Issues in Clinical Trial Designs for Devices

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Clinical Investigator Training Course
November 12, 2019

Learning Objectives

- Understand the medical device review process
- Identify unique aspects of device trials
- Review CDRH's strategic priorities and how they impact device studies

What is a Medical Device?

The Section 201(h) of the Food, Drugs and Cosmetics Act defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized.

- **As simple as a tongue depressor or a thermometer**
- **As complex robotic surgery devices**

Medical Device Classification

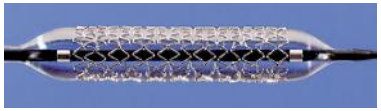
- Class I
  - General Controls
  - Most exempt from premarket submission

- Class II
  - Special Controls
  - Premarket Notification [510(k)]

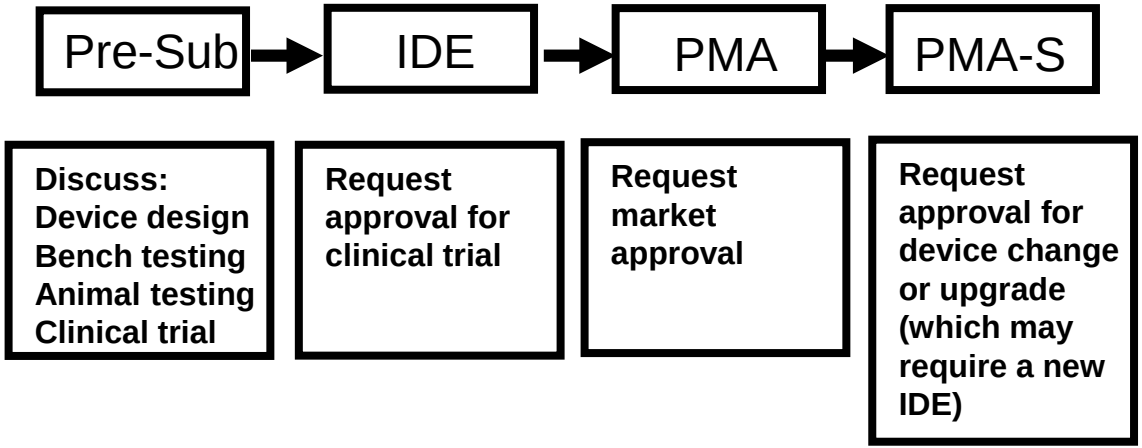
"Substantial Equivalence"
10-15% have clinical data

- Class III
  - Premarket Approval
  - Require Premarket Application [PMA]

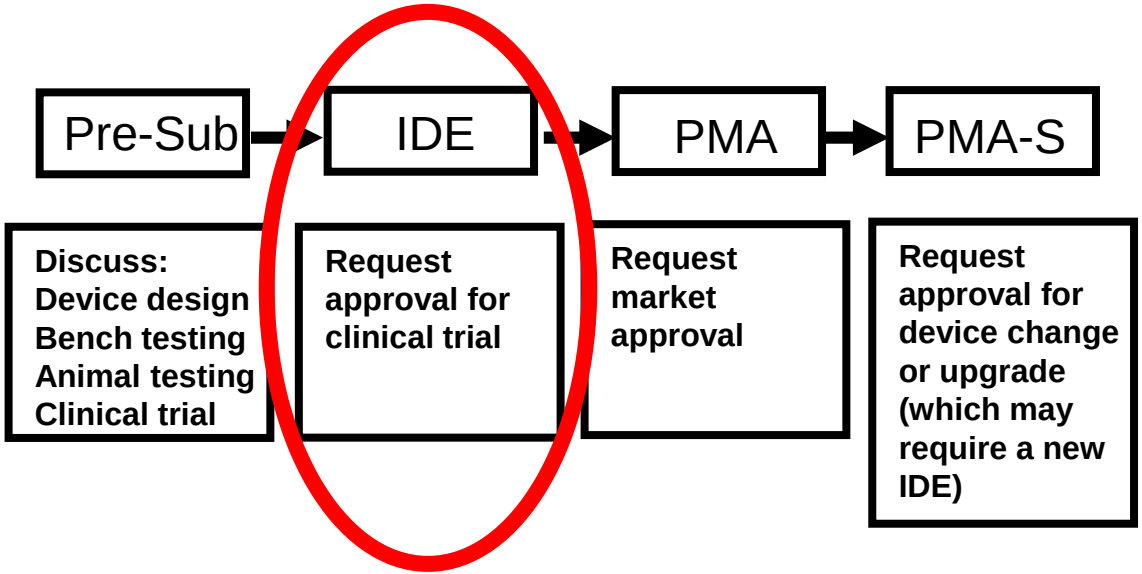
"Reasonable Assurance of Safety and Effectiveness"
Bench-Animal-Clinical



Stages of review for PMA device



Today's focus:



What is an Investigational Device Exemption (IDE)?

