# Medical Device Clinical Evidence: IDEs and Beyond

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# Learning Objectives

To understand:

- When a Q-submission might be useful
- When an IDE is required for device clinical study
- IDE application and FDA decisions on applications
- FDA authority for postmarket studies/surveillance as it relates to the conduct of clinical studies
- Real World Evidence and NEST

# Agenda

- Introduction
- Q-Submissions
- Investigational Device Exemptions (IDEs)
- Clinical Studies to address Postmarket Questions
- Real World Evidence and the National Evaluation System for health Technologies (NEST)

# Agenda

- **Introduction**
  - Device Classification
- Q-Submissions
- Investigational Device Exemptions (IDEs)
- Clinical Studies to address Postmarket Questions
- Real World Evidence

# Device Premarket Submissions

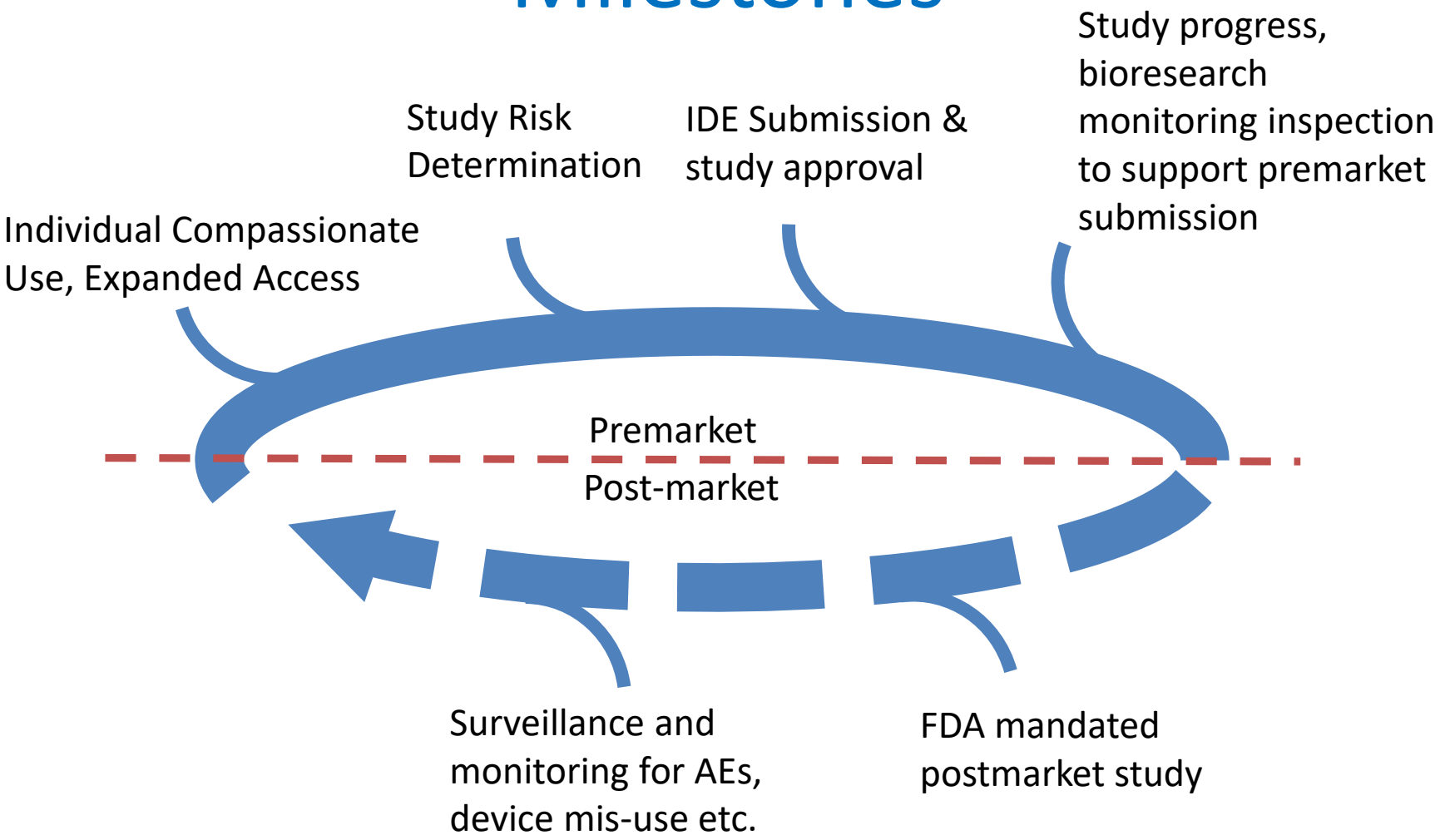
| Submission Type | Device Class | | |
|---|---|---|---|
| | Class I | Class II | Class III |
| Regulatory Controls | Less → More | | |
| Q-Submission | ✓ | ✓ | ✓ |
| Investigational Device Exemption (IDE) | Not dependent on device Class, rather on if the investigation is a significant risk. | | |
| Premarket Approval Application (PMA) | | | ✓ |
| 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

