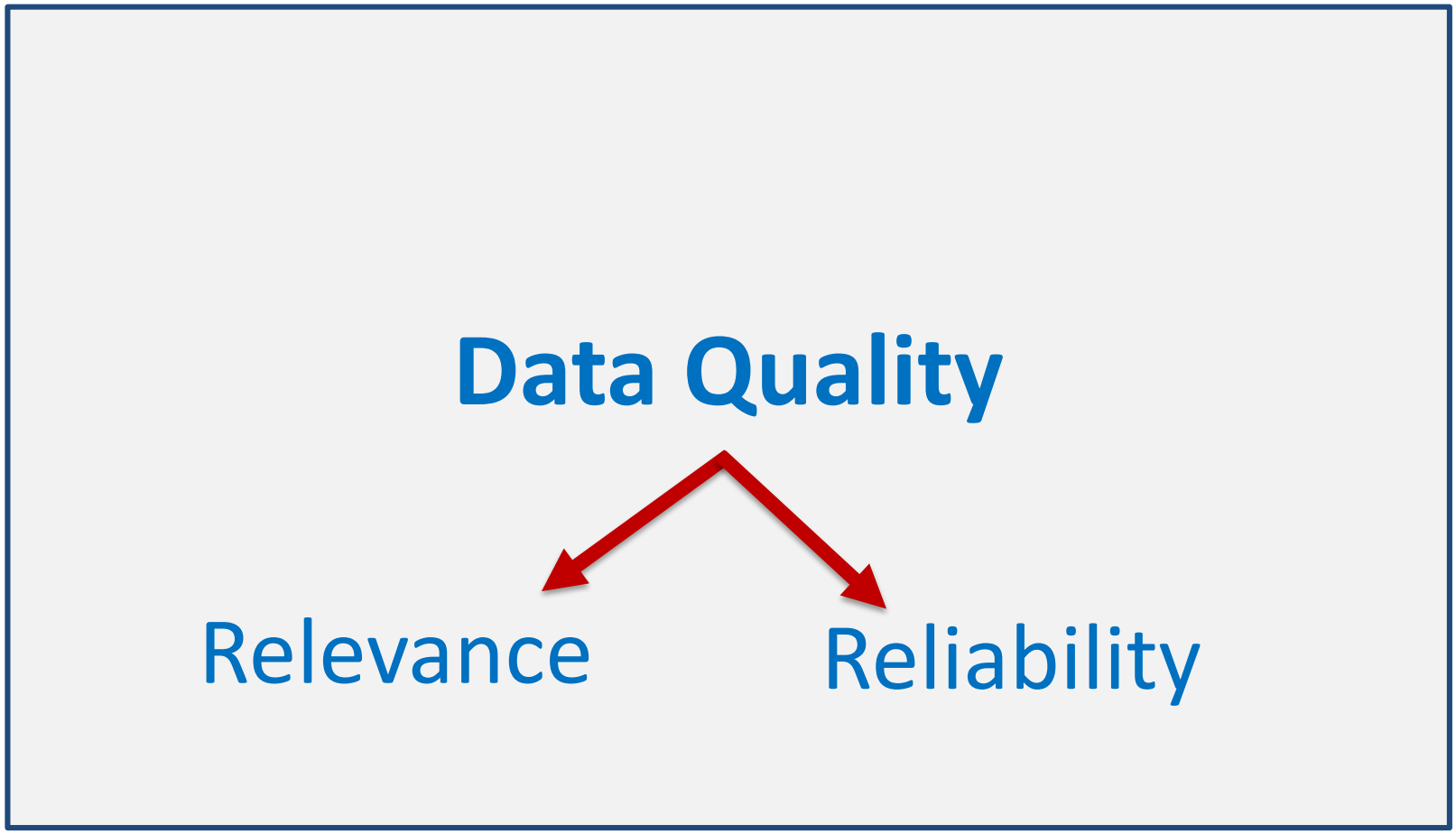
- Well-controlled investigations,
- Partially controlled studies,
- Studies and objective trials without matched controls,
- Well-documented case histories conducted by qualified experts,
- Reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

Not Acceptable

- isolated case reports,
- random experience,
- reports lacking sufficient details to permit scientific evaluation, and
- unsubstantiated opinions

are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.

21 CFR 860.7(c)(2)


Data Quality
Relevance
Reliability

Characteristics for RWE Evaluation – Relevance –

The data adequately addresses the applicable regulatory question or requirement.

Examples of factors to be evaluated:

- Appropriate variables collected, e.g. device exposure
- Endpoint definitions consistent and meaningful
- Assessment schedule captures endpoints of interest
- Population is appropriate and representative
- Study protocol and/or analysis plan appropriate for question

Characteristics for RWE Evaluation – Reliability –

Reliability includes factors related to overall data quality

RWD data reliability is assessed using characteristics of:

- Data Accrual
- Data Assurance – Quality Control

RWE Reliability Evaluation
– Data Accrual –

Some aspects of data collection for consideration:

- Pre-specification of:
  - Standardized common data elements (CDE) to be collected
  - Unambiguous CDE definitions
  - Structured data formats for CDE population
  - Methods for CDE aggregation and documentation
  - Timeframe for data element collection
- Data sources and technical data capture methods
- Patient selection to maximize real-world population representation and minimize bias
- Patient protections

RWE Reliability Evaluation – Data Quality Assurance –

People and processes in place during data collection and analysis to minimize errors and ensure integrity.