FDA approval of an IDE is required for US human study of a significant risk device which is not approved for the indication being studied.

Types of IDEs

- Feasibility study
  - May provide support for a future pivotal study or may be used to answer basic research questions
  - Not intended to be the primary support for a marketing application
  - Endpoints and sample size generally not statistically driven
  - Generally ~10-40 patients but may be larger
  - FDA review is primarily focused on safety and whether the potential benefit or value of the data justifies risk

  - Early Feasibility Studies (EFS) program supports research early in device development (generally < 15 subjects)

Types of IDEs

- Pivotal study
  - Generally intended as the primary clinical support for a marketing application
  - Designed to demonstrate a “reasonable assurance of safety and effectiveness”
  - Endpoints and sample size statistically driven
  - Designed to assess both safety and effectiveness
  - FDA review is much more complex

Primary Endpoint Design

- Should evaluate the safety and effectiveness of the device in the population expected to be indicated.

- Generally divided into
  - 1 or more “safety” endpoints
  - 1 or more “effectiveness” endpoints

- A study would be considered successful if both the safety and effectiveness endpoints are met.

Sample Size & Follow-Up

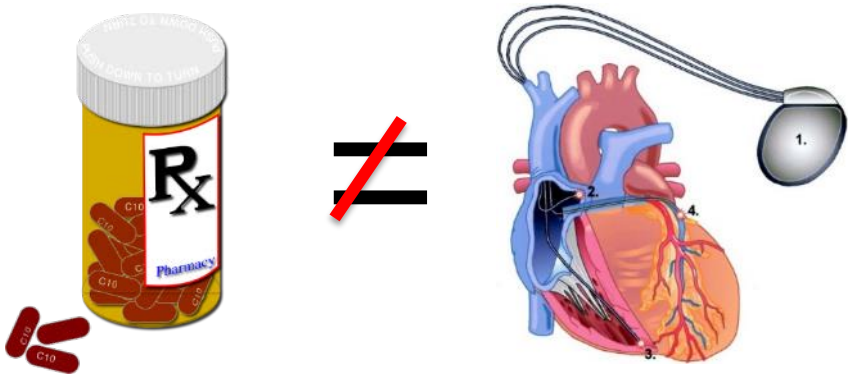
- Driven by either:
  - Primary safety endpoint
  - Primary effectiveness endpoint

- Minimum number of patients and/or minimum duration of follow-up may be required depending on:
  - Understanding of the safety and effectiveness of the device
  - Concerns regarding durability of device safety or effectiveness

Device Trials are Unique

Challenges in medical product development are different for drugs and devices

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



Considerations for device trials

- Device trials tend to enroll fewer participants
- Many assess iterative improvements
- Device design/procedure may be modified during trial
- Adaptive designs increasingly common
- Existing data can substitute for prospective trial data

Device Study Design Examples

Device	Study Design	N
BioMimics 3D Vascular Stent System (Cardiovascular 10/24/2018)[1]	Prospective, multi-center, single-arm study with performance goal	271
Hydrus Microstent (Ophthalmic 8/10/2018)[3]	Prospective, multi-center, randomized (2:1) superiority study	556
Magtrace and Sentimag Magnetic Localization System (Surgical 7/24/2018)[2]	prospective, multicenter, paired comparison, non-inferiority study	160 (+ OUS data)

[1]P180003, [2]P160053, [3]P170034

Unique Examples

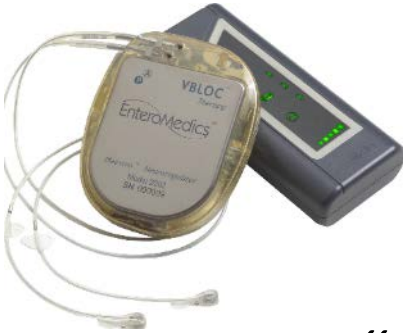
Leveraging Non-Clinical Data

- Revo MRI PMA approved based on modeling data with confirmatory clinical study of 464 subjects