# Device Postmarket Evaluation

| 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 | | ✓ | ✓ |

# Example Clinical Experience Milestones



# Agenda

- Introduction
- **Q-Submissions**

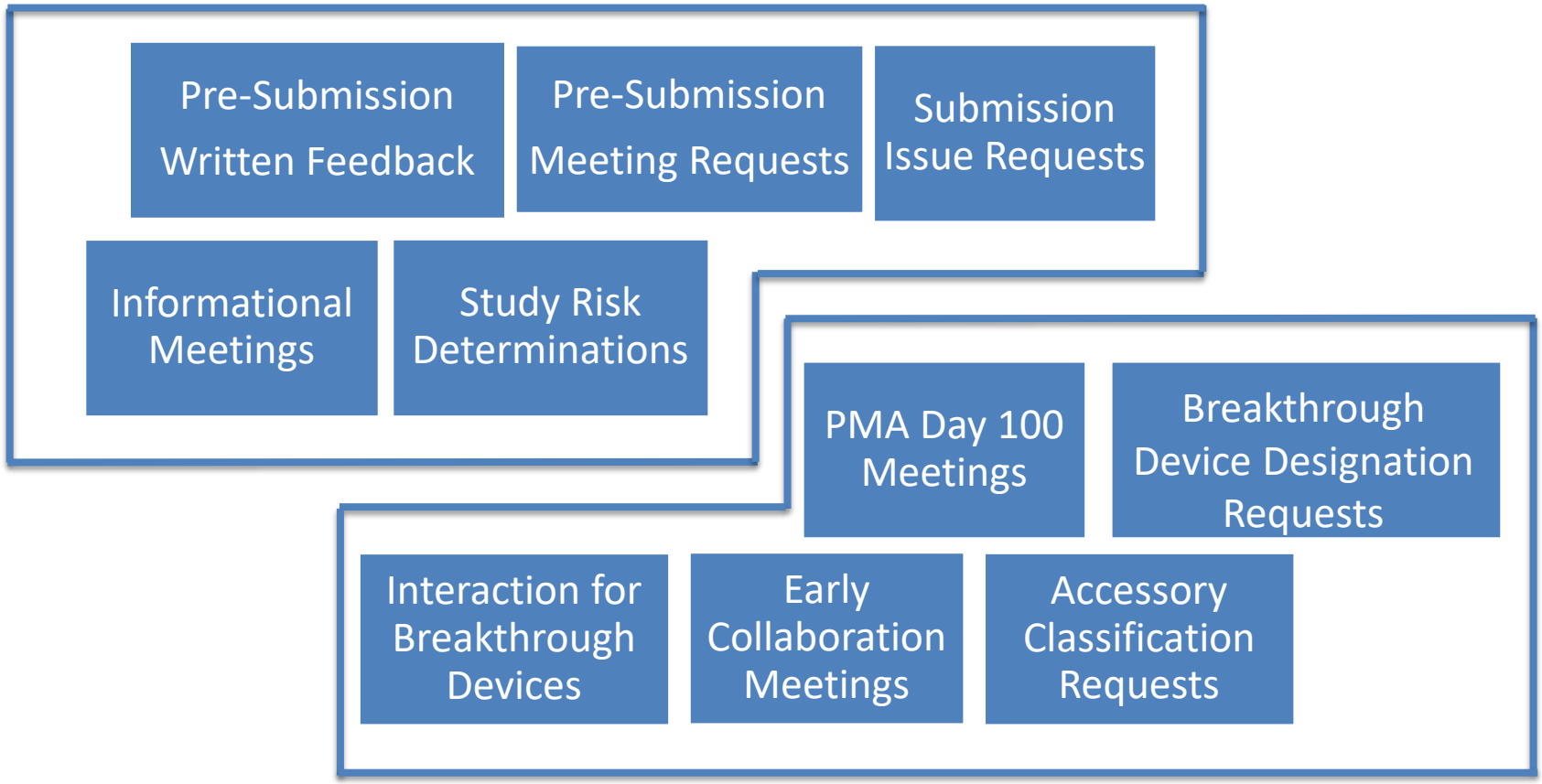
  Pre-submissions, Study Risk Determinations, Informational Meetings
- Investigational Device Exemptions (IDEs)
- Clinical Studies to address Postmarket Questions
- Real World Evidence

# Introduction to Q-Submissions

- Mechanism to request FDA feedback regarding potential or planned regulatory submissions.
- Includes a broad range of submissions covering different types of requests.
- Different Q-submission types include written feedback, in-person meetings, and/or teleconference.
- May be used to address questions about clinical evidence at any stage of device development.

FDA Guidance Document: ***Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program:*** https://www.fda.gov/media/114034/download

# Q-Submission Types



# Pre-Submissions

Requests for feedback from the FDA regarding future premarket submissions, Accessory Classification Requests, or CLIA Waivers

Pre-Submission Meeting

Pre-Submission Written Feedback

- Specific questions
- Recommend 3-4 substantial topics
- Help guide product development, develop protocols, prepare premarket applications

# Study Risk Determinations

Requests for a risk determination for proposed clinical study

- FDA provides final decision in writing
- Risk determination for proposed clinical study defined in 21 CFR 812
- Possible final determinations:

Significant Risk | Non-Significant Risk | Exempt

# Informational Meetings

Meeting intended to share information with the FDA

- No official feedback
- Interactive dialogue
- Topics can include:
  - Device development
  - New technologies
  - Topics outside the scope of other Q-Submissions

# Challenge Question

A Q-submission may be used to request feedback during which stage of device development?

A. Preclinical testing
B. Clinical study design
C. Marketing submission
D. Postmarket study design
E. All of the Above

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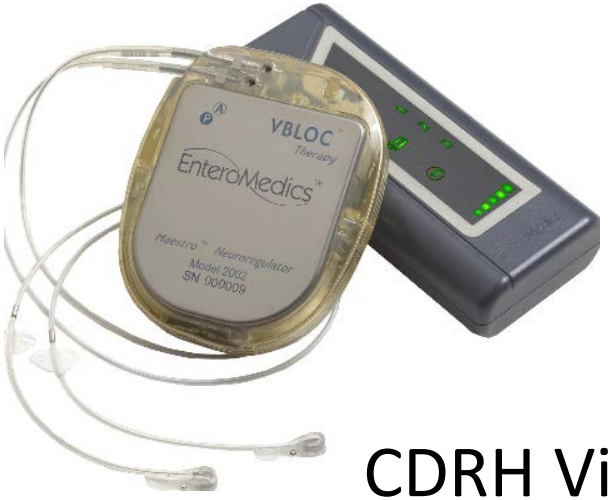
- Introduction
- Q-Submissions
- **Investigational Device Exemptions (IDEs)**
  - IDE Regulations, Application, Decisions, Tips
- Clinical Studies to address Postmarket Questions
- Real World Evidence and NEST

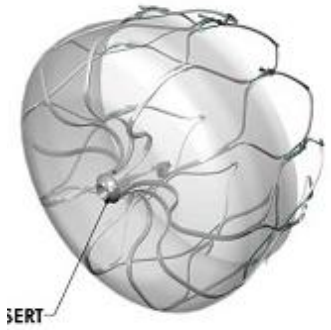
# IDE Regulatory Framework

- Important terms
- What is an IDE and when is one needed?
- Study risk determination




## CDRH Vision Statement

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

# Section 520(g) of the FD&C Act

*"It is the purpose of this subsection to encourage, to the extent consistent with the **protection of the public health and safety** and with ethical standards, the **discovery and development of useful devices** intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose."*

# “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

# 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

21 CF 812.1

# Sponsor

Individual, partnership, corporation, association, scientific or academic establishment, Government agency or organizational unit of a Government agency, and any other legal entity who:

- Takes responsibility
- Initiates investigation

21 CFR 812.3(l) and (n)

# Investigator

An individual or responsible leader of a team who:

- Actually conducts a clinical investigation
- Under whose immediate direction a test article is administered, dispensed, or used on a research subject

21 CFR 812.3(i)

# Sponsor Responsibilities

- Select qualified **investigators** and provide them with information they need to conduct the investigation properly
- 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**

21 CFR 812 Subparts C and G

# Investigator Responsibilities

- Ensure investigation is conducted according to **investigational plan, signed agreement, FDA or IRB conditions of approval** and **applicable FDA regulations**.
- Protect **rights, safety, welfare** of subjects under care.
- Obtain **informed consent** in accordance with 21 CFR 50.
- Supervise **device use** and comply with final **device disposition** directions.
- Maintain adequate **records** (e.g., informed consent, observations including AEs, protocol deviations, etc.)
- Grant **inspections** to FDA (establishments and records)
- Prepare and submit **reports** (e.g., annual progress, final, etc.)

21 CFR 812 Subparts E and G

# Sponsor-Investigator

- Individual who, alone or with others, initiates & actually conducts an investigation:
  - Under whose immediate direction a test article is administered, dispensed, or used
  - The obligations include those of an investigator and a sponsor.

21 CFR 812.3(o)

# Does the Study Fall Under 812?

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.

