

Welcome to today's FDA/CDRH Webinar

Thank you for your patience while we register all of today's participants.

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

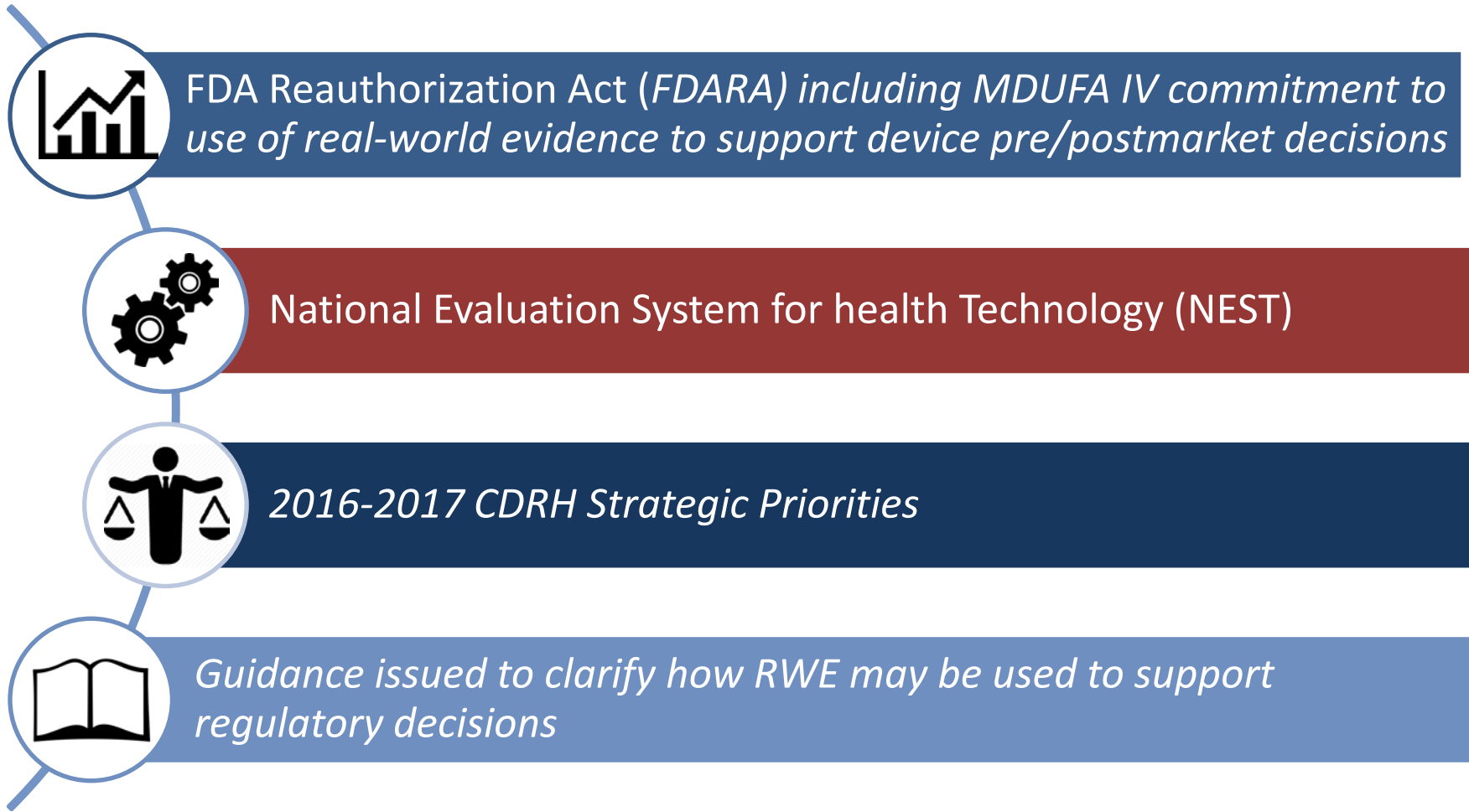
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Agenda

- Background
- Differences between draft and final version
- Regulatory framework
- Highlights and scope of final guidance
 - Overview of selected sections
 - Examples
- Questions

Context for RWE Guidance



Definitions from the Guidance



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

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

Collection



Analysis



Use



Guidance addresses issues related to processes of:

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



Structure of the Guidance

- Scope and Definitions
- Background and Context
- General Considerations for use of RWE
- Investigational Device Exemption (IDE) Requirements
- Data Quality – Relevance and Reliability
- Examples

