

Clinical Trials and Investigational Device Exemptions

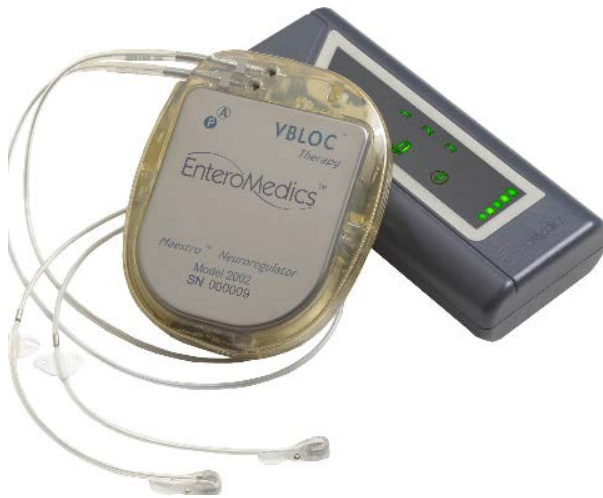
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Investigational Device Exemption Program
Clinical Trials Program
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

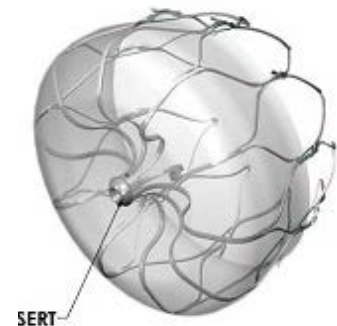
FDA Clinical Investigator Training Course
November 15, 2018

Learning Objectives

- To understand the regulatory context of device clinical investigations
- To understand when an IDE is required
- To understand the IDE application process and FDA decisions on those applications
- To understand ways to have more successful IDE submissions



“Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.”



CDRH Vision Statement

Investigational Device Exemptions

*The purpose of this part is to encourage, to the extent consistent with the **protection of public health and safety**, ... the **discovery and development of useful devices** intended for human use....*

21 CFR 812.1

Overview

- What is an IDE and when is one needed?
- The IDE application and beyond
- Tips for successful IDE submissions

Overview

- **What is an IDE and when is one needed?**
- The IDE application and beyond
- Tips for successful IDE submissions

Investigational Device Exemption

- 21 CFR 812.1:
 - “...An approved **investigational device exemption (IDE)** permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be **shipped lawfully** for the purpose of **conducting investigations** of that device....”
- An IDE is a **regulatory submission** that permits clinical investigation of devices.

Approved IDEs are Exempt from Regulations Pertaining to:

- Misbranding
- Registration
- Performance Standards
- 510(k)
- PMA
- HDE
- Good Manufacturing Practices (GMPs) **except Design Controls**
- Color Additive requirements
- Banned Devices
- Restricted Device requirements

Some Terminology

- **Investigation:** clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device (also study)
- **Sponsor:** initiates, but does not actually conduct, the investigation
- **Investigator:** actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject
- **Institutional Review Board (IRB):** reviews, approves (initially and continuing) biomedical research at a given institution

Provisions of the IDE Regulation

- Describes **applicability** of the IDE regulations
- Provides **administrative** information
- Outlines the contents of the **IDE application**
- Describes **FDA actions** on IDE applications
- Assigns **responsibilities** to all participants in clinical investigation

Studies Subject to the Regulation

- To gain initial safety and effectiveness information to support further study
- To support marketing application [PMA, HDE, 510(k) or *de novo*]
 - New device
 - New use of legally marketed device (“off-label use”)
- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned)