# When do IDE Regulations Apply?

- *21 CFR 812.2(a)*

**Clinical Investigation** to determine device safety and effectiveness

- New device or

  New use of legally marketed device (e.g., "off-label use")
- Possible Examples:
  - Sponsor-investigator/Academic studies - even if no marketing application planned
  - Study to gain initial safety and effectiveness information to support further study (e.g., feasibility study)
  - Manufacturer-sponsored study to support marketing application [PMA, HDE, 510(k) or De Novo]

# When is an IDE Needed?

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

| | | |
|---|---|---|
| **Significant Risk (SR)** | *812.3(m) Full Requirements* | Requires Approval from FDA<br>IRB review required.<br>A significant risk ***device*** presents a **potential for serious risk to the health, safety, and welfare of a subject…** |
| **Non-Significant Risk (NSR)** | *812.2(b) Abbreviated Requirements* | No submission to FDA required.<br>IRB review required. |
| **Exempt** | *812.2(c)* | No submission to FDA required.<br>IRB review required.<br>*Specific Categories of Exempt Studies in 812.2(c)(1)-(7)* |

FDA Guidance Document: ***Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies***

https://www.fda.gov/media/75459/download

# IRB Role in Risk Determination

- **Sponsor** makes initial determination
- **IRB reviews** the sponsor's determination (21 CFR 812.2(b)(1)(ii))
  - Information provided by the sponsor includes device description, prior investigations, investigational plan, subject selection, risk assessment and rationale used in making its SR or NSR determination
- If the IRB disagrees with a sponsor's NSR assessment, the IRB must inform the clinical investigator, and where appropriate, the sponsor. (21 CFR 812.66)
- FDA is available to help and is final arbiter when IDE is submitted or if asked by sponsor, investigator, or IRB

FDA Guidance Document: ***Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies***

https://www.fda.gov/media/75459/download

# Challenge Question

True or False:
The IDE regulations in 21 CFR 812 describe three tiers of study category with different levels of regulatory oversight: significant risk, non-significant risk, and exempt.

# Challenge Question

**True** or False:

The IDE regulations in 21 CFR 812 describe three tiers of study category with different levels of regulatory oversight: significant risk, non-significant risk, and exempt.

# The IDE Application

- Application package
- Review considerations
- Decisions and letters

# IDE Application Contents

**812.20(b) IDE Application**

- Sponsor name/address
- Report of prior investigations & investigational plan
- Description of manufacturing
- Investigator agreements
- Certification of investigator agreements
- IRB information
- Other institutions
- Sales information
- Environmental assessment
- Labeling
- Informed consent materials

**812.27 Report of Prior Investigations**

- Bibliography
- Summary of unpublished information
- GLP and GCP compliance statements

**812.25 Investigational Plan**

- Purpose
- Protocol
- Risk analysis
- Device description
- Monitoring procedures
- Labeling
- Informed consent materials
- IRB information
- Other institutions
- Records and reports

FDA Device Advice – IDE Application: https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/ide-application

# FDA Review of IDE 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

# 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)
  - May inform device design (early feasibility study)

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

# Feasibility vs. Pivotal IDEs: Example FDA Review Considerations

| | Early Feasibility (EFS) | Traditional Feasibility | Pivotal |
|---|---|---|---|
| Number of subjects | ~15 or less | Variable, but can be large (e.g., 100) | Typically large and often Statistically Driven |
| Study Purpose | Obtain initial insights and gather safety information | Capture preliminary S and E information and to plan a pivotal study | Capture definitive evidence of safety and effectiveness |
| Device Design | Changes anticipated | Near final or final design | Final design |
| Justification for study initiation | May rely on device design and leveraged information | Generally supported by more nonclinical (or prior clinical) data than EFS | Relies on comprehensive nonclinical and prior clinical data |
| Statistical Analysis Plan | Generally N/A | Generally N/A | Appropriate for Study Design/Hypothesis |
| Primary Focus of FDA Review? | Primarily safety. Why is clinical testing next step? | Primarily safety. Will study generate useful information for further clinical study? | Will the study as designed support the desired claims and indications for use? |

Sponsors may choose **not** to conduct all three types of studies in the United States or at all.

# Feasibility vs. Pivotal IDEs: Example FDA Review Considerations

| | Early Feasibility (EFS) | Traditional Feasibility | Pivotal |
|---|---|---|---|
| Study Concept | Reasonable Study Conceptually? | | |
| Enrollment criteria? | Appropriate for Study Goals? | | |
| Mitigation of potential risks | Adequate for Device and Study Goals? | | |
| Informed Consent | Appropriate for Device and Study Risks? | | |
| Study Conduct and Monitoring | Appropriate for Study Design? | | |

Sponsors may choose **not** to conduct all three types of studies in the United States or at all.

# FDA Decisions and Letters

- **Approval**
  - Approves the study 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 Guidance Document: ***FDA Decisions for Investigational Device Exemption Clinical Investigations*** https://www.fda.gov/media/81792/download

# Other Elements of FDA Letters

Concerns regarding **study design not related to protecting study subjects** conveyed as attachment to decision letter

**Study Design Considerations -** Study design recommendations unrelated to subject protection, e.g.,

- Primary, secondary endpoints and study success criteria
- Randomization, blinding, and control plan
- Follow-up duration and assessments, case report forms
- Enrollment criteria, Statistical plan, etc.

**Future Considerations -** Issues relevant for future submissions, e.g.,

- Testing needed for future marketing application
- Recommendations for future pivotal study design
- Limitations on future claims based on study design

# Summary: FDA Letters

- 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.

FDA Guidance Document: ***FDA Decisions for Investigational Device Exemption Clinical Investigations*** https://www.fda.gov/media/81792/download

# Other IDE 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

# Tips for IDE Submission

- Common pitfalls
- Recommendations

# Common Pitfalls for Submissions

- Inadequate detail regarding the **device or the methods** used in the study
- Inadequate **basic safety/performance** data
  - Describe device components and materials, principle of operation and key characteristics
  - Clarify version of device tested compared to version for clinical study
  - Describe preclinical test conditions, success criteria, and results
- Inadequate **justification** for why clinical data are truly needed at this stage.
  - Rationale why preclinical tests were conducted and support clinical study
- Inadequate **procedures** in place (or discussion of those procedures) to **maximize patient safety**
- Inadequate **informed consent** document