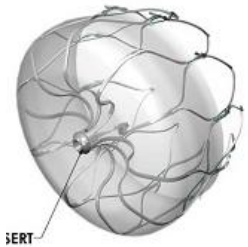
Leveraging Registry Data

- Edwards Sapien Transcatheter Heart Valve expanded indication based in part on data from the Transcatheter Valve Therapy (TVT) registry

Towards our vision



"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

CDRH 2014-2015 Strategic Priorities

Strengthen the Clinical Trial Enterprise

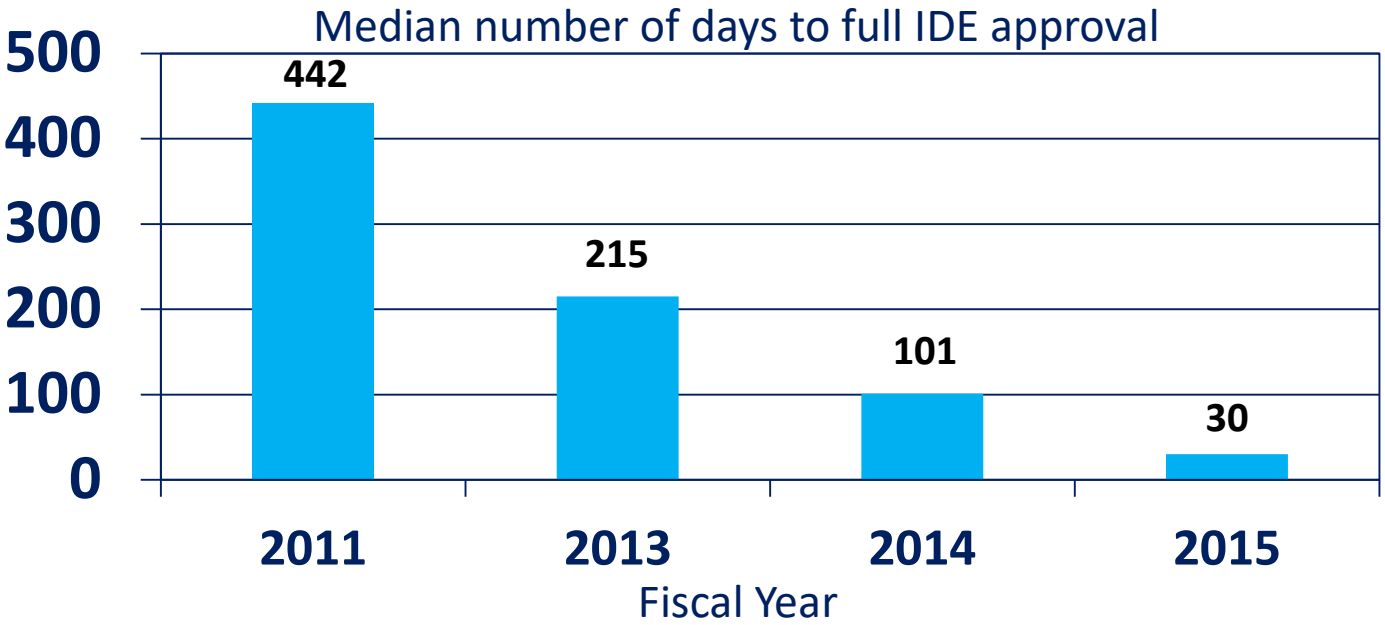
- Improve efficiency of IDE review
- Increase number of Early Feasibility Studies