Types of device studies

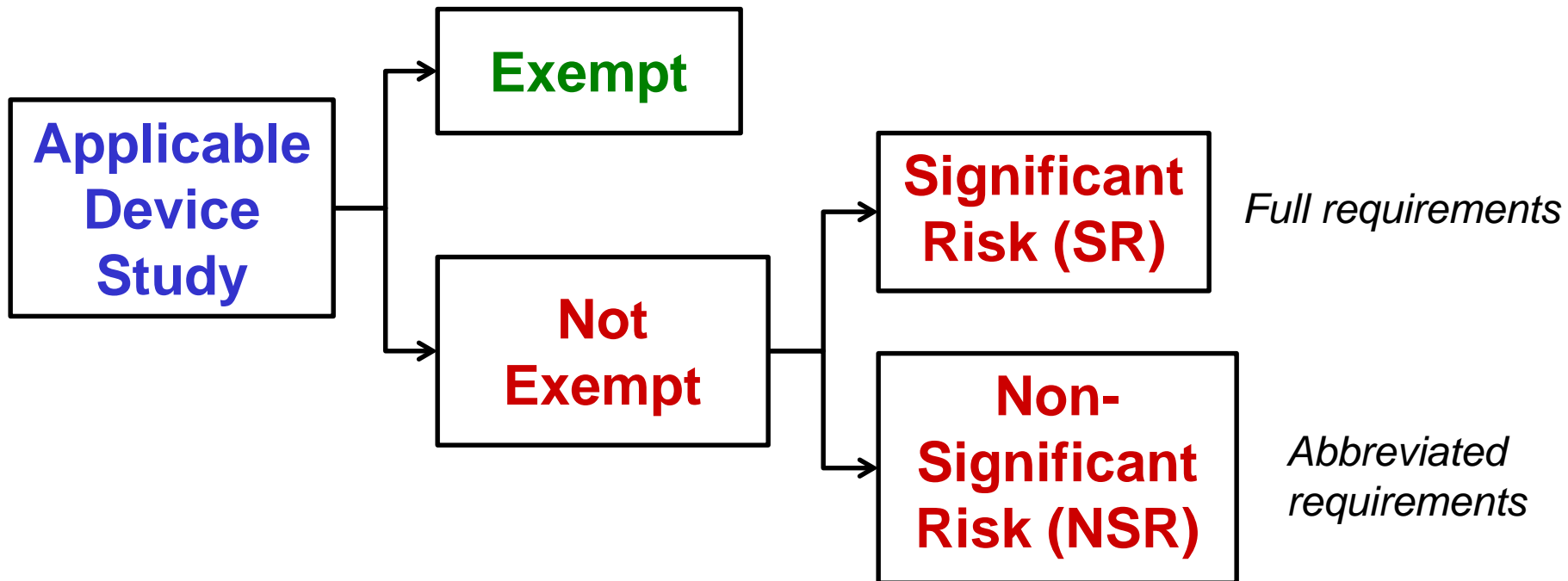
- **Feasibility Studies**

- Intended to gather preliminary information regarding
 - Safety profile and potential for effectiveness
 - Refinements to device or future study
- Not intended to provide primary support for marketing
- Generally not statistically driven (n ≈1-40 subjects)
- Early feasibility studies to inform device design

- **Pivotal Studies**

- Intended to provide the primary clinical data in support of a future marketing application
- Statistically driven sample size and hypotheses

When is an IDE needed?



Is it an “applicable” device study?

General applicability of the IDE regulations:

812.2(a) General. This part applies to all clinical investigations of devices to **determine safety and effectiveness**, except as provided in paragraph (c) of this section.

“Practice of Medicine”

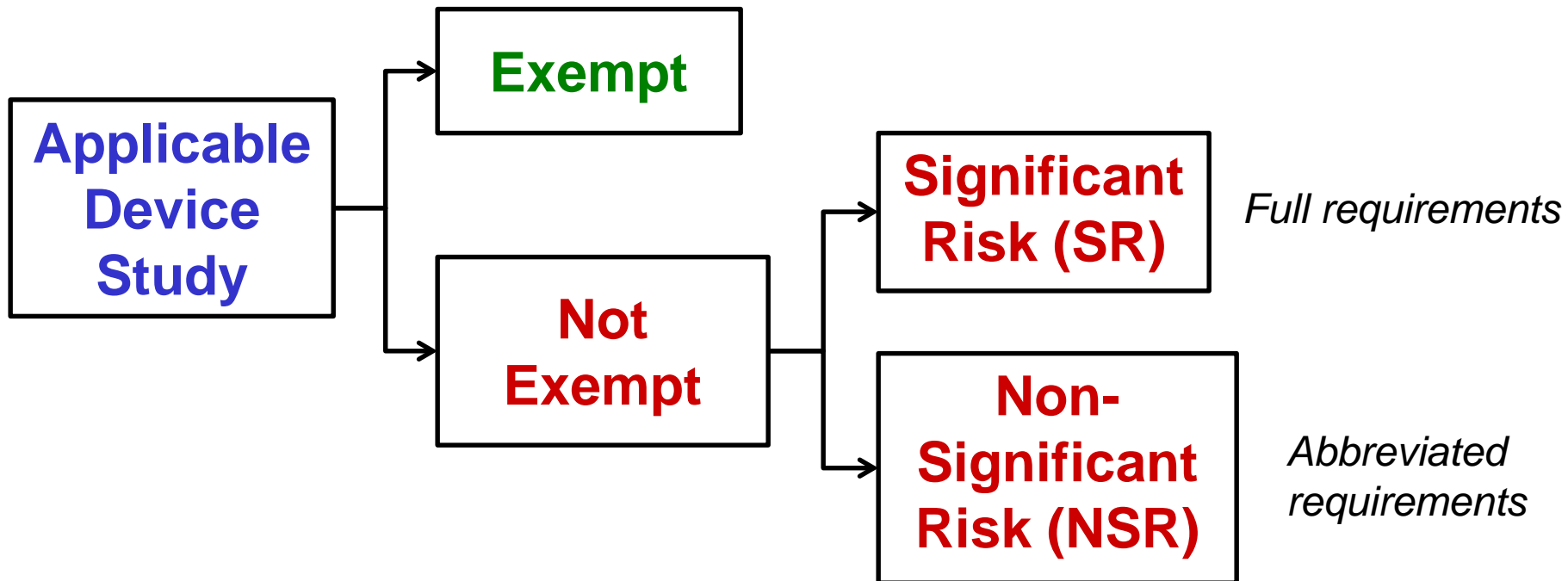
“Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship....”

From Section 1006 of the FD&C Act

“Practice of Medicine”

- Not an investigation/study
- Physician should:
 - Be well informed about the product
 - Use firm scientific rationale and sound medical evidence
 - Maintain records on use and effects
- **IDE not required**; institution may require IRB review/approval and informed consent
- Other prohibitions still apply

When is an IDE needed?

