# LUNCH

*(networking session)*

# Real World Evidence from a Global Perspective & NEST Update

# The Future of Global Evidence Generation: Advancing the Role of Innovative Data and Methods

Michelle McMurry-Heath, MD, PhD

Worldwide Vice President, Regulatory Affairs Preclinical and Clinical Affairs

Global Head, Evidence Generation

Johnson & Johnson Medical Devices

# Michelle McMurry-Heath, MD, Ph.D.

Michelle McMurry-Heath leads the clinical, preclinical, and regulatory teams for the medical device companies of Johnson & Johnson. She is also the Global lead for Evidence Generation. In her roles, she leads the evidence and approval strategy development for companies that range from Electrophysiology (Biosense Webster) to orthopedics (DePuy Synthes) to general surgery (Ethicon) in 150 markets around the globe. She is physician and scientist with more than two decades of experience. After studying biochemistry at Harvard University, Dr. McMurry-Heath became the first African-American to receive both M.D. and Ph.D. degrees from Duke University. Trained in pediatrics and immunology, Dr. McMurry-Heath has committed her life's work to providing patients with better health information and greater clinical options through science and innovation policy. She oversaw health for Senator Joseph Lieberman and was the senior health policy advisor for the Lieberman for President Campaign. She was the founding director of the Aspen Institute's Health, Biomedical Science and Society Initiative which brought pharmaceutical and diagnostic leaders together with leaders in the patient advocacy and health care to focused projects on issues ranging from regulation to tackling chronic diseases in the context of health insurance reform. Her health diplomacy work included projects in 11 countries, including Cambodia and Rwanda.

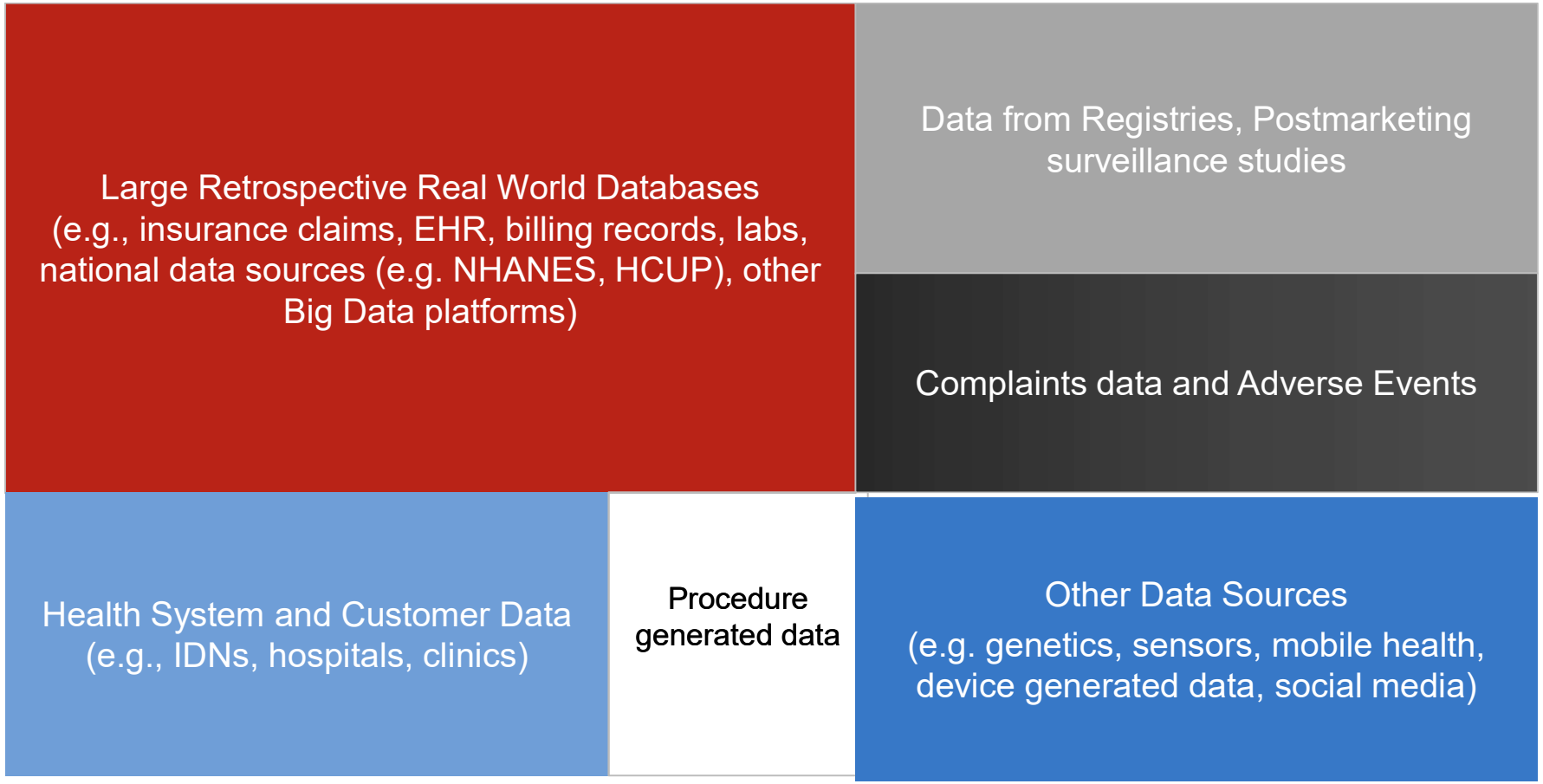
From 2010-14, Dr. McMurry-Heath was the Associate Center Director for Science in CDRH science at the FDA's Center for Devices and Radiological Health (CDRH). Dr. McMurry-Heath led the FDA team tasked with defining a new role for patients in the regulation of medical devices and diagnostics. She drew on this experience as the primary architect of the Medical Device Innovation Consortium (MDIC), a novel public-private partnership between the FDA and almost 50 members of the medical technology industry and patient advocacy community. MDIC members have pooled resources and talent to take on some of the most intractable topics in medical device innovation: optimizing clinical trials, applying computer modeling to device design and regulation, compliance science, pathways for insuring the clinical validity of new diagnostics, and the science behind measuring patient preferences. She joined Johnson & Johnson in 2014, as Worldwide Vice President of Regulatory Affairs Dr. McMurry-Heath unified all the business and regional regulatory teams into one global organization and implemented a new global approach to regulatory policy and service to 100 smallest markets. She assumed responsibility for the clinical and preclinical device teams in July, 2017 to drive synergies and improve quality across the functions and develop a comprehensive evidence generation strategy to promote market introduction and acceptance of device innovation.

Johnson & Johnson MEDICAL DEVICES COMPANIES

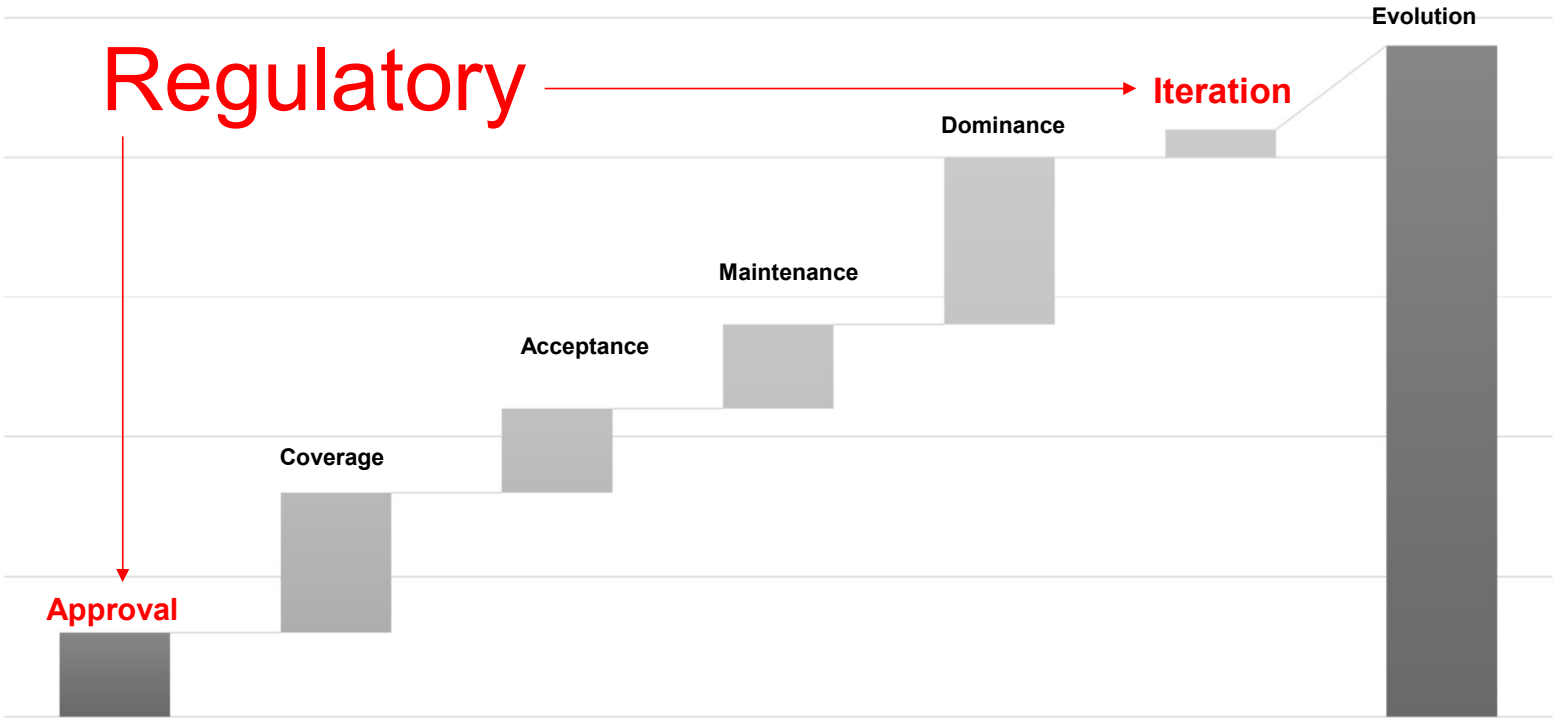
# The Future of Global Evidence Generation: Advancing the role of innovative data and methods