Scope of the Guidance

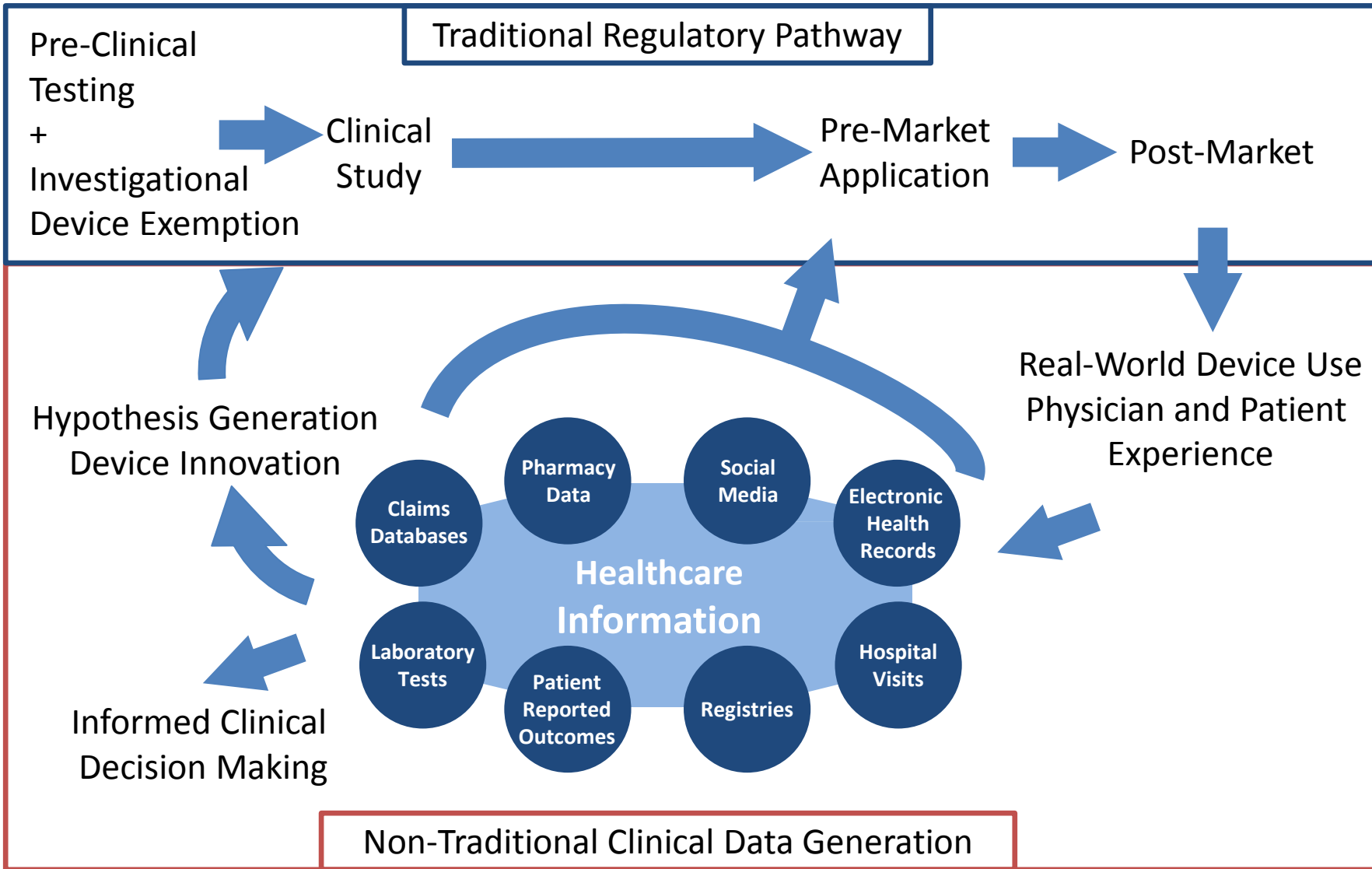
Guidance Discusses:

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

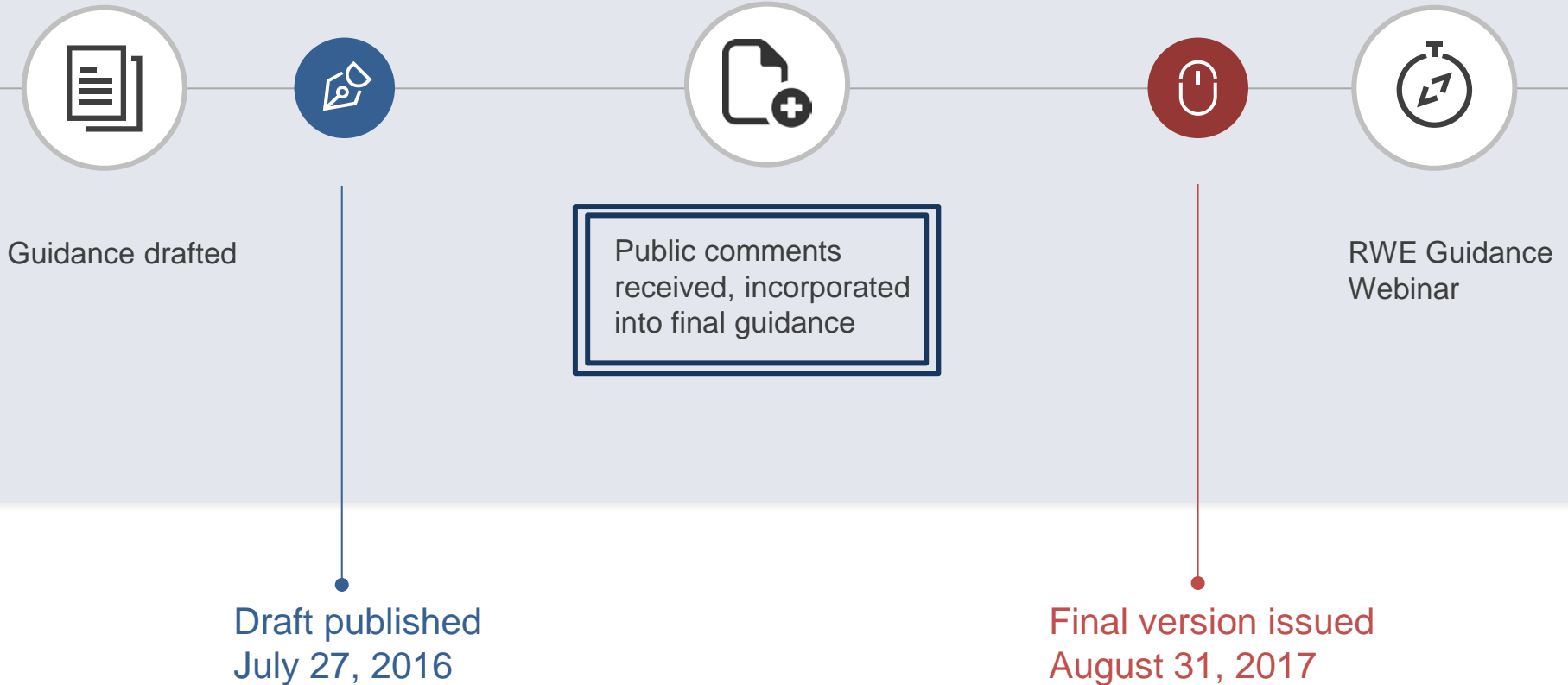
Outside the Scope of the Guidance:

- 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.

Evidence in Regulatory Decisions



Guidance Publication Timeline



Responses to Stakeholder Feedback



- **Clarify the scope of the guidance regarding devices types.**
 - Reiterated that this guidance applies to all devices as defined in 201(h) of the FD&C Act.
- **Is there a deterministic score sheet for RWE applicability?**
 - No such uniform score sheet is possible. We further clarified the factors we will consider.
- **Does RWE lower data requirements?**
 - No. The evidentiary standard—reasonable assurance that a device is safe and effective—is unchanged.
- **Clarify IDE and Human Subject Protections for RWE.**
 - Included additional information for when an IDE is needed.

Data Quality

Valid Scientific Evidence

- 21 CFR 860.7(c)(1)
 - 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.

What is Acceptable?

- 21 CFR 860.7(c)(2)

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.

What is Not Acceptable?

- 21 CFR 860.7(c)(2) continued
...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.

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

Safety

Are there reasonable assurances, based on valid scientific evidence that probable benefits to health from use of the device *outweigh any probable risks?* [860.7(d)(1)]

Effectiveness

Is there reasonable assurance, based on *valid scientific evidence* that the use of the device in the target population will provide *clinically significant results?* [860.7(e)(1)]

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 –



Aspects of data collection to consider:

- 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.