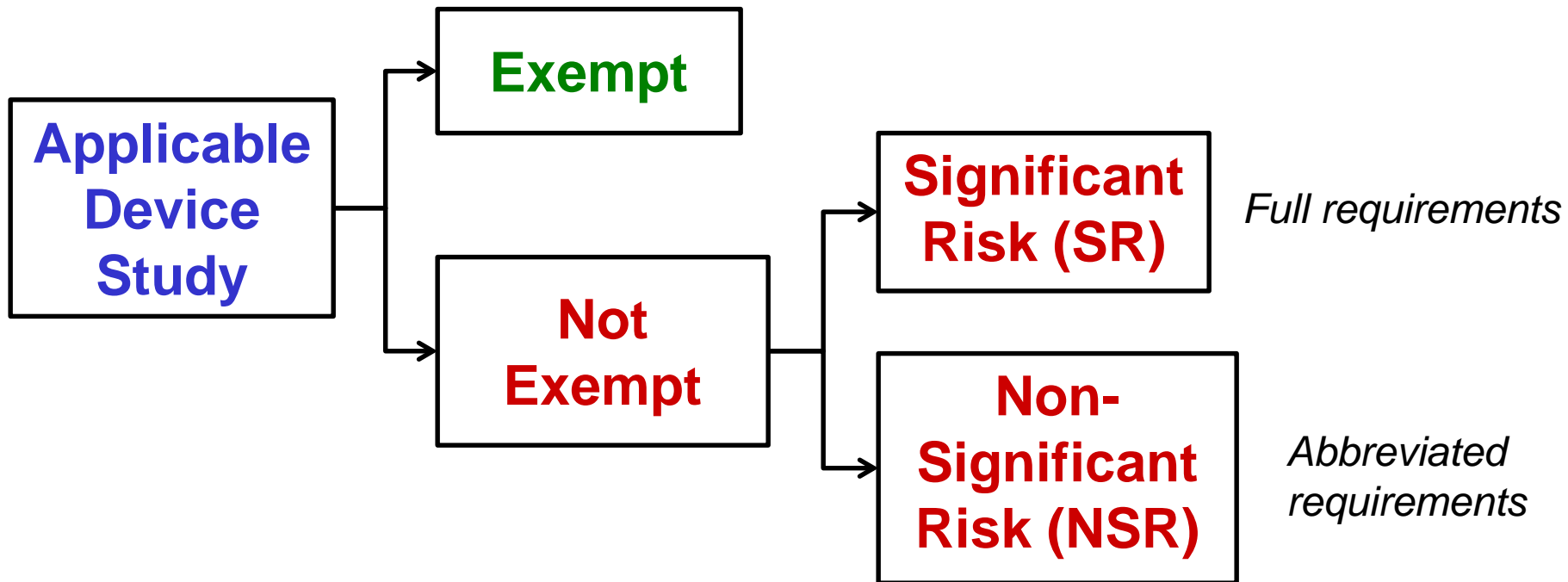


Exempt Studies (21 CFR 812.2(c))

No IDE Needed

- Commercial devices used in accordance with labeling
- Many diagnostic devices
- Testing of consumer preference, of a modification, or of a combination of devices
 - if not for the purpose of determining safety or effectiveness and not putting subjects at risk:
- Veterinary devices
- Research on/with laboratory animals
- Custom devices as defined in 812.3(b)

When is an IDE needed?



Non-Exempt Studies

- **Non-Significant Risk** – does not require IDE submission to FDA
 - abbreviated requirements
 - Labeling (812.5)
 - IRB Approval (56)
 - Informed Consent (50)
 - Monitoring (812.46)
 - Records and Reports (812.140(b)(4) and (5), 812.150(b)(1) - (3) and (5) - (10))
 - Annual and Final Progress Reports are not required
 - Promotion (812.7)
- **Significant Risk** – can not begin until FDA approves IDE (full requirements)

Significant Risk (SR) Study

- A significant risk *device* presents a **potential for serious risk to the health, safety, and welfare of a subject** and is:
 - An implant; or
 - Used in supporting or sustaining human life; or
 - Of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health; or
 - Otherwise poses a risk

812.3(m)

- **Study** risk based on the **proposed use** of a device in an investigation, **NOT** the **device alone**

Non-Significant Risk (NSR) Studies

- IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies.
- A NSR device study may start at the institution as soon as the IRB reviews and approves the study
 - Abbreviated IDE requirements (labeling, IRB, consent, monitoring, reporting, prohibition on promotion)
 - No IDE submission to FDA needed

Significant Risk Studies

- Full IDE requirements apply
- Sponsor submits IDE application to FDA
- FDA renders decision within 30 calendar days
- If approved, sponsor obtains IRB approval
- After both FDA and IRB approve the investigation, study may begin

Study Risk Determination Inquiries to FDA

- Sponsor submits “Study Risk Determination” Q-Submission
 - Cover letter, Device Description, Protocol
- FDA issues letter indicating if study is
 - Basic physiological research
 - Exempt
 - Not exempt: SR or NSR
- FDA is final arbiter

Resources:

[Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff](#)

[Significant Risk and Nonsignificant Risk Medical Device Studies](#)

Overview

- What is an IDE and when is one needed?
- **The IDE application and beyond**
- Tips for successful IDE submissions

The IDE Application (812.20)

- Name and address of sponsor
- Report of prior investigations and investigational plan
- Manufacturing, processing, packing, and storage of device
- Investigator agreement (example, listing, certification)
- List of the name, address, and chairperson of each IRB
- Participating institutions
- Amount to be charged for device
- Environmental assessment
- Labeling
- Subject materials including informed consent
- Additional information requested by FDA

Investigational Plan (812.25)

Includes:

- Purpose of study
- Study protocol
- Risk analysis
- Device description
- Monitoring procedures
- Labeling, consent materials, IRB and institutional information
- Records and reports

FDA Review of the Application

- FDA sends acknowledgement with IDE number: GYYxxxx (e.g. G160001)
- IDE sent to appropriate review division based on intended use
- Lead reviewer assembles team of experts to review the application and make decision with management concurrence within 30 days
- FDA issues a decision letter to the sponsor

FDA Decisions and Letters

- **Approval**
 - Approves the trial for specified number of sites and subjects
 - Enrollment can begin once IRB approval is obtained
- **Approval with conditions**
 - Approves the trial for specified number of sites and subjects provided conditions (deficiencies) are addressed within 45 days
 - Enrollment can begin once IRB approval is obtained
- **Disapproval**
 - Study may not begin
 - Deficiencies will be listed
 - Sponsor must address deficiencies and obtain FDA approval to start study

FDA Review of Feasibility IDEs

- Focused on safety
- Critical issues
 - Reasonable study conceptually?
 - Adequate preclinical validation of device?
 - Why is clinical really the next necessary step?
 - Appropriate mitigation of potential risks?
 - Appropriate enrollment criteria?
 - Patients adequately informed?
 - Sample size appropriate?