**Michelle McMurry-Heath, MD, PhD**
WW Vice President of Regulatory and Clinical Affairs
Global Head of Evidence Generation
Medical Devices Companies of Johnson & Johnson

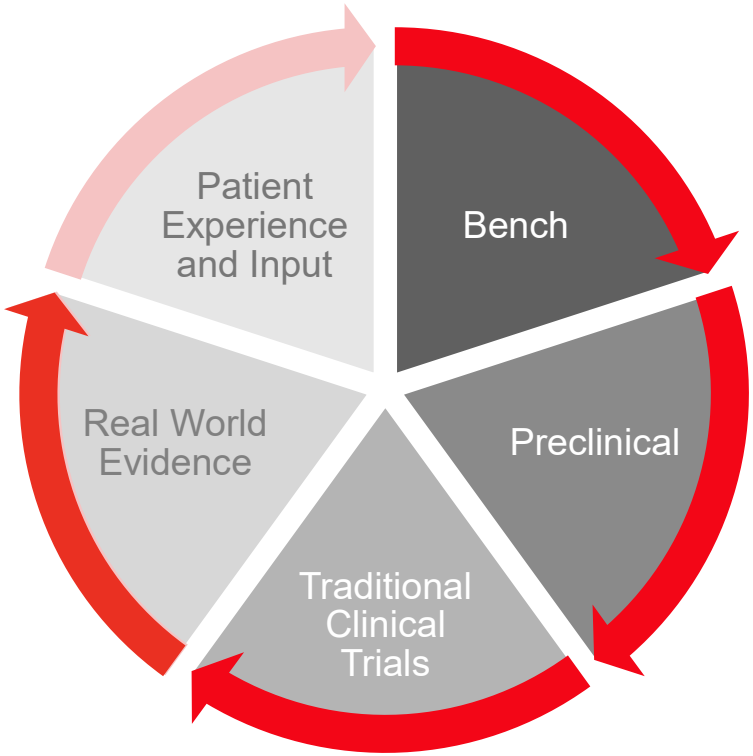
# Diversity of Real-World Data (RWD) Types



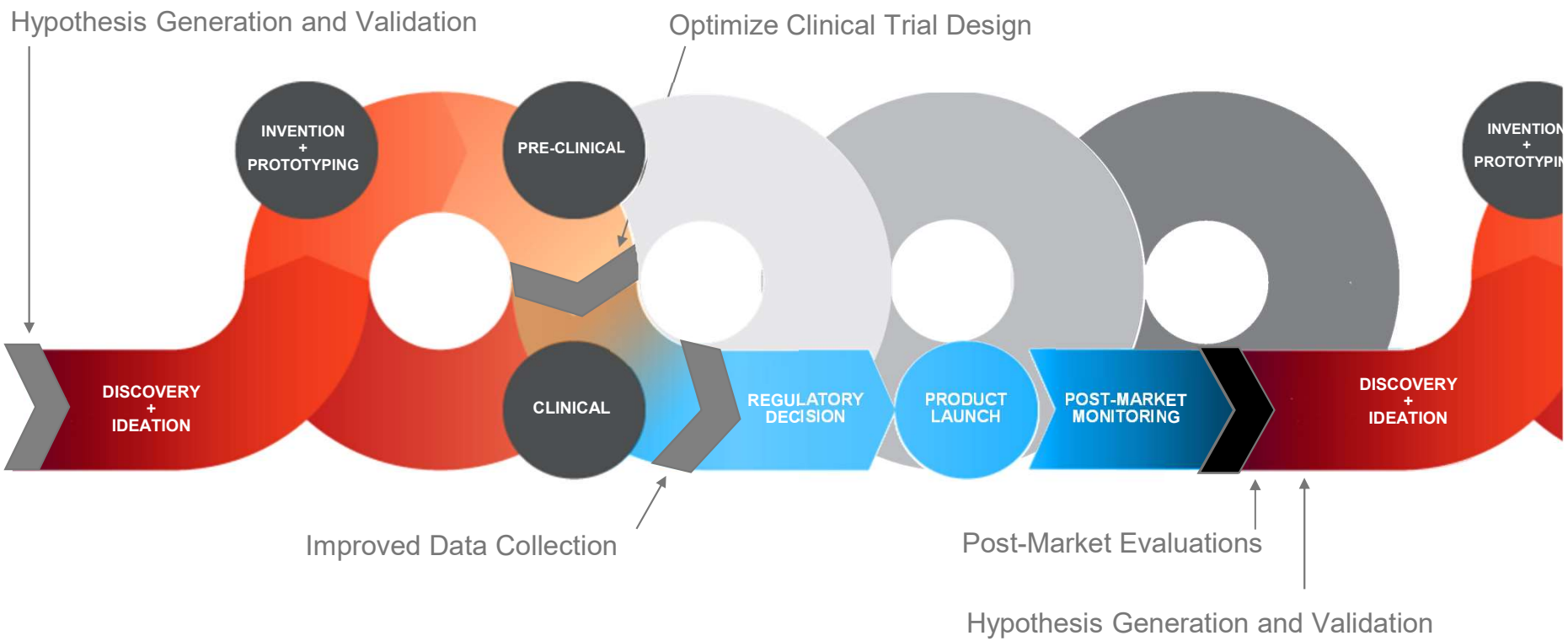
# Total Product Life Cycle Evidence Generation Needs



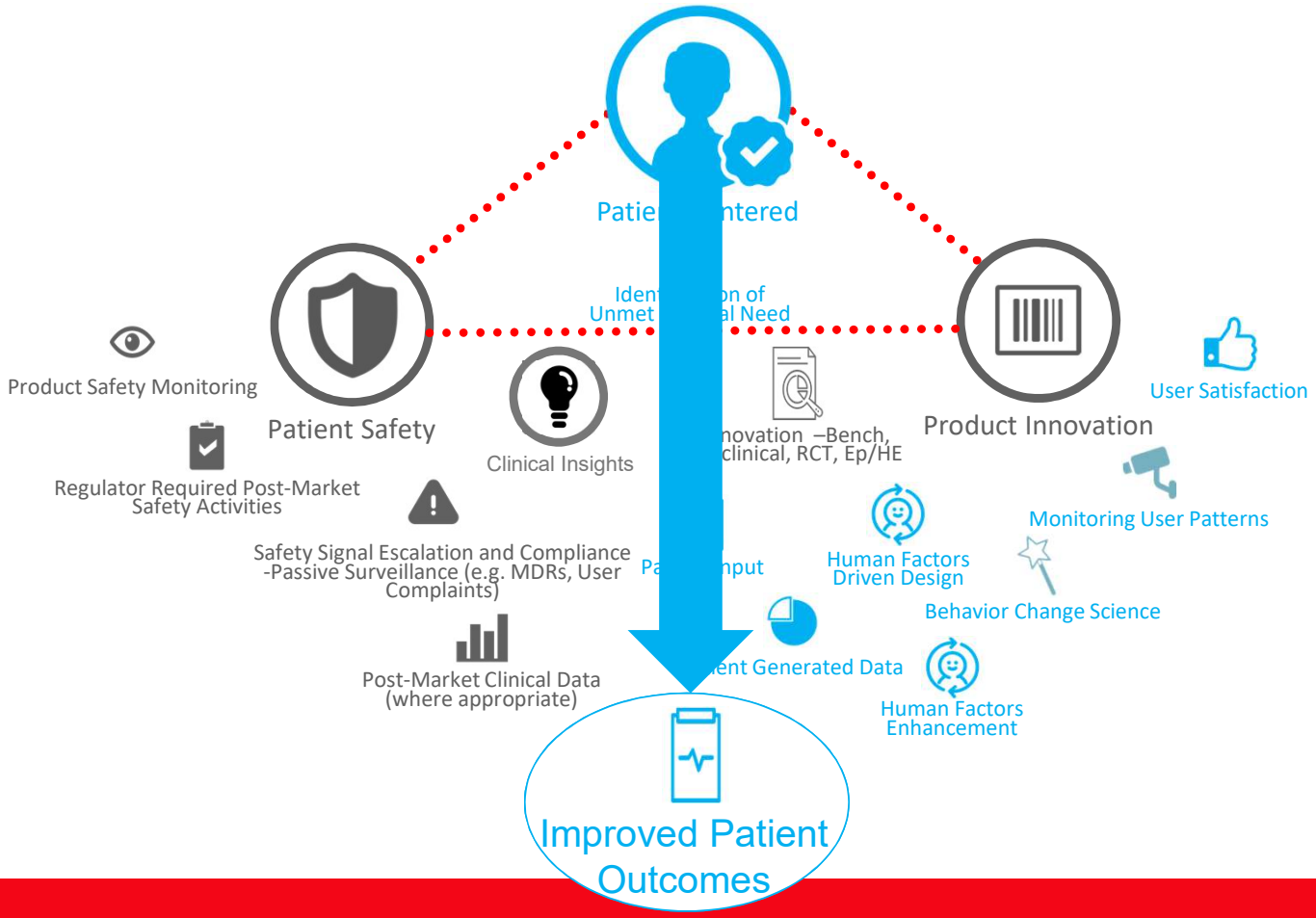
# Integrated New Types of Clinically-Relevant Data into an Evolving Evidence Portfolio