Strike the Right Pre/Post-Market Balance

Provide Excellent Customer Service

Strengthen the Clinical Trials Enterprise

>90% Reduction in Time to IDE Approval



Flexible Approaches

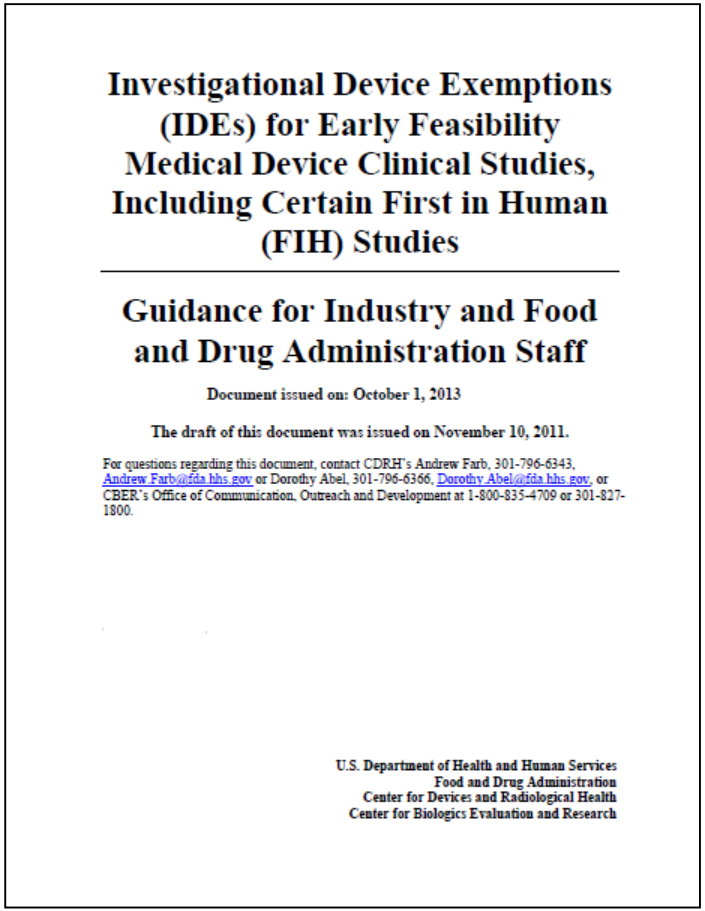
The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry

Amended by
Food and Drug Safety and Innovation Act
and 21st Century Cures

Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions

Early Feasibility Studies

- 17 EFS in FY2013
- 53 EFS in FY2018



Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 1, 2013

The draft of this document was issued on November 10, 2011.

For questions regarding this document, contact CDRH's Andrew Farb, 301-796-6343, Andrew.Farb@fda.hhs.gov or Dorothy Abel, 301-796-6366, Dorothy.Abel@fda.hhs.gov, or CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

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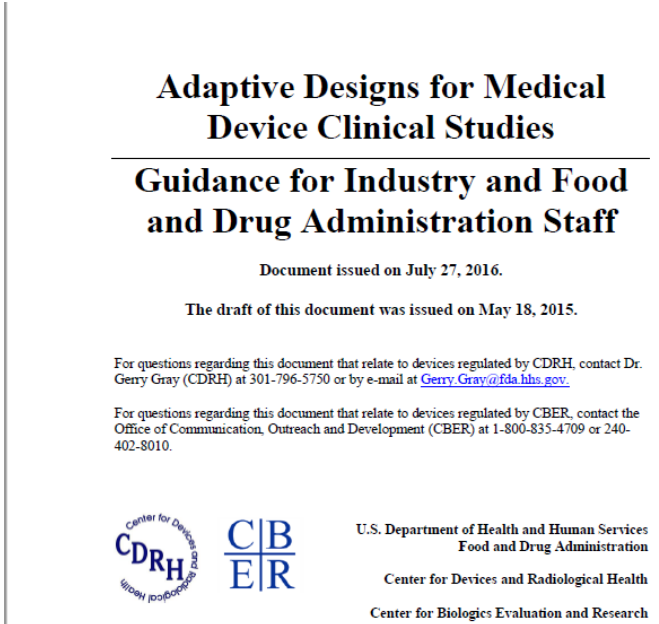
Adaptive Designs

July 27, 2016

- Adjust sample size during study
- Stop early for futility or success
- Modify population during the study



Adaptive Designs for Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on July 27, 2016.

The draft of this document was issued on May 18, 2015.

For questions regarding this document that relate to devices regulated by CDRH, contact Dr. Gerry Gray (CDRH) at 301-796-5750 or by e-mail at Gerry.Gray@fda.hhs.gov.

For questions regarding this document that relate to devices regulated by CBER, contact the Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 or 240-402-8010.

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21st Century Cures Act – Breakthrough Devices

Subtitle F—Medical Device Innovations

SEC. 3051. BREAKTHROUGH DEVICES.

(a) IN GENERAL.—Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.) is amended by inserting after section 515B, as added by section 3034(b), the following:

"SEC. 515C. BREAKTHROUGH DEVICES.