FDA Review of Pivotal IDEs

- Focused on safety and plan for collecting and evaluating study data
- Additional critical issues
 - Trial endpoints
 - Randomization, blinding, follow-up, etc.
 - Study conduct and monitoring
 - Statistical analysis plan

IDE decision making

IDE **Disapproval** is appropriate when:

- Probable risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained
- Study does not pose a reasonable scientific question and/or is not designed to collect data related to that scientific question
- IDE does not comply with regulations, omits material or contains untrue statements

IDE decision making

- Concerns regarding the **study design** that **are not related to protecting study subjects** are not the basis for a disapproval
 - FDA will convey these concerns to the sponsor for their consideration as an attachment to our decision letter

Other Elements of FDA Letters

Study Design Considerations

- Recommendations regarding study design (unrelated to subject protection), for example:
 - Primary and important secondary endpoints and study success criteria
 - Randomization and control plan
 - Blinding (masking)
 - Follow-up duration and assessments
 - Statistical plan
 - Case report forms
 - Enrollment criteria
 - Core labs and independent adjudication committees

Other Elements of FDA Letters

Future Considerations

- Issues relevant for future submissions, for example:
 - Testing needed for future marketing application
 - Recommendations for future pivotal study design
 - Limitations on future claims based on study design

Summary: FDA Letter

- Decisions – Can you start the study?
 - Approval
 - Approval with Conditions
 - Disapproval
- } Require deficiencies to be addressed
- Study Design Considerations and Future Considerations do NOT require a response.
 - Guidance: [FDA Decisions for Investigational Device Exemption \(IDE\) Clinical Investigations](#)

Sponsor Responsibilities

- Select qualified **investigators** and provide them with information they need
- Ensure proper **monitoring**
- Obtain **IRB and FDA** review and approval
- Control **devices**
- **Comply** with labeling, prohibition of promotion, import and export requirements (Subpart A).
- Maintain adequate **records**
- Grant **inspections** to FDA (establishments and records)
- Prepare and submit **reports**

Other FDA Submissions

- **Supplements** (812.35)
 - Change in protocol
 - Change in device
- **Reports** (812.150)
 - Annual progress
 - Unanticipated adverse device effects
 - Enrollment and follow-up completion
 - Withdrawal of IRB or FDA approval
 - Current list of investigators
 - Final report
- Responses to any deficiencies are submitted as **amendments**
- All Original IDEs, Reports, Supplements, and their amendments have a 30-day review clock

Overview

- What is an IDE and when is one needed?
- The IDE application and beyond
- **Tips for successful IDE submissions**

Tips for Successful IDE Submissions

- **Before Submission**

- Q-submission Program
 - Study Risk Determination
 - Informational Meeting
 - No expectation of feedback
 - Pre-Submission
 - Request for feedback from FDA in the form of a written response or meeting on specific questions
- Review relevant guidance and internet resources

**Requests for Feedback on Medical Device Submissions:
The Pre-Submission Program and Meetings with Food and Drug Administration Staff**

Guidance for Industry and Food and Drug Administration Staff

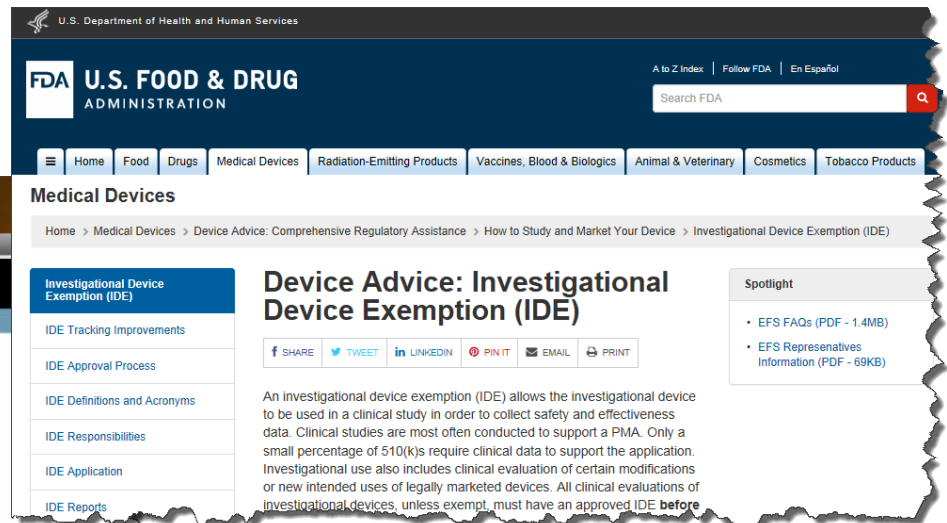
Other FDA Resources

- [CDRH Learn](#)

- IDE Basics
- Early Feasibility Studies
- Clinical Trial Program Updates
- Pre-Submissions
- Many more!

- [Device Advice](#)

- [Investigational Device Exemptions](#)
- [Breakthrough Devices \(Expedite Access Pathway\)](#)



Tips for Successful IDE Submissions

- **IDE Application**

- Follow eCopy guidelines
- Organize clearly (e.g., use a master table of contents with continuous numbering)
- Ensure all required elements are included (see checklist on Device Advice)
- “Tell the Story”
 - Provide basic information to support FDA review
 - Provide rationale for adequacy of data provided
- Be consistent throughout submission
- Address previous FDA submissions, interactions, and feedback

Examples of Basic Questions

- Describe device components and materials
- Describe principle of operation and key characteristics
- Clarify version of device tested compared to version for clinical study
- Clarify what testing was done with rationale
- Provide adequate description of test conditions, success criteria, and results

Tips for Successful IDE Submissions

- **During review**
 - Be available and responsive for interactive review
 - Be aware of review process/timeline
- **After receiving a deficiency letter**
 - Prepare organized response
 - Respond point by point
 - Use numbering in letter

Summary

- IDE regulations encourage discovery and development of medical devices while protecting public health and safety
- IDE applications to FDA are needed for significant risk studies of device safety and effectiveness that are not exempt
- IDE regulations, guidance documents and web resources describe IDE application contents and FDA actions on those applications
- High quality submissions allow reviewers to focus on substantive questions for more efficient review

Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors – Medical Devices

www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm

- Frequently Asked Questions About Medical Devices
- Significant Risk and Nonsignificant Risk Medical Device Studies

- Sponsor's Responsibilities For Significant Risk Device Investigations

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049859.htm

Resources

- Guidance: FDA Decisions for IDE Clinical Investigations
www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf
- Standard Operating Procedures Review of IDE Application-Specific Issues
www.fda.gov/MedicalDevices/deviceregulationandguidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm384135.htm
- Guidance: IDEs for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

Questions



Medical Device Postmarket Evaluation

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Center for Devices and Radiological Health

FDA Clinical Investigator Training Course

November 15, 2018

Overview

- Definitions
- FDA Authority for Postmarket Surveillance of Medical Devices
- National Evaluation System for health Technology (NEST)
- Epidemiology Regulatory Science Program (ERSP)

EPIDEMIOLOGY IN REGULATORY ENVIRONMENT

Medical Device Epidemiology

The study of the use and effects of medical devices in human populations by conducting adverse event surveillance, targeted studies, and original research to evaluate device safety, effectiveness, and trends associated with device use.

Device Classification

A Risk-Based Paradigm

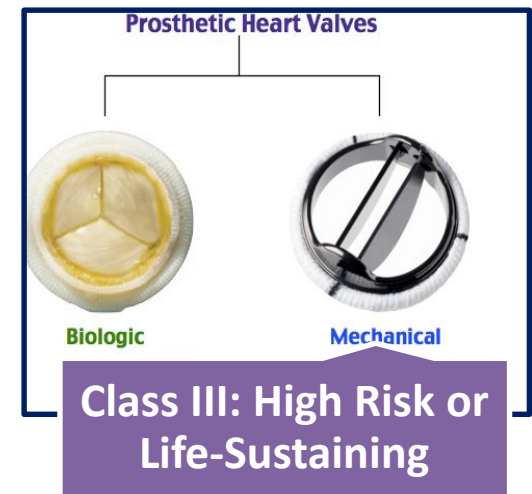
Medical devices are classified and regulated according to their degree of risk to the public.



Class I: Minimum or No Risk



Class II: Moderate Risk



Types of CDRH Regulatory Submissions

Submission Type	Device Class		
	Class I	Class II	Class III
Q-Submission	✓	✓	✓
Investigational Device Exemption (IDE)	Not dependent on device Class, rather on if the investigation is a significant risk.		
Premarket Approval Application (PMA)			✓
Humanitarian Device Exemption (HDE)			✓
Premarket Notification (510K)	✓	✓	✓*
de Novo Request	✓	✓	

* Rare instances for some pre-amendment Class III devices for which the Agency has yet to down classify or call for PMAs

Traditional Mechanisms

POSTMARKET SURVEILLANCE

FDA Postmarket Surveillance Authority

Postmarket Surveillance Tool	Device Class		
	Class I	Class II	Class III
Medical Devices Adverse Event Reporting 21 CFR 803.3	✓	✓	✓
Post-Approval Studies Program 21 CFR 814.82, FD&C Act Section 513(a)(3)(C)			✓
Postmarket Surveillance Program FD&C Act Section 522, 21 CFR 822		✓	✓

21 CFR 814.82

POST-APPROVAL STUDIES

Post-Approval Studies Program

- Ordered at time of device approval
- Authority under CFR Title 21 Section 814.82
 - (a) FDA may impose post-approval requirements at the time of approval ...
 - (2) Continuing evaluation and reporting on the safety, effectiveness, and reliability of the device for its intended use. . .
- Section 513(a)(3)(C) of the FD&C Act
 - FDA may consider whether postmarket data collection or other conditions might be structured so as to permit approval, subject to those conditions
- If clinical study then compliance with:
 - 21 CFR 50 Protection of Human Subjects
 - 21 CFR 56 Institutional Review Boards

PAS Best Used for:

Descriptive Long-Term Evaluation

- Extended follow-up of premarket study
- Device effect sustainability
- Adverse events

Benefit/Risk Uncertainty Evaluation

- Data not available otherwise
- Learning curve/training
- Sub-groups of patients
- Long-term Benefit/Risk
- Rare Adverse Events

Other Considerations

- Need for Bench testing/Animal studies
- Advisory Panel Recommendations
- **Existing surveillance mechanisms or infrastructure**

Section 522 of the FD&C Act, and 21 CFR 822

POSTMARKET SURVEILLANCE STUDIES

Postmarket Surveillance Studies

- A Class II-III device that meets any of the below statutory criteria may be subject to a postmarket surveillance Order if questions arise.

Statutory Criteria	Per Section 522 FD&C Act
Criterion 1	Failure of the device would be reasonably likely to have a serious adverse health consequence .
Criterion 2	<i>Expected</i> to have significant use in pediatric populations.
Criterion 3	Intended to be implanted in the body for more than one year.
Criterion 4	Intended to be a life-supporting device used outside of a user facility .

- Postmarket Surveillance can be ordered at any time during total product life cycle.
- Prospective surveillance up to 36 months for non-pediatric studies.
- FDASIA 2012
 - Surveillance must commence within 15 months of the Order

Postmarket Surveillance Studies

Concepts	Definition per Regulation
Serious adverse health consequence	Per 822.3(j) ... any significant adverse experience related to a device, including device-related events that are life-threatening or that involve permanent or long-term injuries or illnesses.
Significant Pediatric Use	New provision as of FDAAA 2007 “Significant” pediatric use is defined on a case-by-case basis Leeway written into the statute to allow for studying devices not specifically labeled for pediatrics
Life-supporting or life-sustaining device used outside a device user facility	Per 822.3(f), [it] means that a device is essential to, or yields information essential to, the restoration or continuation of a bodily function important to the continuation of human life and is used outside a hospital, nursing home, ambulatory surgical facility, or diagnostic or outpatient treatment facility. A physician's office is not a device user facility.