# Opportunities to Integrate RWD into the Total Product Life Cycle



# Advancing the Role of Novel Data in Innovation



# Addressing key technical challenges

- Promote mechanisms to access RWD
  - Leverage existing sources of RWD (e.g., registries)
  - Linking data sources to enable long-term follow-up
  - Create mechanisms to support and collect better data on patient care and recovery (e.g., digital tools)
- Collaborate to create shared resources and tools
  - Establish criteria to assess the fit-for-purpose for RWD
  - Develop appropriate analytic methods
  - Advance the science of patient input
  - Identify opportunities to gather data on hard to capture products (e.g., plates, screws, surgical tools)
- Support globally harmonized practices and policies
  - Addressing the evidentiary needs of various regulatory bodies (e.g., EUMDR)

# CDRH RWE Overview and FDA's Perspective on Future RWE

Josh Chetta, PhD

Biomedical Engineer

ODE

FDA

# Josh Chetta, PhD

Josh Chetta is currently working in the Clinical Trials Program in FDA's Office of Device Evaluation in CDRH, helping to support the Center's efforts to better leverage information from real world device use to inform regulatory decisions. Josh earned his undergraduate degree in Biology from the University of Chicago, and a doctorate in Bioengineering from the University of Maryland. He spent a few years as a post-doctoral fellow at the NIH's Clinical Center before joining CDRH in 2014 as a premarket reviewer. For the past year he has worked as part of an inter-Office team tasked with identifying needs and developing tools and resources for staff to help CDRH implement the RWE Guidance Document.

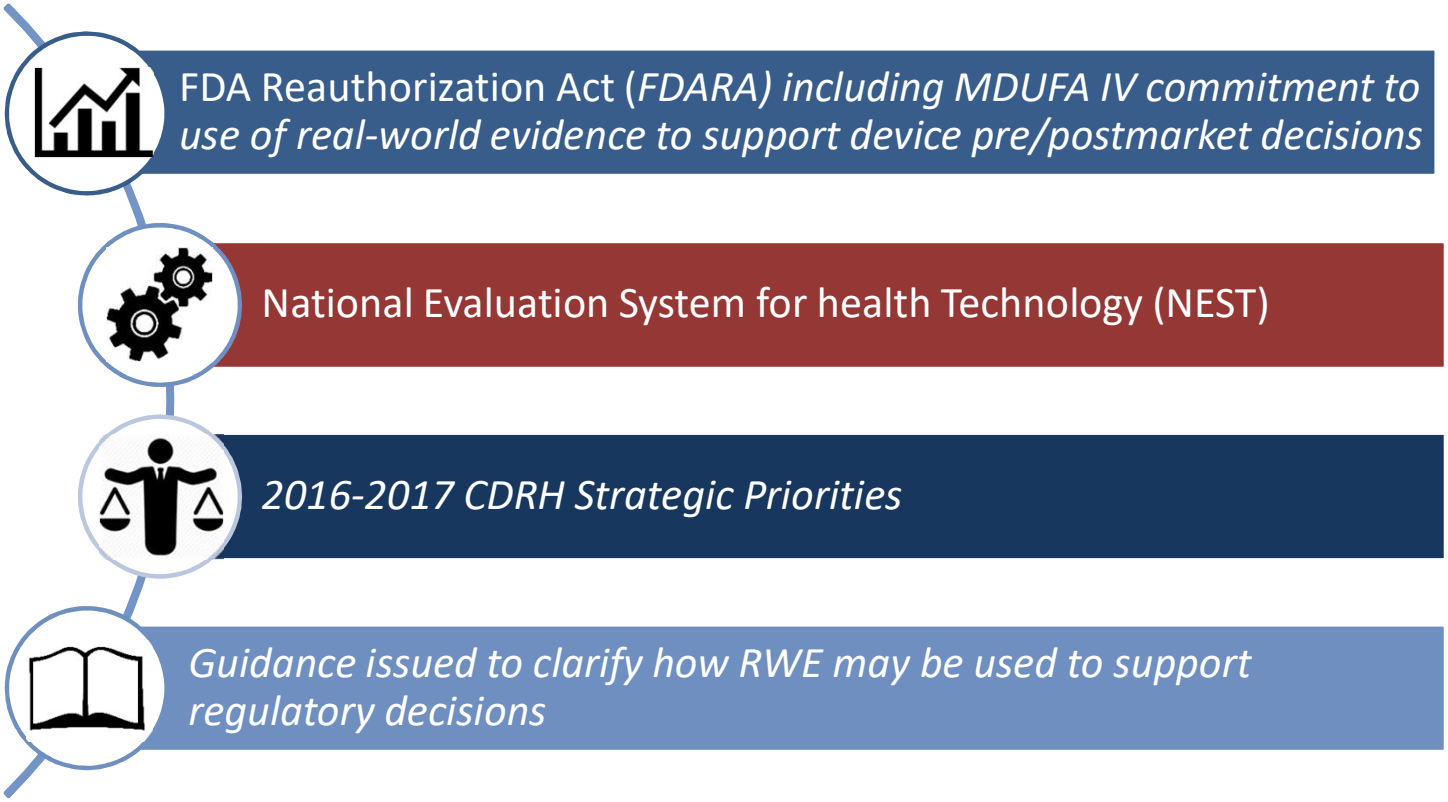
# The Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Joshua Chetta, Ph.D.
Clinical Trials Program
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

# 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**

# CDRH Activities to Support RWE



# Strategic Priority to Establish NEST: Accomplishments in 2016-2017

- ☑ Awarded Cooperative Agreement to MDIC to establish a Coordinating Center for NEST
- ☑ Continued promotion of UDI (Unique Device Identifiers) into health care systems that can be used in device evaluation
- ☑ Collaborative efforts with MDEpiNet and other entities to support real-world data source development and implementation

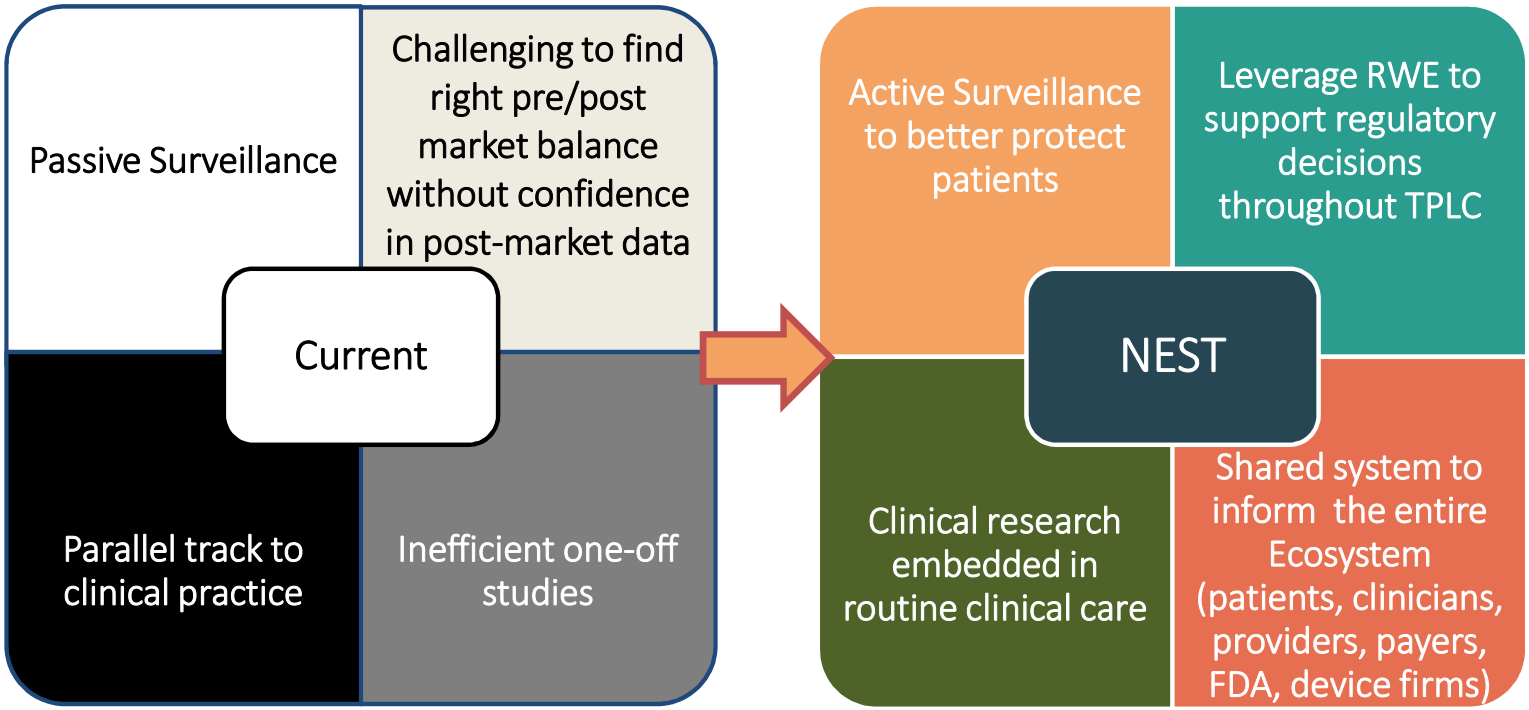
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592694.pdf
https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm301912.htm

# Strategic Priority to Establish NEST: Accomplishments in 2016-2017

- Gained **access** to more than 103 million electronic **patient records** with device identification (from national and international clinical registries, claims data, and EHRs).
- Increased the number of pre- and post-market **regulatory decisions** that used real-world evidence by 193 percent since 2016 - compared to FY2015 baseline.
- Issued **final guidance** to clarify how real-world evidence may be used to support pre- and post-market regulatory decisions.