Expedited Access Pathway -> Breakthrough Devices

21st Century Cures Act – Breakthrough Devices

FDA shall:

"(B) take steps to ensure that the design of clinical trials is as efficient and flexible as practicable, when scientifically appropriate;

"(C) facilitate, when scientifically appropriate, expedited and efficient development and review of the device through utilization of timely postmarket data collection with regard to application for approval under section 515(c); and

Medical Device Safety Action Plan (2018)

- Vision for refining oversight of device safety throughout the Total Product Life Cycle (TPLC)

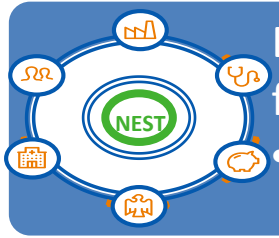
- 5 Focal Areas:
  1. Establish a robust medical device patient safety net in the US
  2. Explore regulatory options to streamline and modernize timely implementation of postmarket mitigations
  3. Spur innovation towards safer medical devices
  4. Advance medical device cybersecurity
  5. Integrate CDRH's premarket and postmarket offices and activities to advance the use of a TPLC approach to device safety

Safer Technologies Program (STeP)

- STeP Draft Guidance Issued September 19, 2019*
- Voluntary program for medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.
- Intended to help patients and health care providers have more timely access to these medical devices
- Key Program Principles:
  - Expedite device development and review
  - Opportunities for interaction to efficiently support device development
  - Increased opportunity for senior management involvement

*https://www.fda.gov/media/130815/download

CDRH 2016-2017 Strategic Priorities



Establish a National Evaluation System for Medical Devices

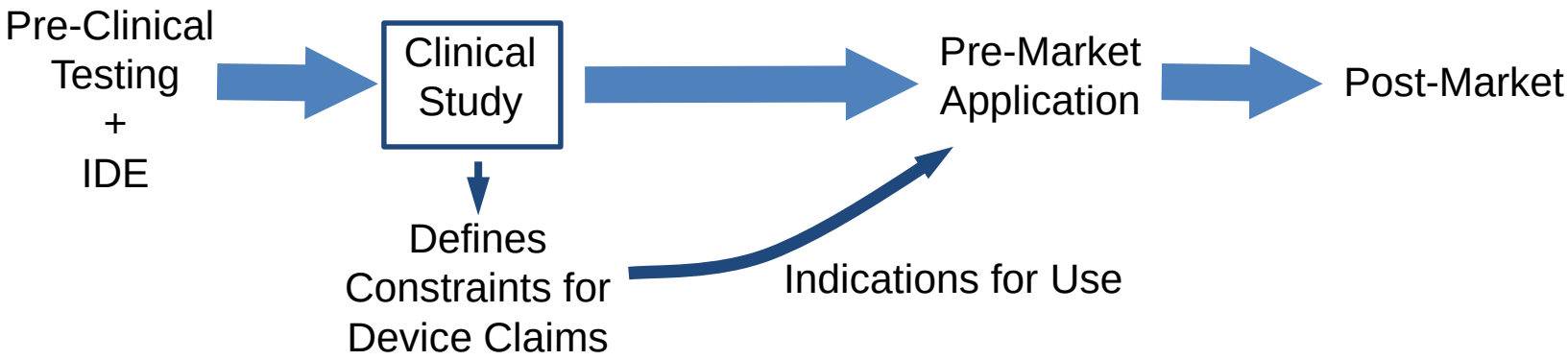
- Access and use of real-world data in decisions