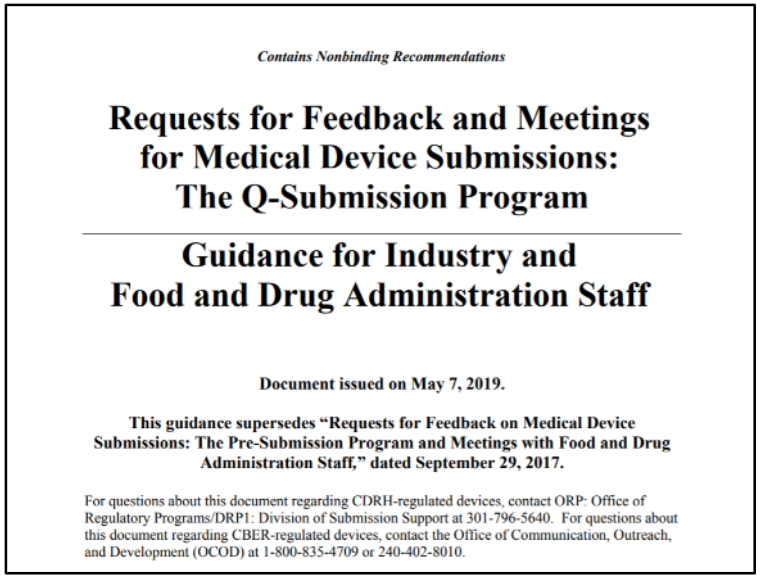
# Tips for Successful IDE Submissions

- **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

*FDA Device Advice – IDE Application: https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/ide-application

# 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



*Contains Nonbinding Recommendations*

**Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program**

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

**Document issued on May 7, 2019.**

**This guidance supersedes "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff," dated September 29, 2017.**

For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs/DRP1: Division of Submission Support at 301-796-5640. 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.

# 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

# Agenda

- Introduction
- Q-Submissions
- Investigational Device Exemptions (IDEs)
- **Clinical Studies to address Postmarket Questions**
  - Post Approval Studies and Postmarket Surveillance
- Real World Evidence and NEST

# FDA Postmarket Evaluation and 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 (PAS) Program 21 CFR 814.82, FD&C Act Section 513(a)(3)(C) | | | ✓ |
| Postmarket Surveillance Program FD&C Act Section 522, 21 CFR 822 | | ✓ | ✓ |

# PAS Program (21 CFR 814.82)

# Section 522 Program (21CFR 822)

# FDA Authority: PAS Program

- Postmarket Monitoring for Class III devices
- Section 513(a)(3)(C) of FD&C Act (21 U.S.C. 360c)
  - … the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.
- CFR 21 Section 814.82(a)(2) for PMAs and CFR 21 Section 814.126(a) for HDEs
  - Post-Approval studies can be imposed at time of approval to continue evaluation and reporting on the safety, effectiveness*, and reliability of the device for its intended use.

* Probable benefit for HDEs

# Criteria for PAS Need

- **Breakthrough Program:** To facilitate new technology and allow devices to, when appropriate, reach market distribution sooner, with additional postmarket data collection as CoA.
- **Long Term Evaluation Descriptive - Extended Follow-up of Premarket Cohorts:** Leveraging premarket cohorts by extending their follow up for long-term data to be obtained postmarket as a CoA.
- **Long Term Evaluation Benefit/Risk Question - Data are not available Otherwise:** To address unanswered questions that are not necessary to demonstrate premarket reasonable assurance of device safety and effectiveness. This includes benefit risk questions of short term, learning curve/training, performance in specific subgroups, or adverse events.
- **Non-Clinical:** Questions on laboratory, bench testing (e.g., wear testing, fatigue testing), animal testing (e.g., device or material implanted in animal), or explant/failure analysis.

# FDA Authority: Section 522 Studies Program

- Postmarket Surveillance for Class II and III devices
- Section 522 of the FD&C Act (21 U.S.C. 360 l)
  - Statutory Criteria (next slide)
- CFR 21 Section 822
- 36 months surveillance
  - May order longer surveillance if expected significant use in pediatrics
- Section 616 of the FDA Safety Innovation Act (FDASIA)
  - Orders can be issued at the time of clearance or approval
  - Surveillance must commence within 15 months of order issuance

# 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 | *Expected* 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.** |

# Examples of situations that may raise postmarket surveillance need

- Confirm the nature, severity, or frequency of suspected problems reported in adverse event (AE) reports or in published literature
- Obtain more experience with a change from hospital use to use in the home or other environment or with broader patient populations
- Address long term performance of implantable and other devices
- Assess potential association between a device and AEs, once the device is on the market
  - unexpected or unexplained serious adverse events
  - change in the nature of serious adverse events
  - increase in the frequency of serious adverse events

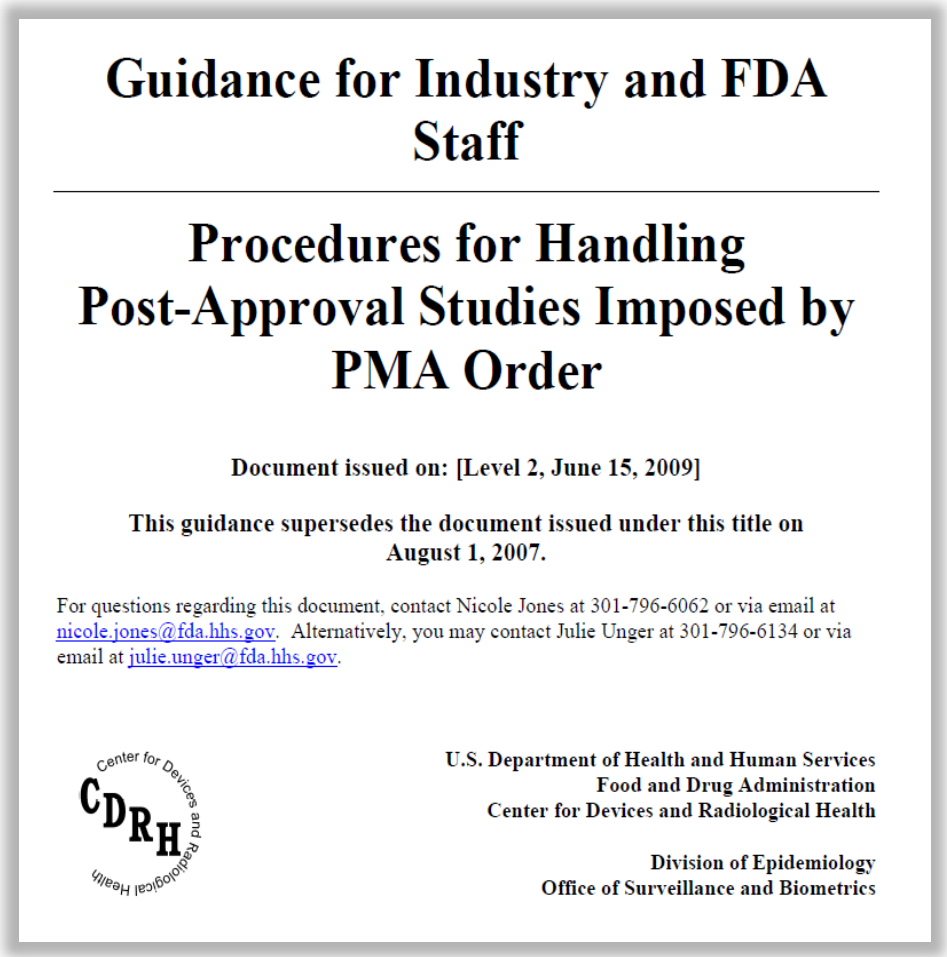
# Components of Protocols/Plans for Postmarket Clinical Studies