When does Section 522 apply?

- Not required for all devices that meet a statutory criterion
- FDA notifies company to conduct postmarket surveillance study via a “522 Order”

Failure to comply with a 522 order can result on:

- Compliance Action:
 - Warning Letter
 - Device misbranded (under section 502(t)(3) of FD&C Act)
 - Seizure of device
 - Civil Money Penalties
 - Prosecution

PAS Protocol and 522 Plan Components

Study questions,
hypothesis, study
design, population

Primary and
secondary
endpoints

Description of
data collection
procedures

Duration of
follow-up and
schedule

Statistical
analysis plan

PAS / 522 Studies Program Challenges

Development of Protocols/Surveillance Plans

- Reaching agreement on protocols/study plan can take time, delaying study start and time to data availability

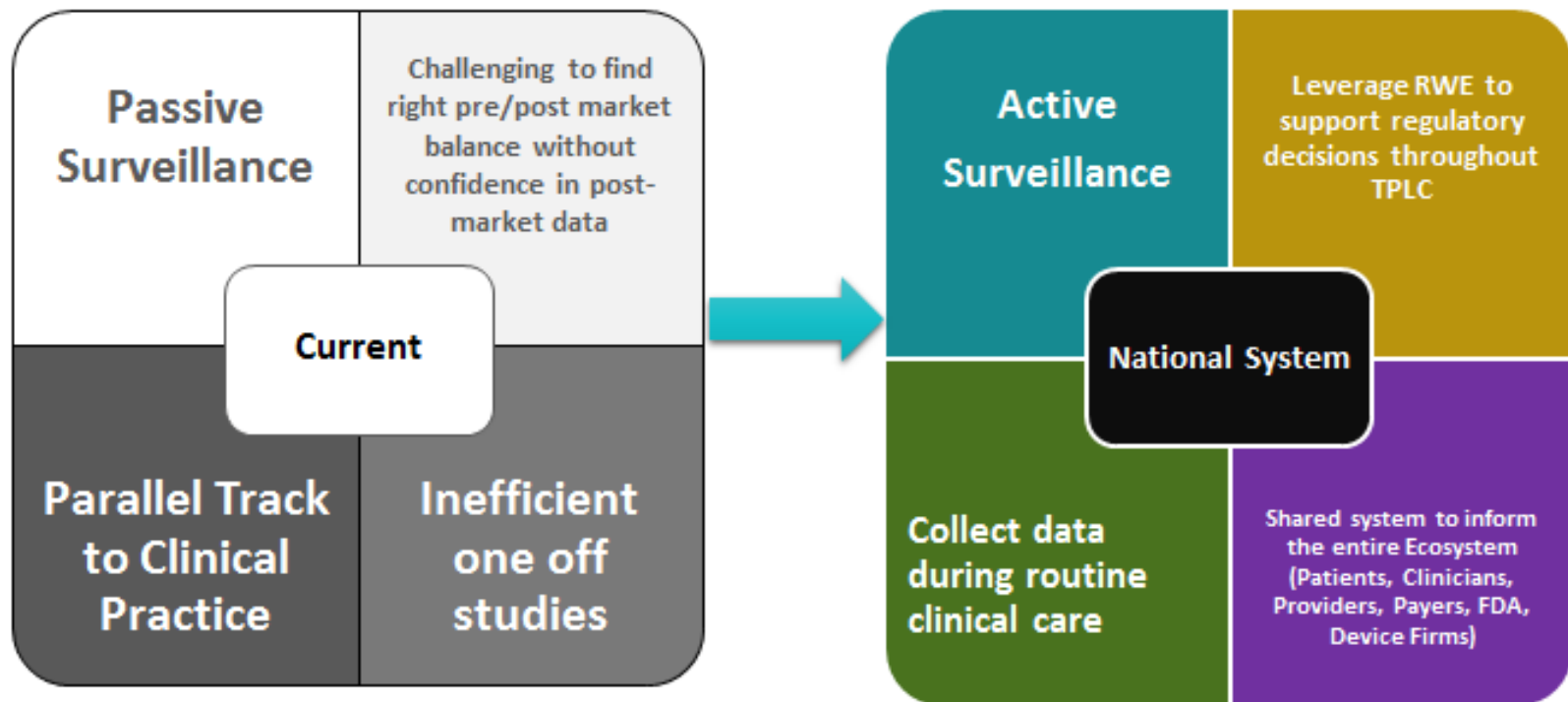
Implementation

- Enrollment of sites and/or subjects
- Maintaining follow-up of subjects
- Device modifications while the study is being implemented

Other Considerations

- Public health aspect of 522 orders
- Communication
- Advanced methodologies
- **Existing Infrastructure**