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 Assurance - Quality Control



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 across sites over time.
 - Evaluation of on-going training programs.



Investigational Device Exemption (IDE) Process and Real-World Evidence (RWE)

RWD and IDE

- Whether collection of RWD requires an IDE depends on if the device is used in the normal course of medical practice or a clinical investigation.
- Under section 1006 of the FD&C act, the FDA does not regulate health care practitioners in the use of legally marketed devices within a legitimate health care practitioner-patient relationship.
 - May include use of legally marketed devices for uncleared or unapproved uses.
- If found to be of sufficient quality, RWD collected during the routine care of patients may be used to support regulatory decisions.

Patient Protections

- Legal framework for patient protection includes:
 - 21 CFR parts 50, 56, and 812
 - Common Rule 45 CFR 46
 - Health Information Privacy and Portability Act (HIPPA)
 - Other federal and local regulations
- RWE Guidance does not address all issues related to patient protection. The focus is on IDE process.

IDE and Informed Consent

- 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 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.

Examples



RWE Use Examples

Labeling Expansion

Registry data regarding safety and effectiveness of unapproved use may support expansion of FDA-approved indications for use

Concurrent control group derived from RWD to support premarket decision

Control Group

Post-Approval Surveillance

Earlier device approval made possible by the use of RWE

RWE supplemented IDE helps FDA come to appropriate regulatory decisions faster

Supplementary Data

- A Class III device was approved based on traditional clinical trials.
 - Widely used outside of the approved indications for use.
 - Limited clinical study data available to support a reasonable assurance of safety and effectiveness for the new use.
- An existing national registry collecting clinical data on this and similar devices identified by the sponsor and the FDA.
 - Safety and effectiveness information collected for all patients; link with administrative claims for long-term outcomes.

Labeling Expansion

- Registry data regarding safety and effectiveness of unapproved use may support expansion of FDA-approved indications for use

Concurrent control group derived from RWD to support premarket decision

Control Group

- Clinical evidence needed to support substantial device changes.
- Ongoing registry identified collecting patient data treated with approved devices with similar intended use during routine medical care.

- Clinical study designed to compare:
 - The use of new device
 - Non-randomized concurrent control group derived from the registry
- After quality evaluation conducted by the sponsor and FDA, the registry was found to provide sufficiently relevant and reliable RWD on the control population.
- Patients received investigational device were enrolled under an approved IDE.
- Concurrent control group were **not** considered a part of the IDE.

RWE supplemented IDE helps FDA come to appropriate regulatory decisions faster

Supplementary Data

- PMA review for a new indication.
- Limited data from prospective clinical trial:
 - Limited follow-up
 - Inadequate data from control group
- Difficulty in interpreting results.
- A pre-existing data source was already collecting and reporting RWD on the control therapies.
- Registry data supplemented and helped interpret the IDE results; additional clinical trial would have been required without the availability of RWD.
- FDA was able to come to an appropriate regulatory decision faster.

- A breakthrough Class III medical device was approved based on randomized clinical trial.
- Sponsor and FDA decided to use data generated from routine clinical care to support postapproval commitments, in lieu of stand-alone clinical trials.
- New registry was created to generate RWD that could meet FDA's data requirements.
- Earlier device approval conditioned on RWD collection and reporting postmarket was made possible by the early construction of the registry.
- Collecting data on other devices with similar design and Indications for Use (IFU) and has been used for
 - Surveillance
 - Analysis of all uses of device to expand IFU
 - Embedded IDE trials for new devices

Post-Approval Surveillance

Earlier device approval made possible by the use of RWE



Conclusions/Requests

- CDRH believes that there is opportunity for greater use of RWD/RWE in regulatory decision making for devices.
- This guidance is designed to provide framework to help stakeholders assess relevance and reliability of RWE.
- CDRH is supporting several efforts to facilitate the development of infrastructure and tools to better access and use RWE for regulatory decision making, including the development of National Evaluation System for health Technology (NEST).
- Please contact us via *pre-submission* or *directly* to let us know how we can help you.

Questions?

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RWE Policy Questions:

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Slide Presentation, Transcript and Webinar Recording will be available at:

<http://www.fda.gov/training/cdrhlearn> Under the Heading: How to Study and Market Your Device; Sub-heading: Cross-Cutting Premarket Policy

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