- Study questions, hypothesis, study design, population
- Primary and secondary endpoints
- Description of data collection procedures
- Duration of follow-up and schedule
- Statistical analysis plan

# Postmarket Clinical Study Compliance

- 21 CFR 50 Protection of Human Subjects
- 21 CFR 56 Institutional Review Boards

# FDA Guidance Documents



**Guidance for Industry and FDA Staff**

**Procedures for Handling Post-Approval Studies Imposed by PMA Order**

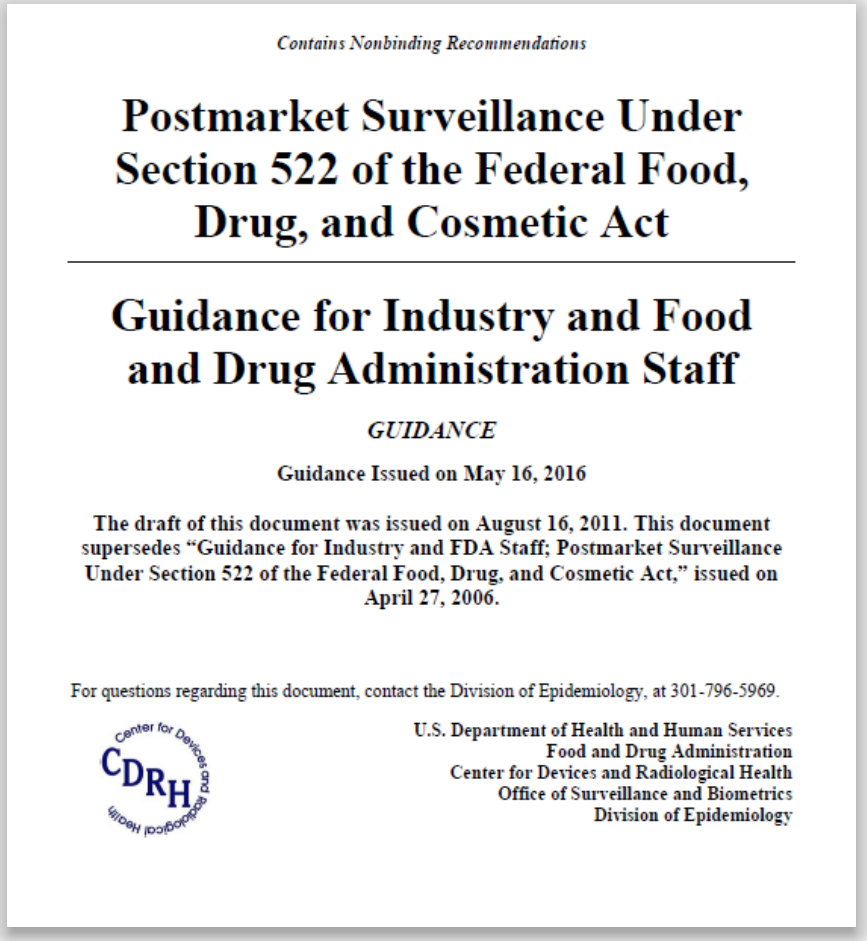
**Document issued on: [Level 2, June 15, 2009]**

**This guidance supersedes the document issued under this title on August 1, 2007.**

For questions regarding this document, contact Nicole Jones at 301-796-6062 or via email at nicole.jones@fda.hhs.gov. Alternatively, you may contact Julie Unger at 301-796-6134 or via email at julie.unger@fda.hhs.gov.

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

**Division of Epidemiology**
**Office of Surveillance and Biometrics**



*Contains Nonbinding Recommendations*

**Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act**

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

***GUIDANCE***

**Guidance Issued on May 16, 2016**

**The draft of this document was issued on August 16, 2011. This document supersedes "Guidance for Industry and FDA Staff; Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act," issued on April 27, 2006.**

For questions regarding this document, contact the Division of Epidemiology, at 301-796-5969.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Devices and Radiological Health**
**Office of Surveillance and Biometrics**
**Division of Epidemiology**

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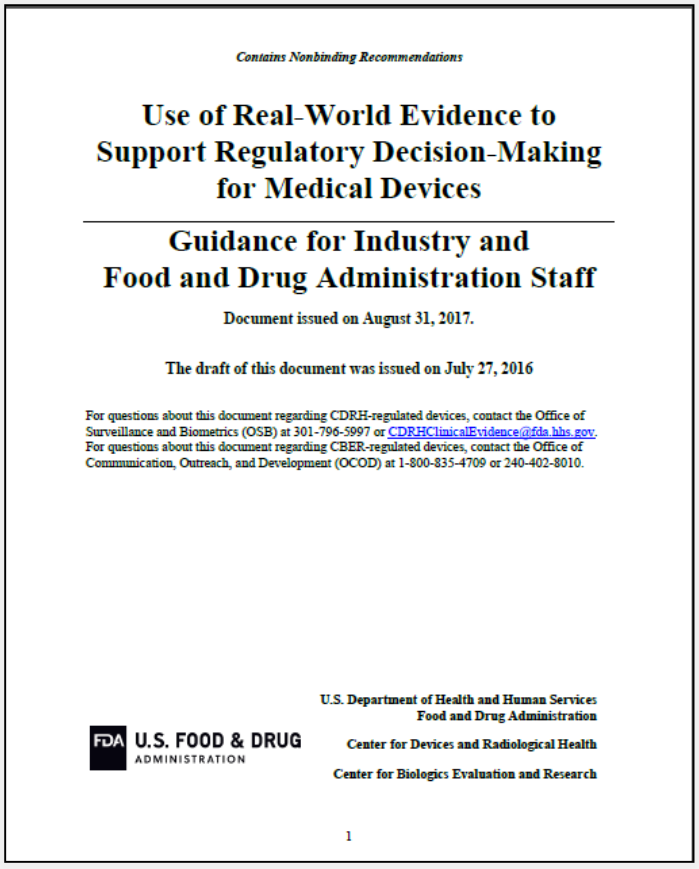
- Introduction
- Q-Submissions
- Investigational Device Exemptions (IDEs)
- Clinical Studies to address Postmarket Questions
- **Real World Evidence and NEST**
  - RWE guidance document, Data Quality, NEST

# Context for RWE Guidance

- FDA Reauthorization Act (*FDARA) including MDUFA IV commitment to use of real-world evidence to support device pre/postmarket decisions*
- National Evaluation System for health Technology (NEST)
- *2016-2017 CDRH Strategic Priorities*
- *Guidance issued to clarify how RWE may be used to support regulatory decisions*

# Real-World Evidence Pathway



*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

Real world Data Sources

EHR / EMR

Device / Patient Registries

Device Generated Data

Mobile Devices

Pharmacy / Lab Data

Administrative Databases (e.g. Claims)