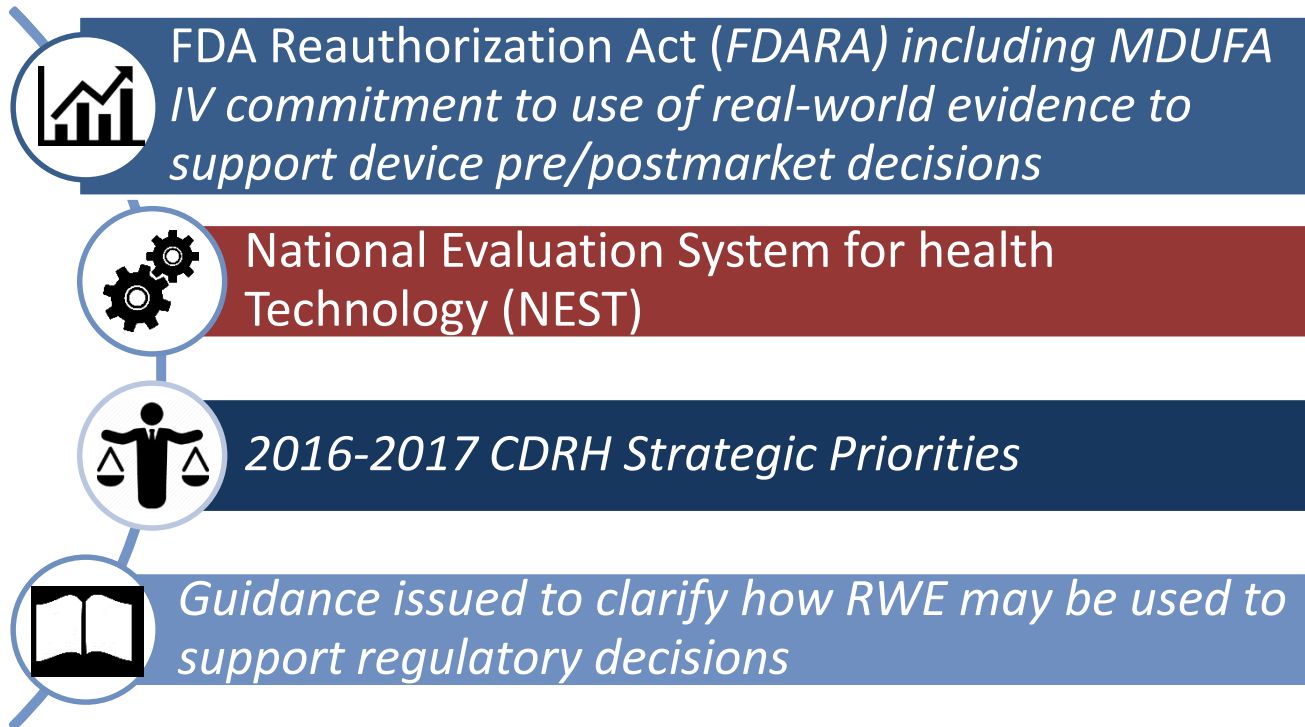
National System Paradigm Shift: Today and Tomorrow Potential to Leverage



NEST

REAL-WORLD EVIDENCE

Context for RWE Guidance



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.

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.

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

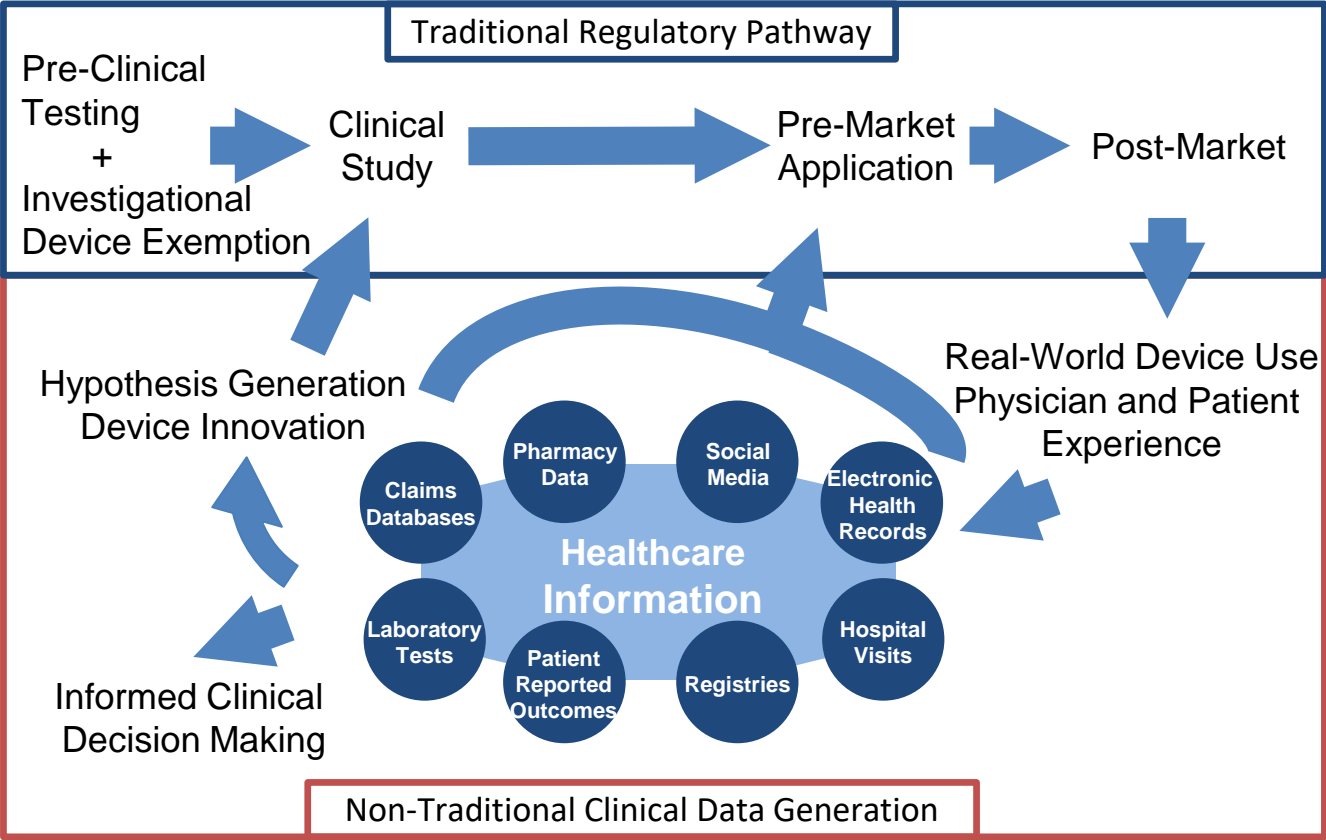
Real-World Evidence (RWE)
 Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD



Guidance addresses issues related to processes of:

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

Evidence in Regulatory Decisions



Potential Regulatory Uses of RWE

- RWE can provide a richer data set to address questions that cannot be answered by pre-market clinical trials
- If sufficiently robust, RWE can provide better information to support pre/post regulatory decision-making
- Use of RWE can decrease time and cost for device evaluation and provide additional options for pre/post market evaluations

How RWE will impact FDA/Stakeholders

- Sponsors/manufacturers may rely on shared infrastructure to conduct evaluations of medical devices.
- Use of shared infrastructure will enable regular, predictable analyses and allow for cross-platform benefit-risk evaluation.