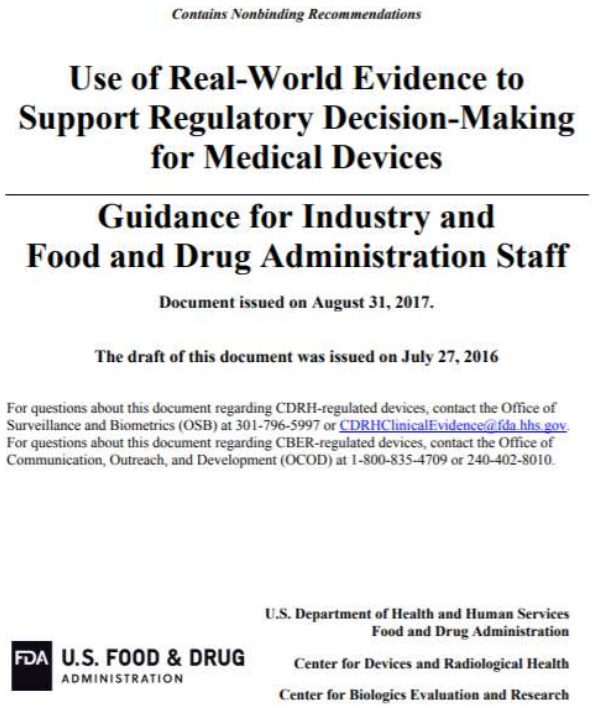
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592694.pdf

# NEST: A Transformative Paradigm



# Final Guidance for Industry and Food and Drug Administration Staff

**Document issued on August 31, 2017**



*Contains Nonbinding Recommendations*

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

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**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

# 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

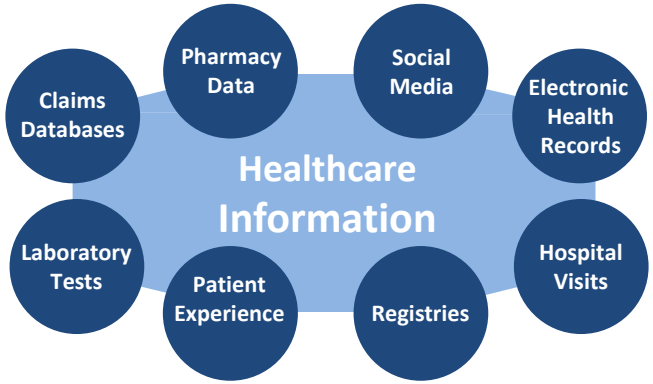
**Real-World Evidence (RWE)**
Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD


Guidance addresses issues related to processes of:

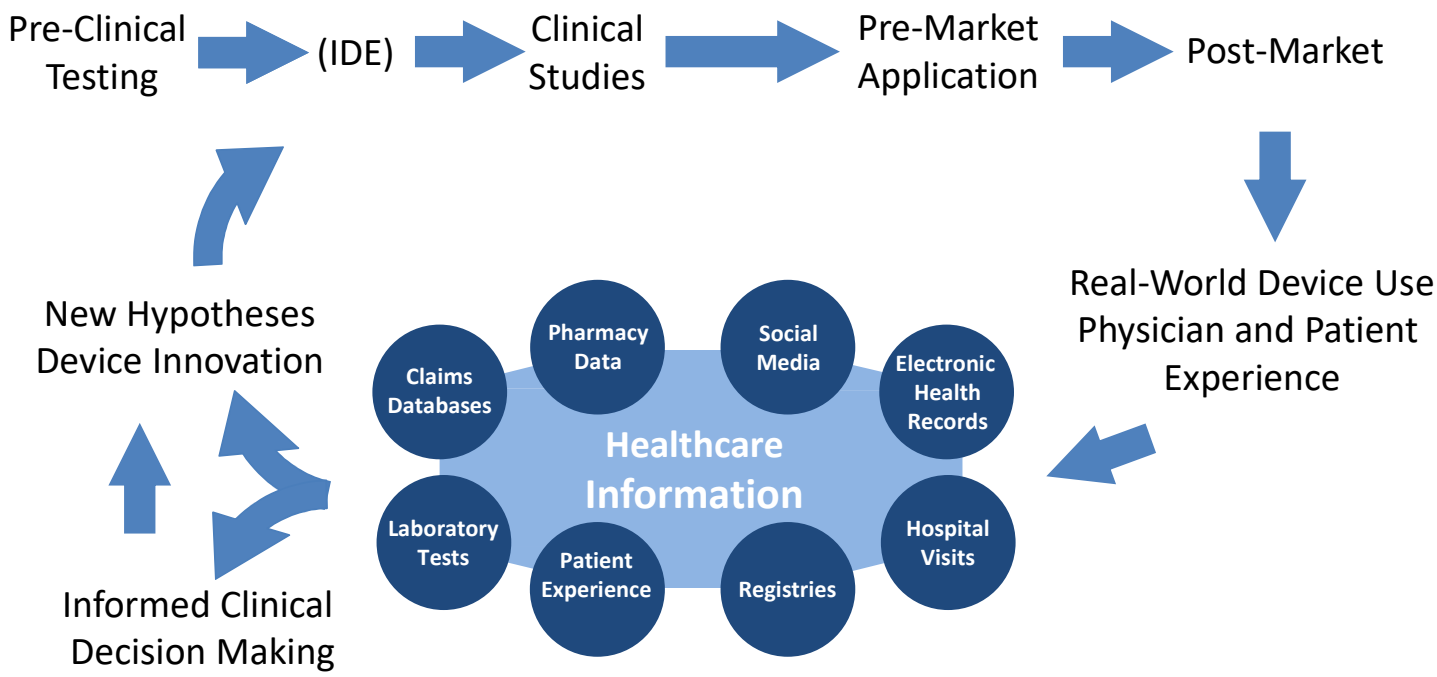
- Generation and collection of RWD
- Analysis of RWD
- When results might be considered valid scientific evidence