# Turning Data into Evidence

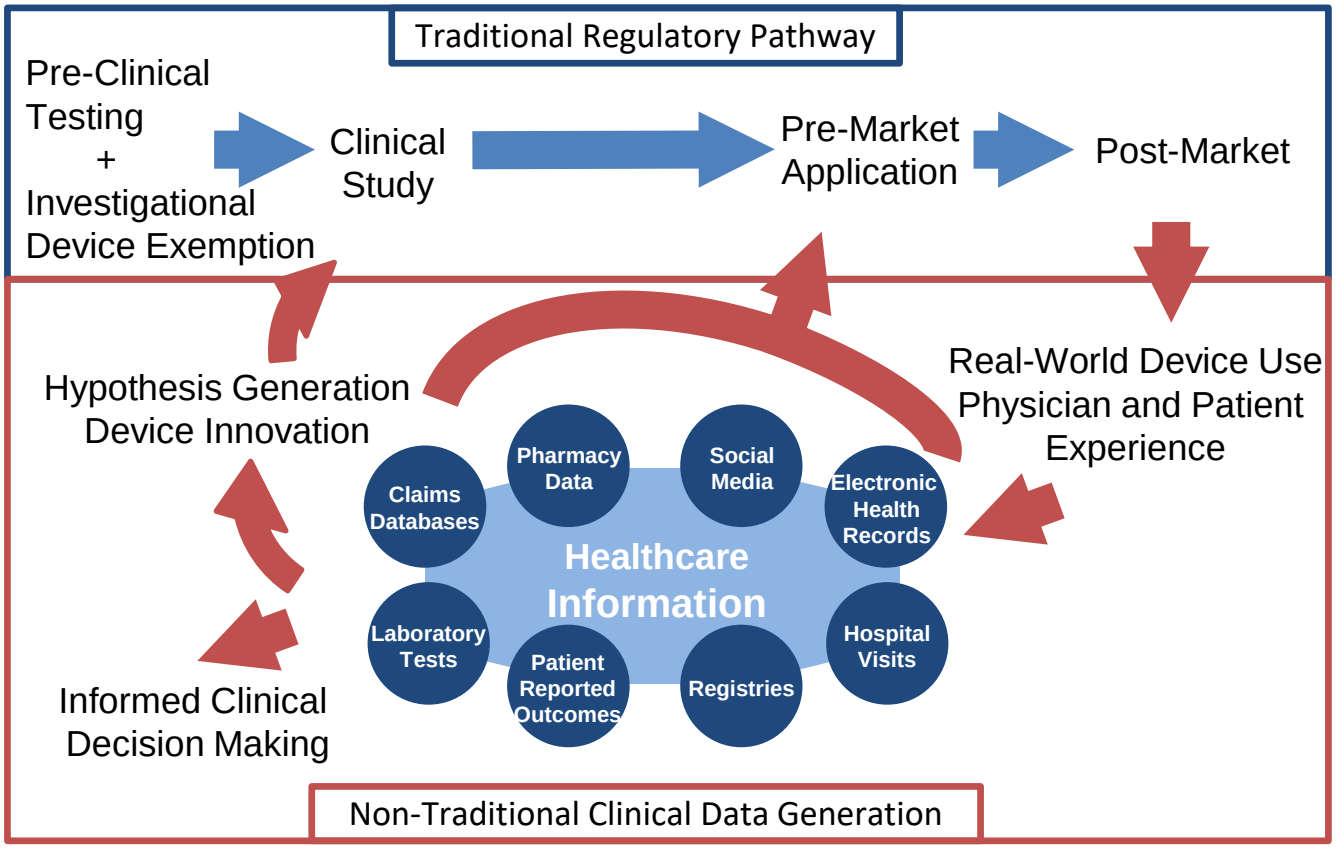
**Real-World Data (RWD)**
Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

**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



# 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**

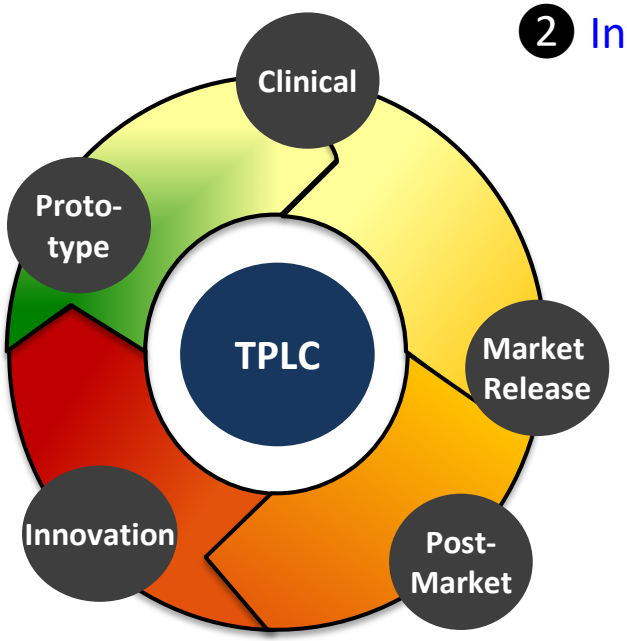
Are there reasonable assurances, based on valid scientific evidence that probable benefits to health from use of the device *outweigh any probable risks? [860.7(d)(1)]*