Partner with Patients

- Patient input in regulatory decisions
- Trial design and PROs

Promote a Culture of Quality and Organizational Excellence

Evidence in Regulatory Decisions

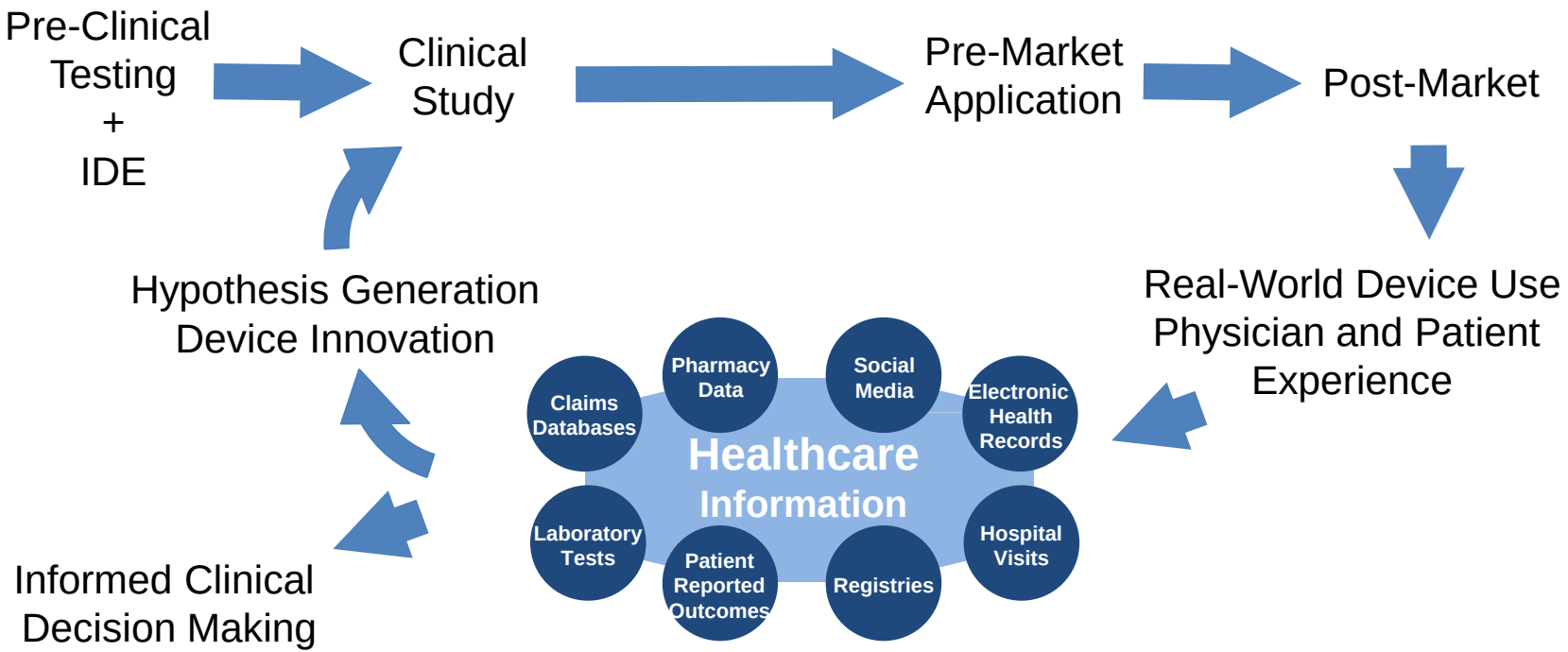


Evidence in Regulatory Decisions

Pre-Clinical Testing + IDE → Clinical Study → Pre-Market Application → Post-Market