# Bringing a Device to Market

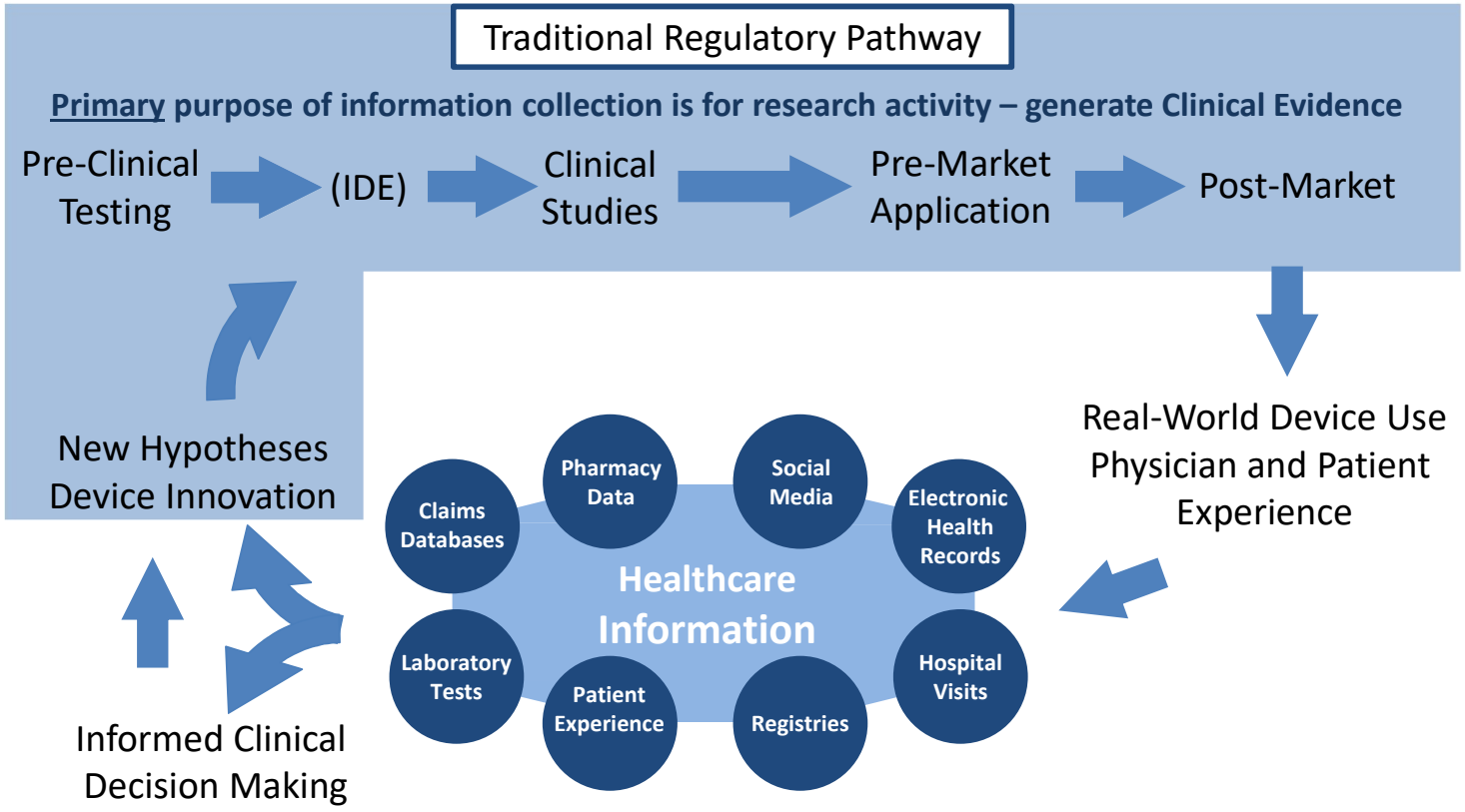
# Electronic Databases

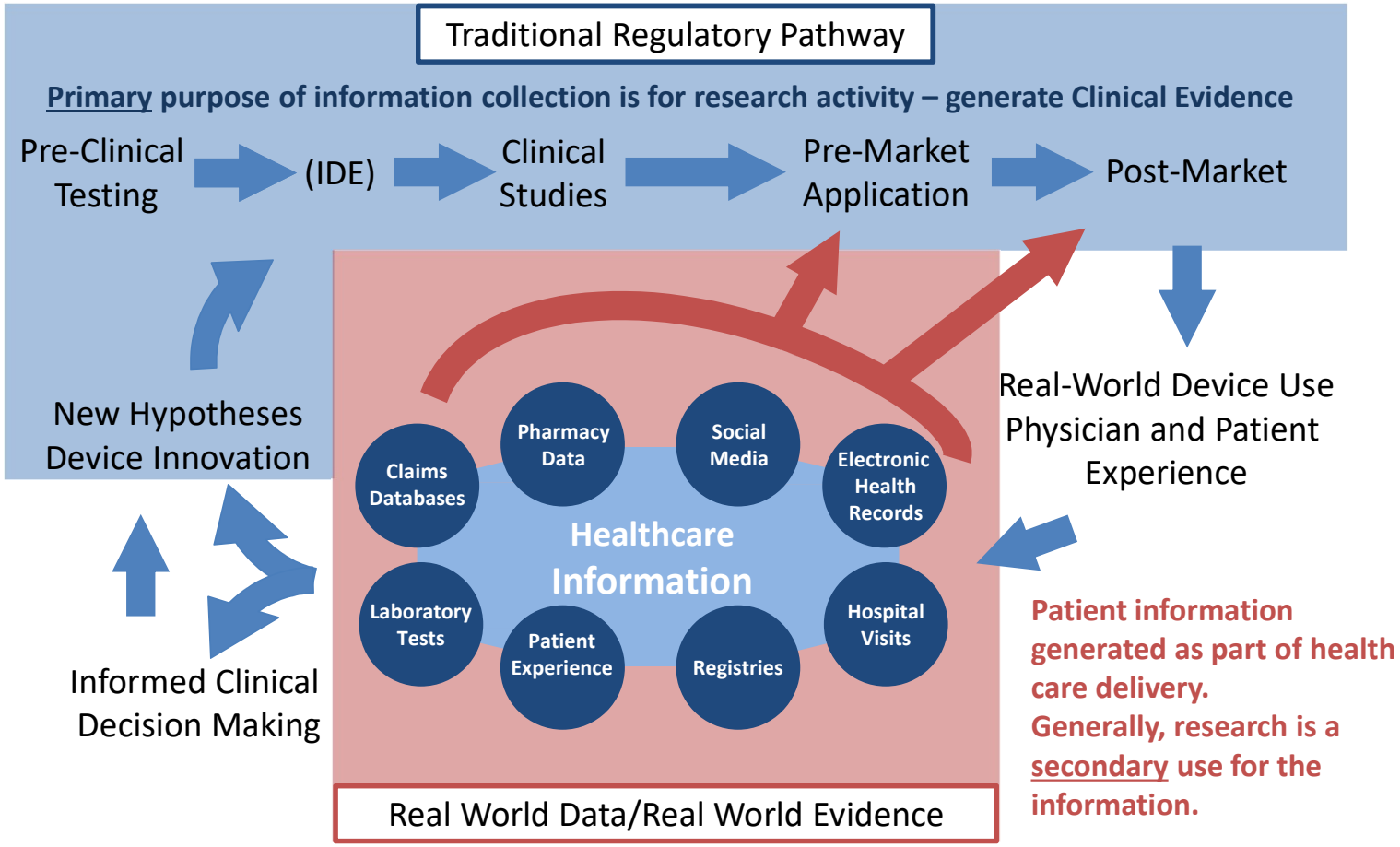
# Device Cycles



# Evidence for Regulatory Decisions

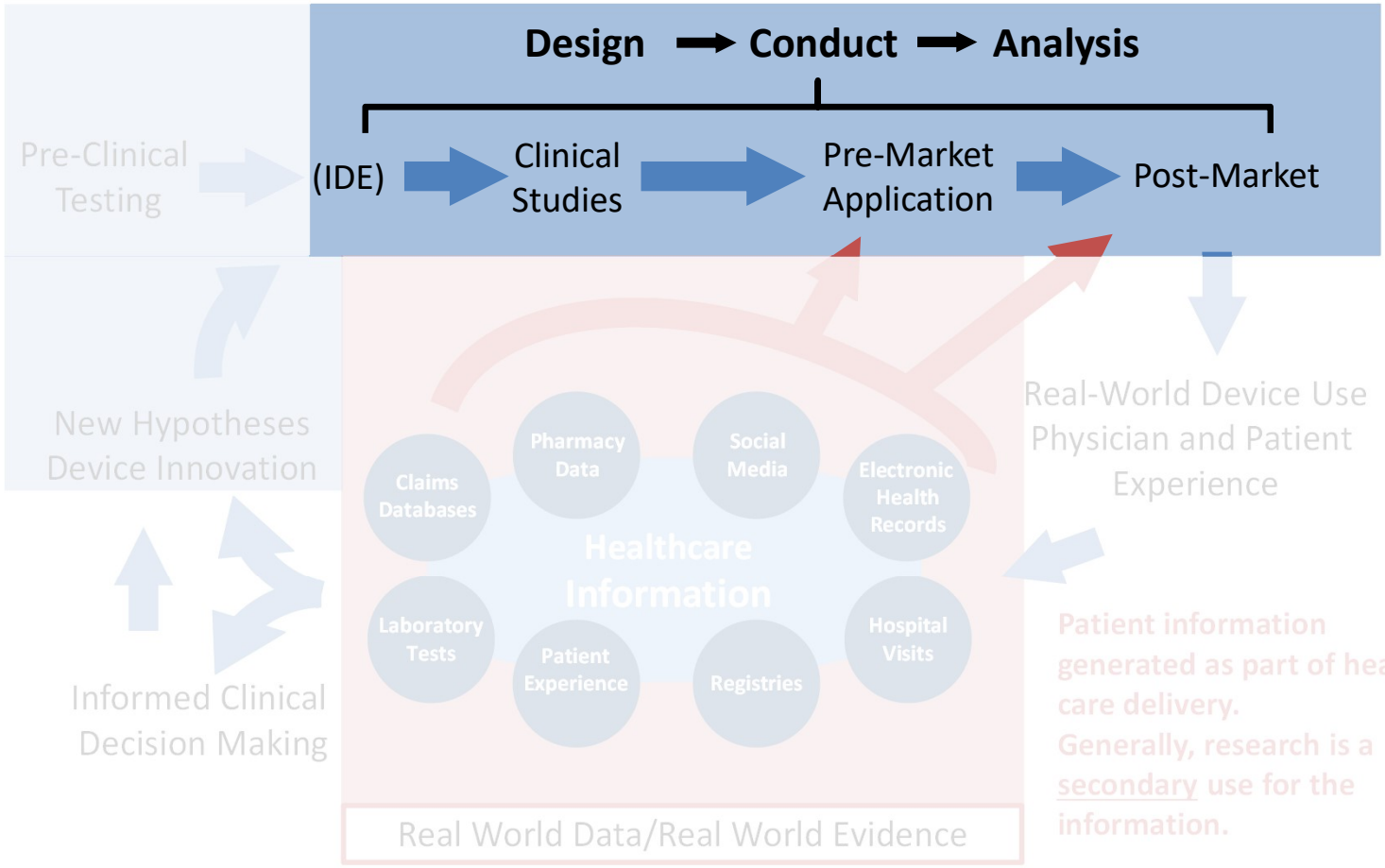


# Real World Data

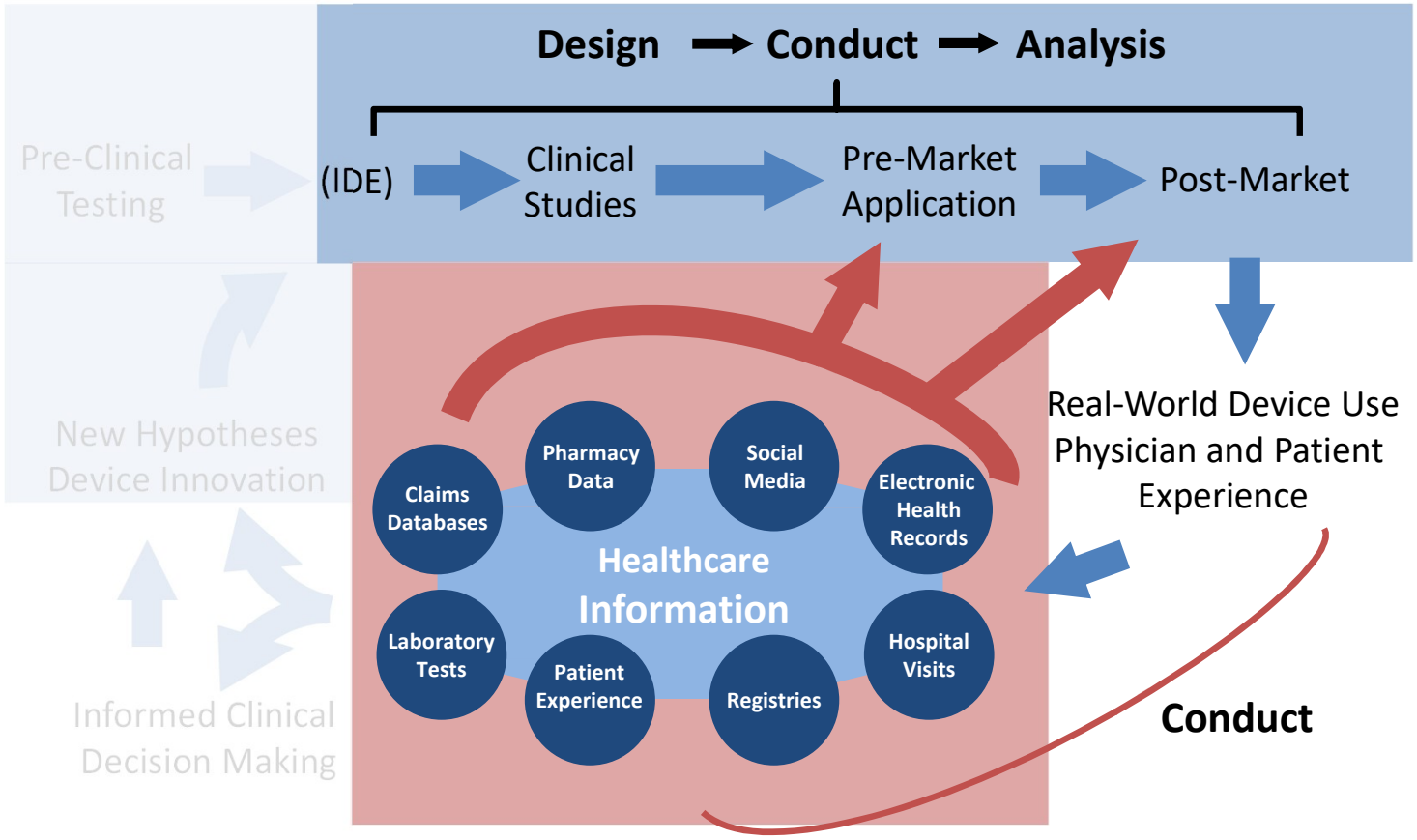