**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)]*

# Potential Usages of RWE for Total-ProductLife-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

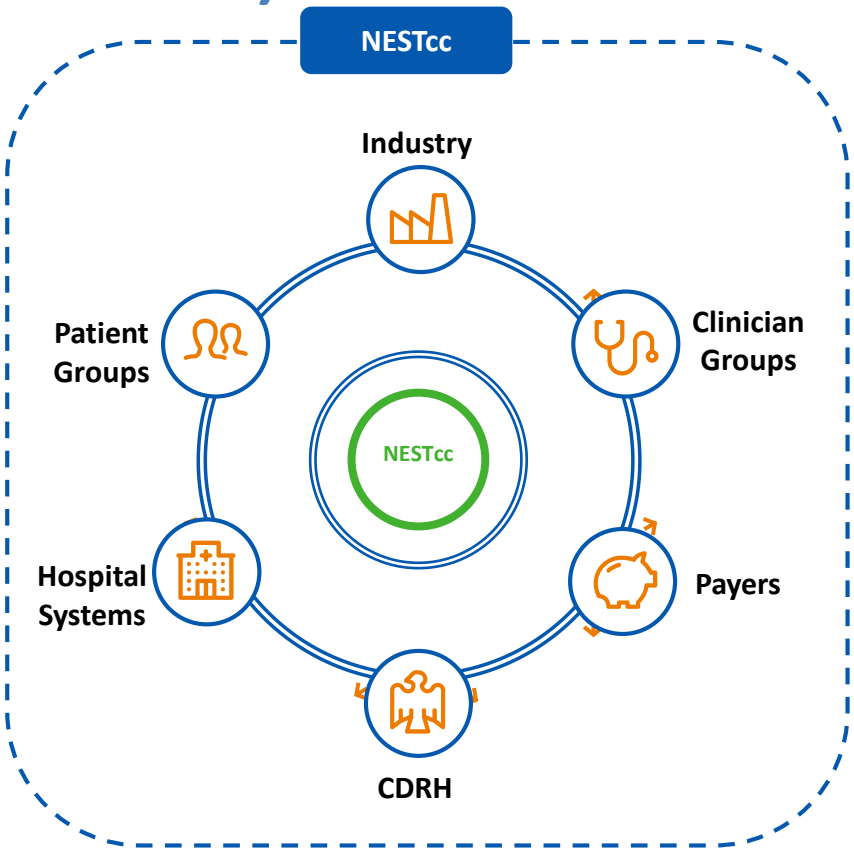
FDA U.S. FOOD & DRUG ADMINISTRATION

# National Evaluation System for Health Technologies (NEST)

# 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



# NEST Coordinating Center

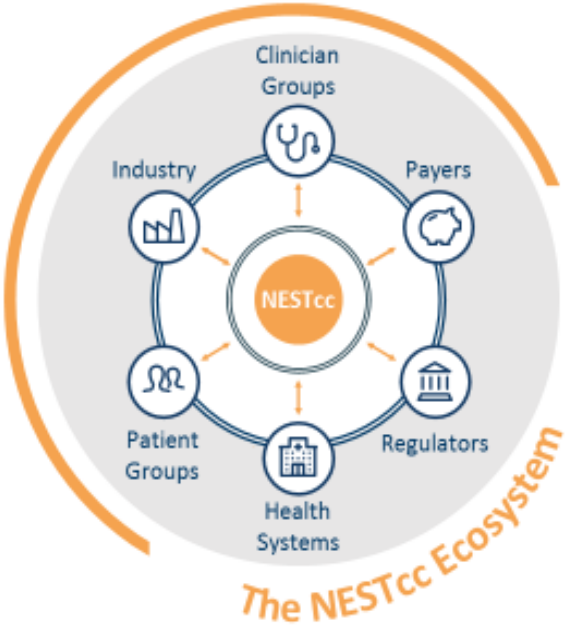
NESTcc's MISSION & VISION

## Mission

To accelerate the development and translation of new and safe health technologies, leveraging Real-World Evidence (RWE), and innovative research.

## Vision

To be the leading organization within the health technology and medical device ecosystem for conducting efficient and timely high-quality Real-World Evidence (RWE) studies throughout the Total Product Life Cycle (TPLC).

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# NEST Coordinating Center

## BUILDING NESTcc'S DATA NETWORK

NESTcc surveyed its Network Collaborators to determine current capabilities, gaps, and priority areas.

**12**
**Network Collaborators**

Duke University Health System • HealthCore • Lahey Clinic • Mayo Clinic • MDEpiNet • Mercy • NYC-CDRN • OneFlorida • PEDSnet • STAR • Vanderbilt University • Yale New Haven Health System

**Network Collaborators represent**

**195** Hospitals

**3,942+** Outpatient Clinics

**Patient data represents**

**494M+*** Patient Records

**Common data models**

- ✓ I2b2
- ✓ OMOP
- ✓ PCORnet
- ✓ Sentinel

**Network Collaborators report regular data refreshes**


**Most cited expertise**

- ✓ Cardiovascular and Cardiac Surgery
- ✓ Women's Health
- ✓ Neurosurgery
- ✓ Gastroenterology
- ✓ Orthopedic

*Does not account for duplicate records

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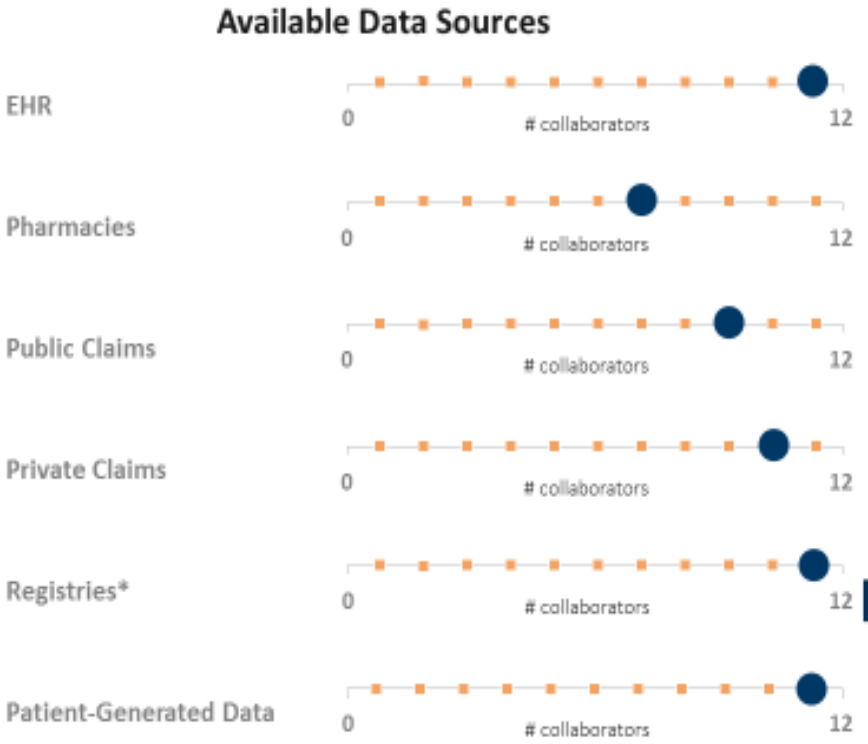
*Numbers reflect data as of February 2018*

# NEST Coordinating Center

## ACCESS TO A RANGE OF RWD SOURCES

The collaborators comprising the NESTcc Data Network have access to a range of available data sources, including those listed below.





***Registries Include (but are not limited to):**

- Anesthesia Quality Institute's National Anesthesia Clinical Outcomes
- Cardiac Catheterization
- Cardiogenic Shock
- Immunization
- Implant registries
- Integrated tumor
- International Consortium Lower-GI
- American College of Surgeons National Surgical Quality Improvement Program
- Oncology
- Pediatric Cardiomyopathy
- Prostate Ablation-Related Energy Devices
- Robotic Surgery
- Society of Thoracic Surgeons National Database
- Society for Vascular Surgery
- Thalassemia Clinical Research Network - Thalassemia Registry
- Vital Records (Birth and Death)

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# Regulatory Submission Application Process