Includes consideration of aspects such as:

- How data elements were populated
- Data source verification procedures
- Data completeness including of confounding factors
- Data consistency/poolability across sites over time
- Evaluation of on-going training programs

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.

Patient Protections

- 21 CFR 812 Investigational Device Exemptions
- 21 CFR 50 Protection of Human Subjects (Informed Consent)
- 21 CFR 54 Financial Disclosure of Investigators
- 21 CFR 56 Institutional Review Boards (IRBs)
- 45 CFR 46 “Common Rule”
- Health Insurance Portability and Accountability Act (HIPAA)
- Other federal and local regulations

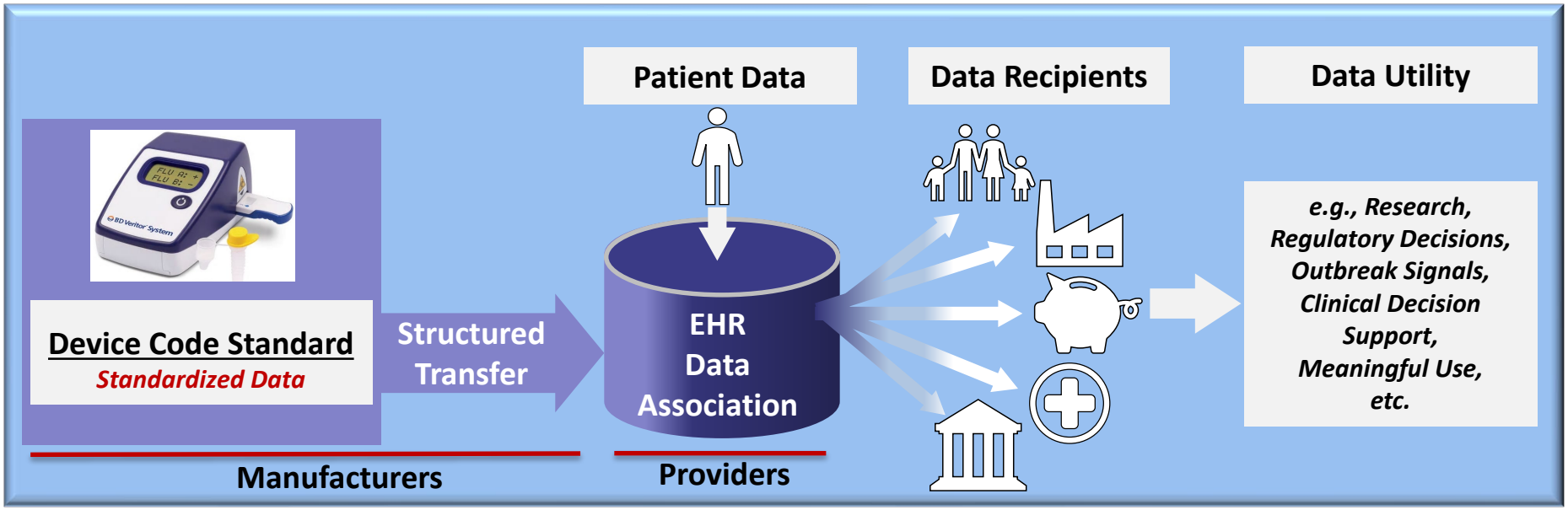
- RWE Guidance does not address all issues related to patient protection - focus is on the IDE process.

Example Case Studies

#	Device (Submission)	Data Source	Use	Action
1	Sequencing assay (510(k))	*Public Next Generation Sequencing database*	Publicly-maintained database support clinical validity of the test in lieu of clinical trials	Indication Expansion
2	Newborn screening assay (De Novo)	*State lab & surveillance databases*	Pivotal clinical trial was embedded in routine clinical practice (under an IDE) in lieu of a traditional pivotal trial.	New Indications
3	Implantable Cardioverter-Defibrillator (PAS)	*Multiple Real World Data sources*	Monitor multiple aspects of real-world device safety and performance using data collected in routine care.	Condition of Approval