**Patient information generated as part of health care delivery.**
**Generally, research is a secondary use for the information.**

# Quality Built In



# Retrospective Analysis



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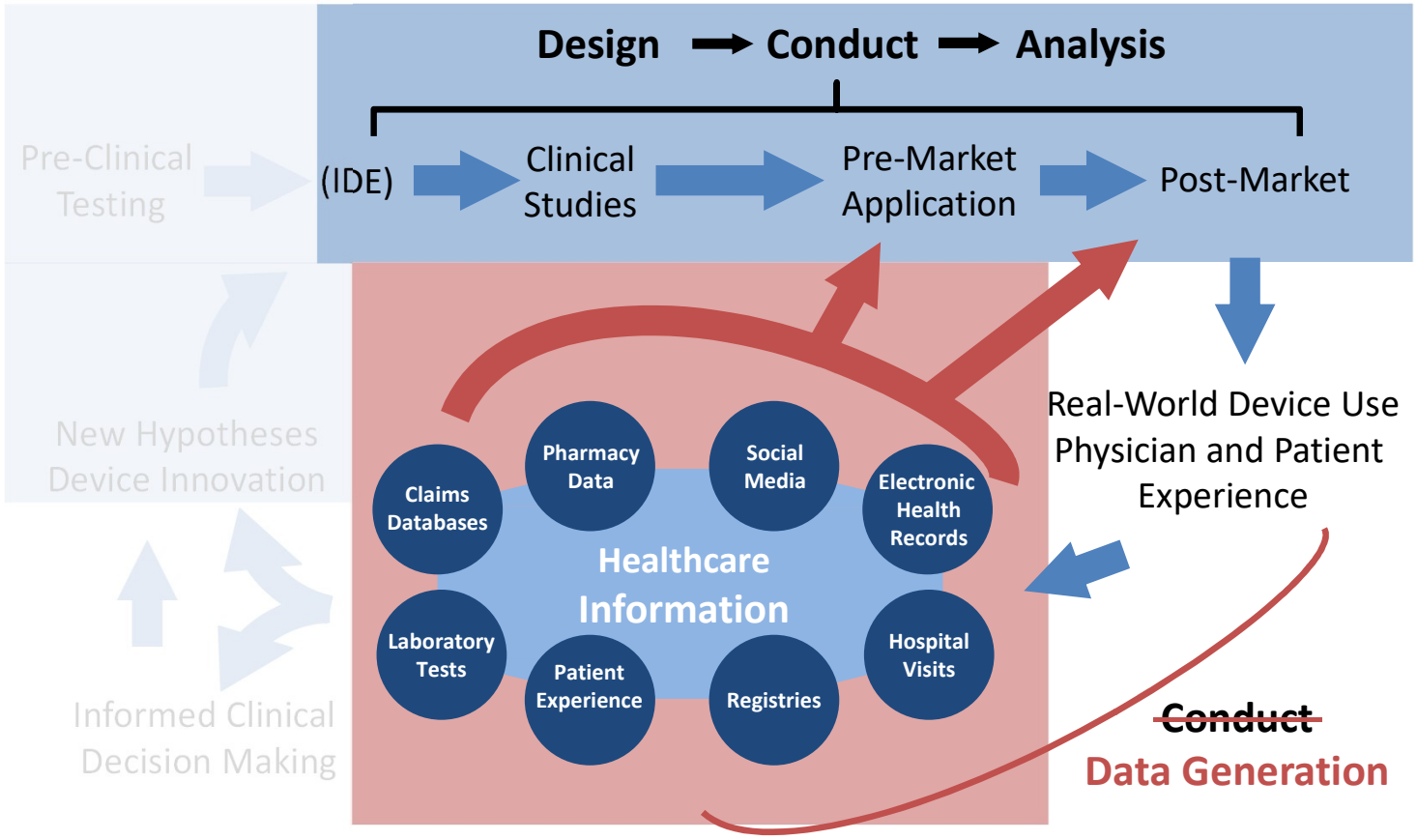

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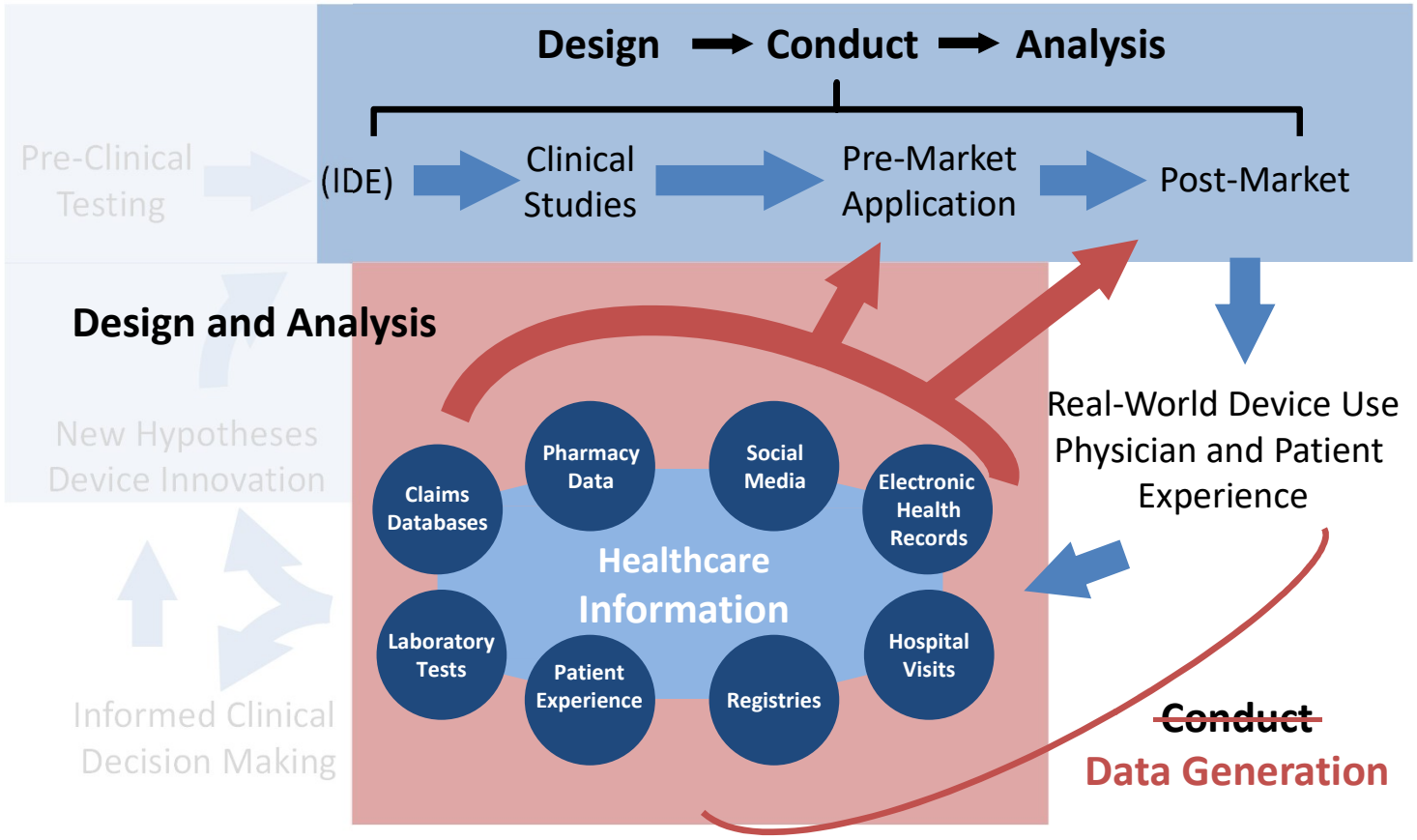