Post-Market → Real-World Device Use Physician and Patient Experience

Evidence in Regulatory Decisions



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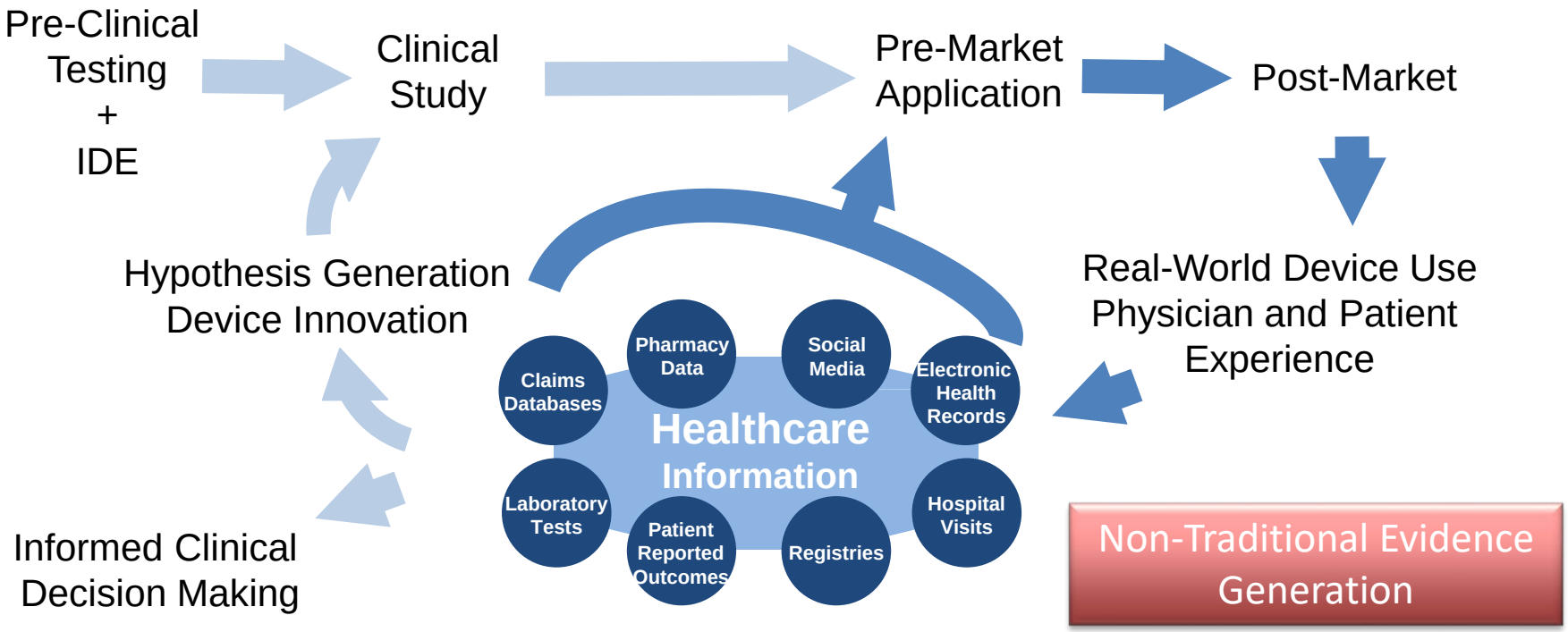
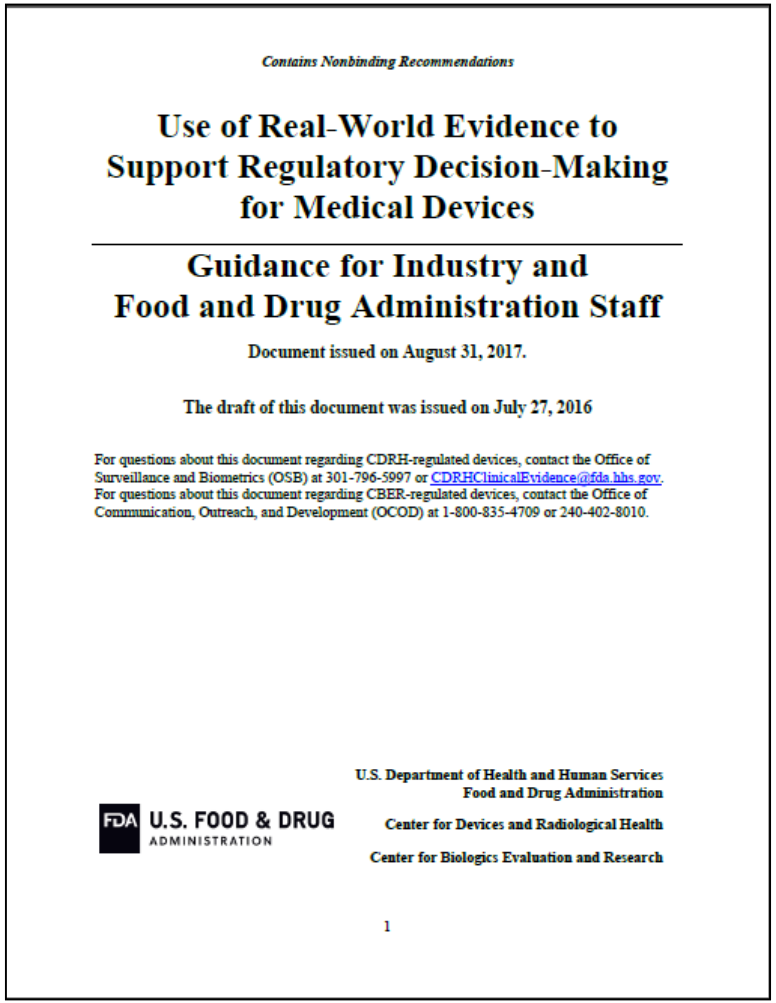


Some Regulatory Uses for RWE

- Control arm for pivotal clinical study
- New indications for approved devices
- Studying new improvements to devices
- Replacing post approval study
- Adverse event reporting
- Shifts to pre-postmarket balance

Clinical Trial Design Innovation: Real-World Evidence Pathway

July 27, 2016



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.