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.

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 a legally-marketed 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.

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)]

Spectra



Regulatory Decisions



Relevance



Reliability

Characteristics for RWE evaluation - Relevance

- The data adequately addresses the applicable regulatory question or requirement, in part or in whole
- Data set factors evaluated address whether the data is collected in a way to ensure
 - Appropriate variables collected, esp. device exposure
 - Endpoint definitions consistent and meaningful
 - Assessment schedule appropriate for capturing endpoints of interest
 - Population is appropriate and representative
 - Experimental/analysis plan appropriate to address question

Characteristics for RWE evaluation - Reliability

- Reliability is a measure of the quality for a RWD source
- RWD data reliability is assessed related to characteristics of:
 - Data Accrual
 - Data Adequacy
 - Data Assurance

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.

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.

Challenges using RWE

- Patient protection/privacy (informed consent; IC)
- RWD sources rarely initiated specifically for regulatory data collection
- Data quality: fewer direct controls on data entry may impact overall data quality for data sources, limiting the applicability of the data.
- Appearance of “lowering the bar”
- Overall system costs/investments
- Lack of acceptance or knowledge of RWE uses by FDA & manufacturers

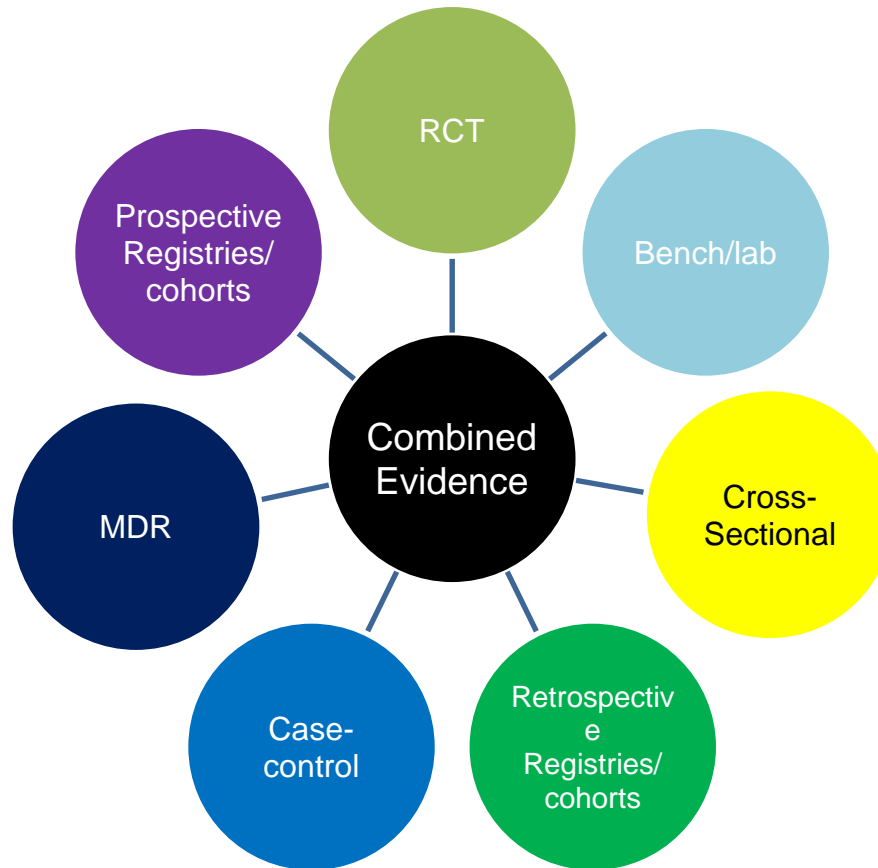
ERSP

CDRH EPIDEMIOLOGY REGULATORY SCIENCE PROGRAM

Division of Epidemiology Regulatory Science Research

- Over 60 ongoing projects dedicated to advancing knowledge needed for development of the NEST.
- Medical Device Epidemiology Network – a public-private partnership working with FDA to advance medical device epidemiology regulatory science
- Explore new ways of using observational data to support regulatory decisions in the pre- and post-market space.

Information Synthesis



Selected CDRH Registry Efforts

- Explore registry capabilities
 - ✓ Active surveillance: short-term and longitudinal (DELTA)
 - ✓ Linkages studies with Medicare claims data (TVT)
- Build methodological infrastructure for registries
 - ✓ International Consortium of Orthopedic Registries (ICOR) – 30 registries from 15 nations
 - ✓ International Consortium of Cardiovascular Registries (ICCR) – 6 registries
- Directly access de-identified patient-level registry data for public health surveillance
 - ✓ Grant of Authority under HIPAA to University of Washington to Collect AED and patient outcome data
 - ✓ ACC/STS TVT registry linked to CMS claims accessed as condition of approval
- Use registry data to expand indications
 - ✓ ACC/STS TVT Registry data used to expand Edwards' Sapien Valve indications

The gaps

- The interpretation of current federal regulations (particularly the Privacy and Common Rules) by various IRBs has created significant obstacles for existing registries.
- New trial designs and data sources rely on development of methodology for analysis
- Rules and regulations regarding direct FDA access to data need to be developed in concert with pre- and post-market review procedures
- Effective public health analysis in the Big Data era requires robust and active collaboration among **ALL** stakeholders



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