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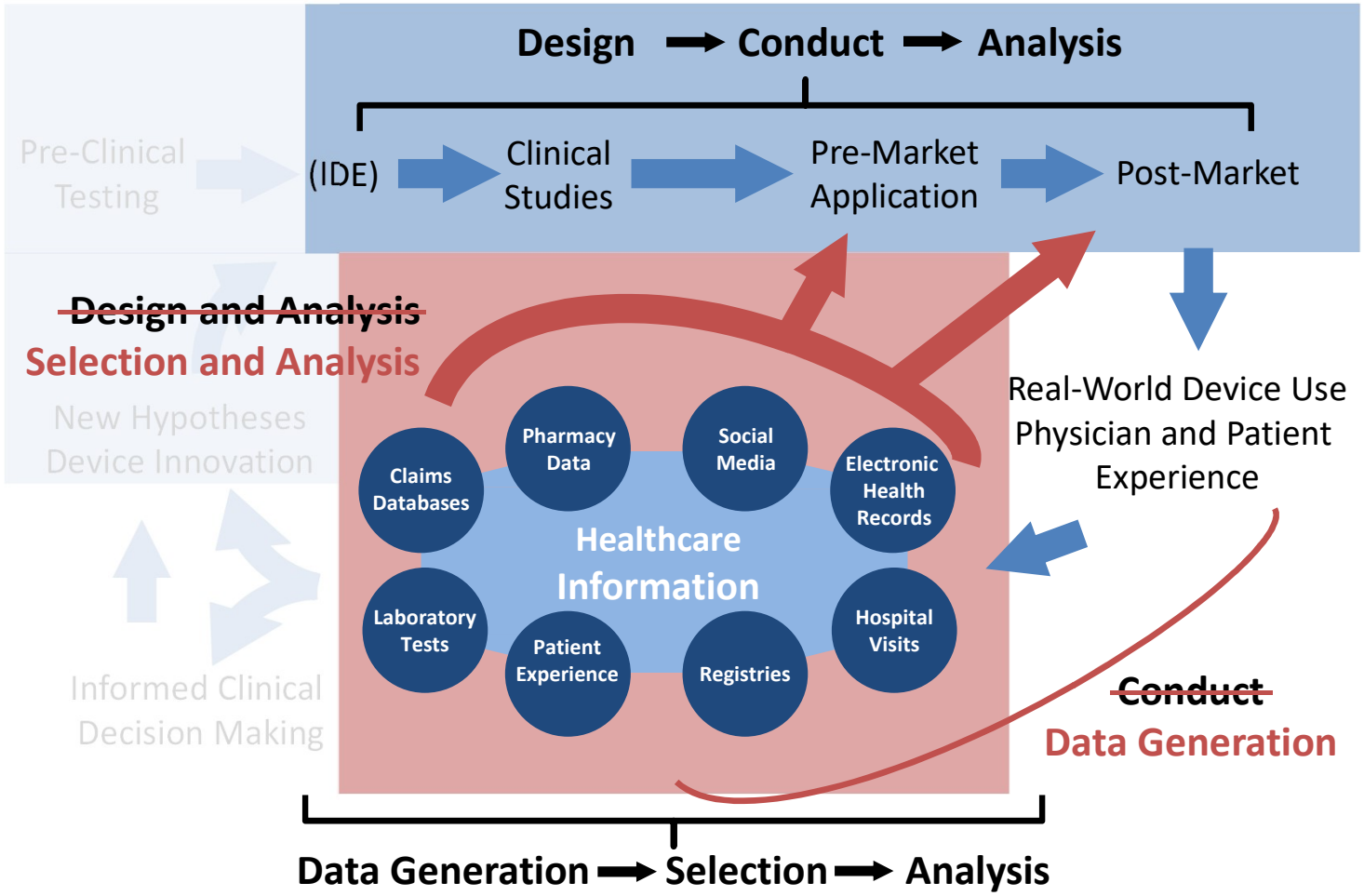
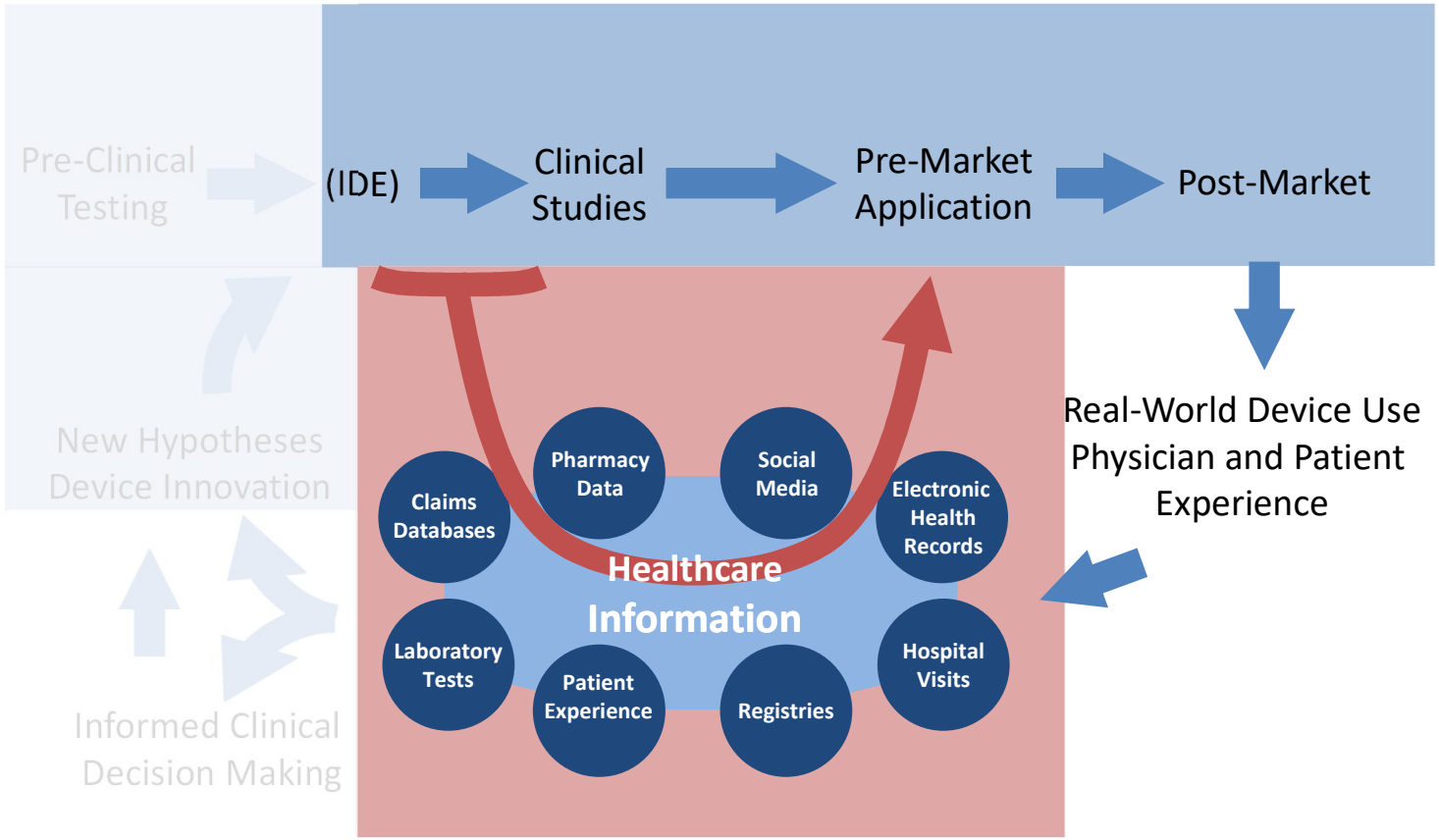


# Embedded Clinical Study



# Examples of RWE USE

# Some Regulatory Uses for RWE

**Control arm for pivotal clinical study**

Concurrent control group derived from real world data to support premarket decision.

**New indications for approved devices**

**Replacing post approval study**

**OPC / PG**

**Supplementary Data**

**Shifts to pre-post-market balance**

# Some Regulatory Uses for RWE

**Control arm for pivotal clinical study**

**Replacing post approval study**

**Supplementary Data**

Safety and effectiveness data collected during real world use may support expansion of labeled use.