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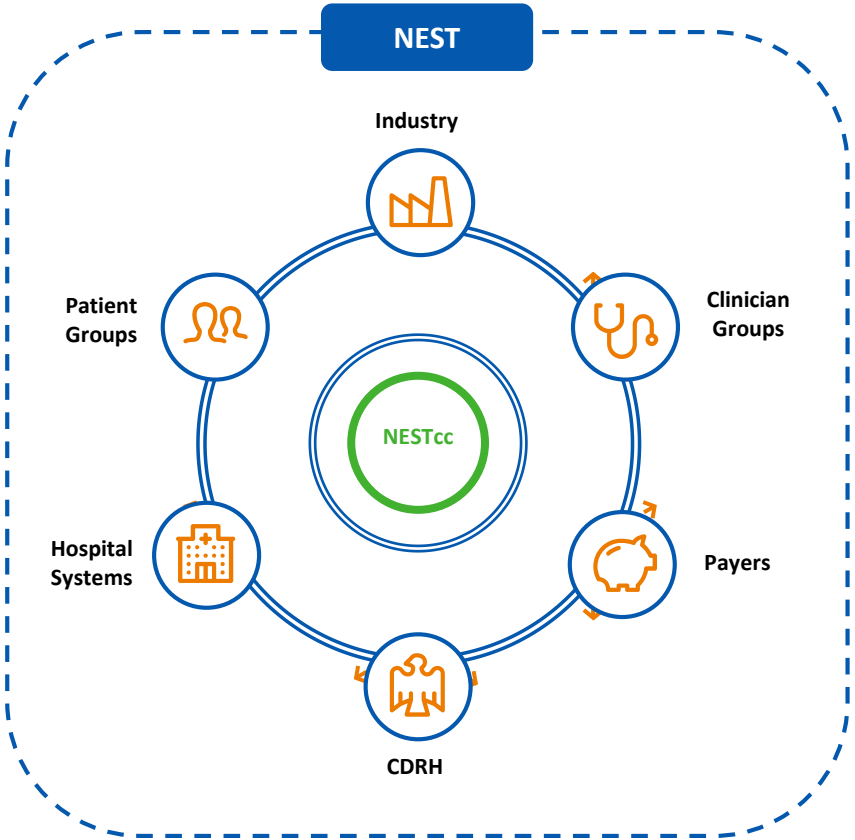
National Evaluation System for Health Technologies (NEST)

- Provide governance, coordination, and standardization
- Expand access to and use of data from clinical practice



Needs for NEST

- Strategic approach for collecting data
- Establishing core data sets
- Establishing common definitions
- Facilitating transfer and linking among interoperable data sources
- Embed research data collection into routine clinical workflow and participating patients' daily activities

Partner with Patients

Patient Perspectives!
Informed Decisions

CDRH 2018-2020 Strategic Priorities

Employee Engagement, Opportunity, and Success

Simplicity

Collaborative Communities

Clinical Trials and Simplicity

- In applying an approach of simplicity, we must tackle the extent of uncertainty encountered.
- Uncertainty is almost always present.
- Uncertainty cannot be a reason for unnecessary delays or requirements.

Clinical Trials and Simplicity

- Simplicity considerations in trial design
  - Typically won't know full benefit-risk profile before device is widely used
  - Even very large trials might not truly reflect benefits and risks
    - Large trials may impose unreasonable costs and time delays that ultimately adversely affect patients.
  - CDRH must balance an appropriate level of uncertainty as one of several factors in decision making.
    - Desire for certainty vs. patient access and unmet clinical needs

Clinical Trial Design Innovation: What can it mean?

Challenge Question

- Which of the following statements about device trials is FALSE:
  - They tend to enroll fewer subjects than drug trials.
  - They are more likely to be blinded or randomized than drug trials.
  - Many assess iterative improvements to devices.
  - The device design may be modified during the trial.

Patients are at the Heart of What We Do

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