# Processing of Regulatory Submissions

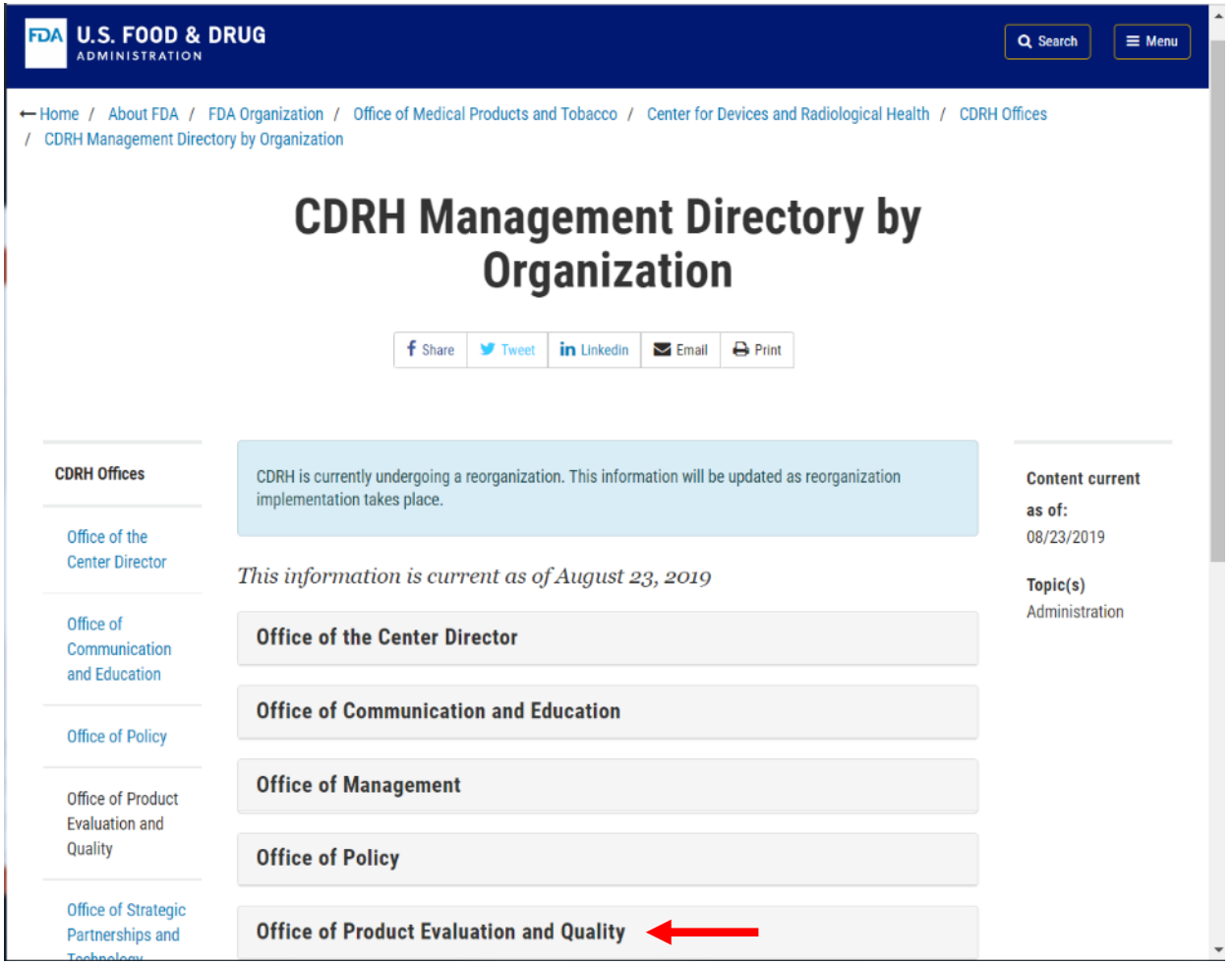
- CDRH Document Control Center and eCopy instructions:
  https://www.fda.gov/medical-devices/how-study-and-market-your-device/ecopy-program-medical-device-submissions

To whom should the submission be addressed?

- CDRH will login and triage all submissions to identify the appropriate review group in the Center.

- NOT necessary to identify a review team or lead reviewer.

# CDRH Directory




https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization

# CDRH Directory

| | | |
|---|---|---|
| **Office of Health Technology 5 (OHT 5: Neurological and Physical Medicine Devices)** | | |
| Office Director | Carlos Pena, Ph.D. | 301-796-6610 |
| Deputy Office Director | John Marler, M.D. | 301-796-4221 |
| Deputy Office Director | Vacant | |
| Chief Medical Officer | Christopher Loftus, M.D. | 301-796-4377 |
| Associate Director | Michael Hoffmann | 301-796-6610 |
| Associate Director for Operations | CDR Avena Russell | 301-796-3805 |
| Associate Director for Professional Development | Vacant | |
| Assistant Director for Professional Development | Vacant | |
| Safety Signal Manager | LT Kelliann Wachrathit (Acting) | 301-796-2753 |
| **Division of Health Technology 5 A (Neurosurgical, Neurointerventional and Neurodiagnostics)** | | |
| Director | Vacant | |
| Assistant Director Neurosurgical Devices | Matthew Krueger | 301-796-5540 |
| Assistant Director Neurointerventional Devices | Xiaolin Zheng, Ph.D. | 301-796-2823 |
| Assistant Director Neurodiagnostics Devices | Jay Gupta | 301-796-2795 |
| **Division of Health Technology 5 B (Neuromodulation and Rehabilitation Devices)** | | |
| Director | Vacant | |
| Assistant Director Neurostimulation-Neurology Devices | Timothy Marjenin | 301-796-6610 |

https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization

# Resources

- Guidance: FDA Decisions for IDE Clinical Investigations

  www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf

- 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

- Sponsor's Responsibilities For Significant Risk Device Investigations

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

# 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

- Clinical Trial and IDE Guidance Documents

  https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/ide-guidance

# Resources

- Procedures for Handling Post-Approval Studies Imposed by PMA Order

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-handling-post-approval-studies-imposed-pma-order

- Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act

  https://www.fda.gov/medical-devices/postmarket-requirements-devices/522-postmarket-surveillance-studies

# Resources

- Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval

- Breakthrough Devices Program: Guidance for Industry and Food and Drug Administration Staff

  https://www.fda.gov/media/108135/download

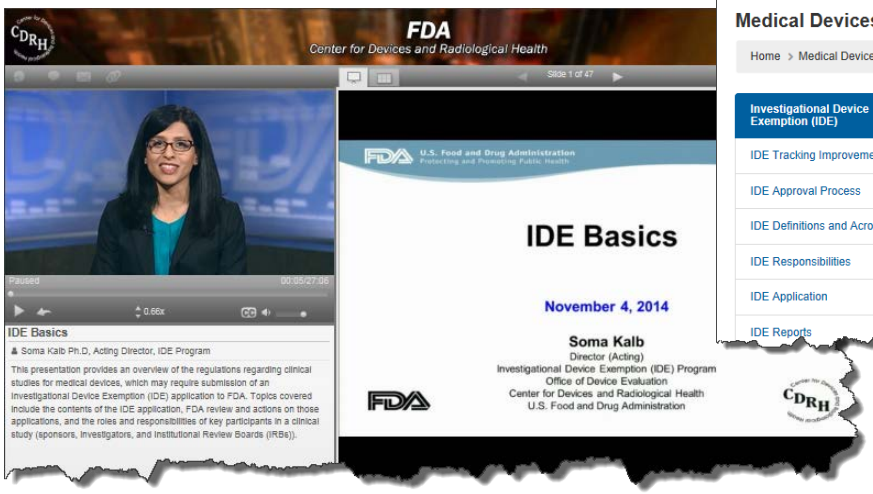
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

  https://www.fda.gov/media/99447/download

# Resources

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

- **Device Advice**
  - Investigational Device Exemptions
  - Breakthrough Devices (Expedited Access Pathway)
  - Postmarket Requirements




# Questions?