Standards Empower Data Utility

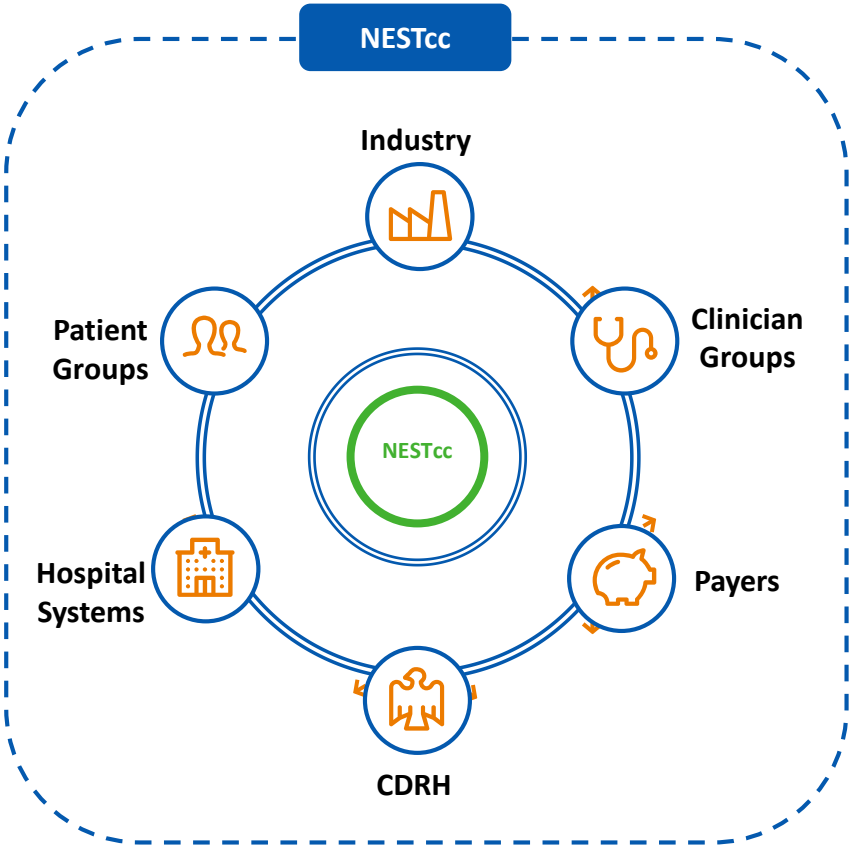
W/Standards:	*Quality in – Quality out.*
W/O Standards:	*Garbage in – Garbage out*



National Evaluation System for Health Technologies Coordinating Center (NESTcc)

An initiative of Medical Device Innovation Consortium (MDIC) to support the generation & use of RWE throughout medical device lifecycle

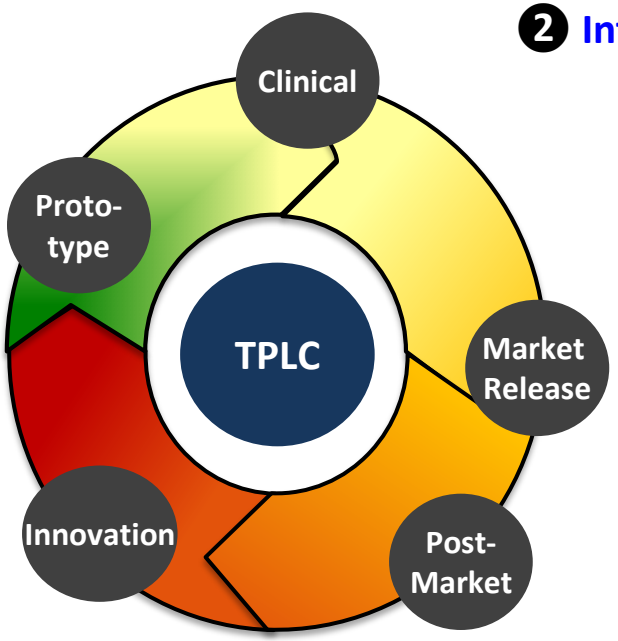
- Provide governance, coordination, and standardization
- Expand access to and use of data from clinical practice
- Strategic approach for collecting data
- Facilitating transfer and linking among interoperable data sources
- Embed research data collection into routine clinical workflow and participating patients' daily activities



https://www.fda.gov/about-fda/cdrh-reports/national-evaluation-system-health-technology-nest

Potential Usages of RWE for Total-Product Life-Cycle Device Evaluation

❶ **Hypothesis Generation** (e.g. treatment effect estimation for comparative studies)



❷ **Inform prospective trial design**

❸ RWE as a **control arm** for a clinical trial

❹ Real-world data source as a **platform to support a clinical trial** (data collection / randomization)

❺ Data collection framework for **post-market condition-of-approval studies**

❻ Adverse event reporting

❼ Generate evidence to support **indication expansions** and **future innovation**

Conclusions/Requests

- FDA believes that there is opportunity for greater use of RWD/RWE in regulatory decision making.
- This guidance is designed to provide framework to help stakeholder assess relevance and reliability of RWE
- CDRH is supporting several efforts to support NEST, and build data infrastructure into registries and EHRs to access RWE valuable in regulatory decisions.
- Please contact us via *pre-submission* or *directly* to let us know how we can help you.

Questions/Comments?

Contact: CDRHClinicalEvidence@fda.hhs.gov

Thank you!

William (Bill) Sutton

萨盾

美国食品药品管理局

驻华办公室助理主任

William.Sutton@fda.hhs.gov

+86 10-8531-3660 Desk Phone