**New indications for approved devices**

**OPC / PG**

**Shifts to pre-post-market balance**

# Some Regulatory Uses for RWE

Control arm for pivotal clinical study

**Replacing post approval study**

Supplementary Data

Use of existing real world data infrastructure to address Post-Approval Study Condition of Approval.

New indications for approved devices

OPC / PG

Shifts to pre-post-market balance

# Some Regulatory Uses for RWE

Control arm for pivotal clinical study

Replacing post approval study

Supplementary Data

Use of real world data to develop numerical objective performance criteria or performance goal.

New indications for approved devices

**OPC / PG**

Shifts to pre-post-market balance

# Some Regulatory Uses for RWE

Control arm for pivotal clinical study

Replacing post approval study

**Supplementary Data**

Information from real world device use may be to supplement, and aid in interpretation of, clinical trial data.

New indications for approved devices

OPC / PG

Shifts to pre-post-market balance

# Some Regulatory Uses for RWE

**Control arm for pivotal clinical study**

**Replacing post approval study**

**Supplementary Data**

Robust real world data collection and reporting in the postmarket setting could facilitate earlier device approval.

**New indications for approved devices**

**OPC / PG**

**Shifts to pre-post-market balance**

# Some Non-Regulatory Uses for RWE

- Informing the community on optimal care
- Identifying needs and gaps
- Market analysis
- Assessing quality of care

# 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.

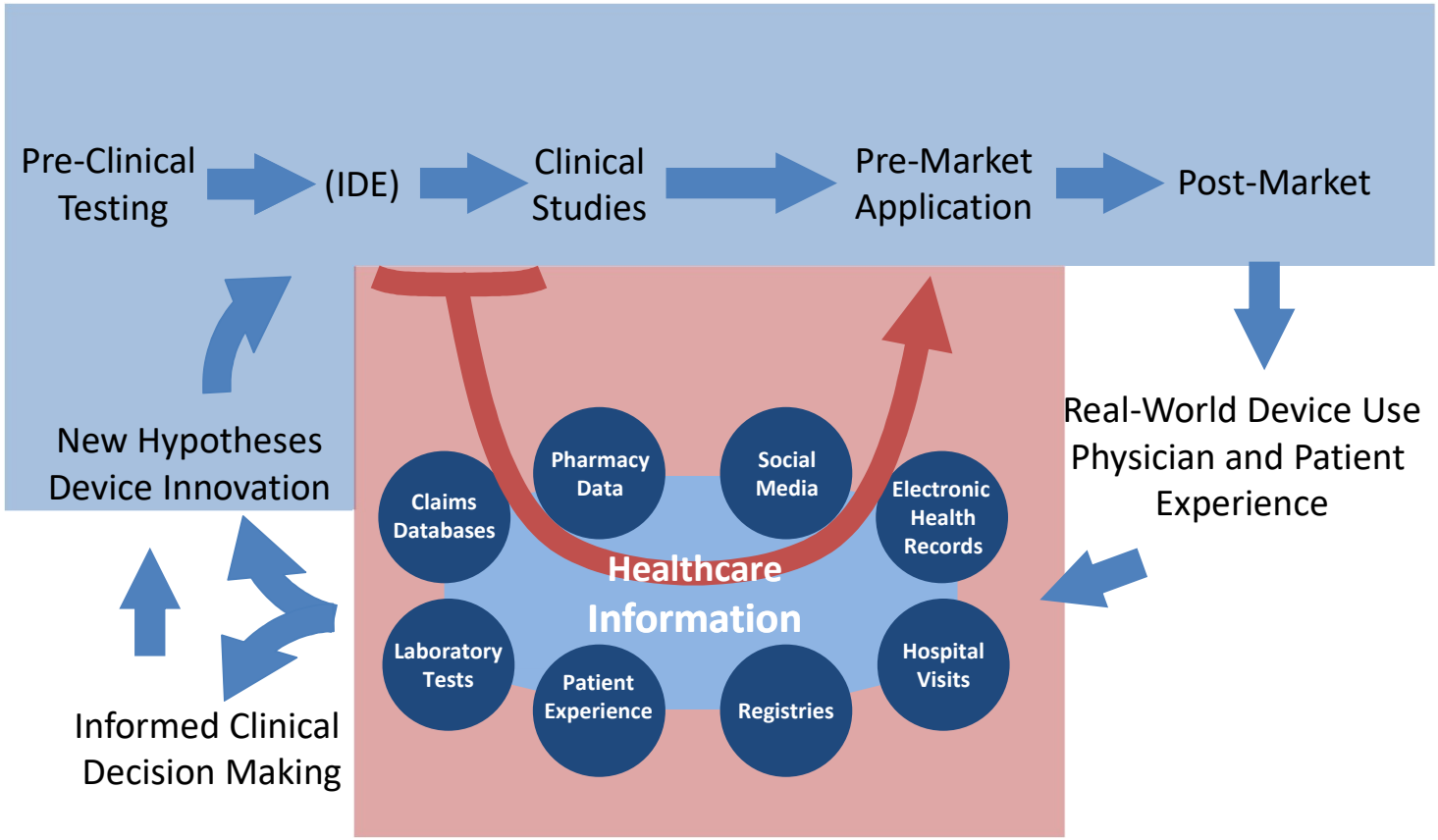
# RWE Reliability Evaluation
# Data Assurance - Quality Control

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

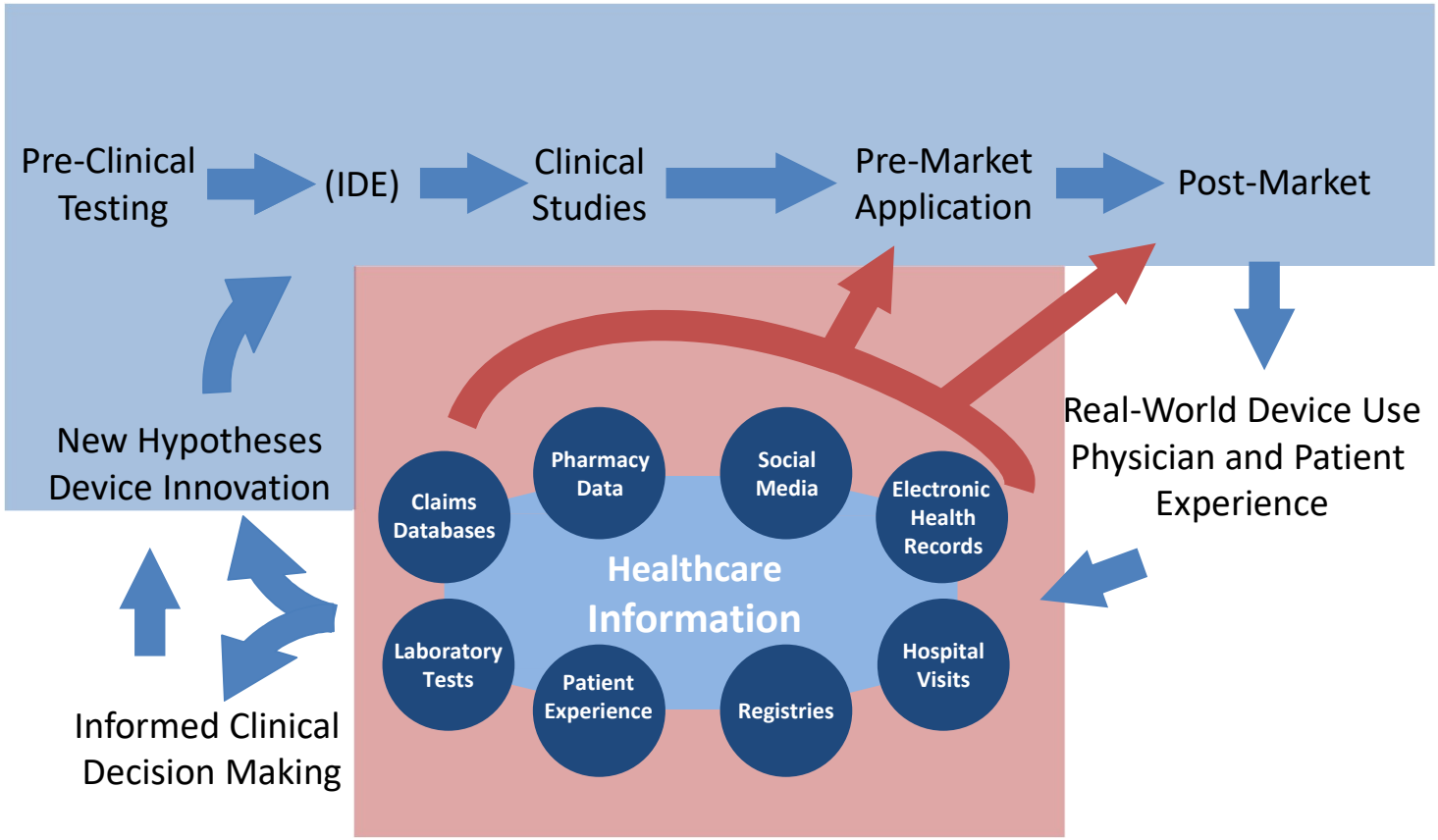
- Includes consideration of aspects such as:
  - How data elements were populated.
  - Data source verification procedures.
  - Data completeness including of confounding factors.
  - Data consistency across sites over time.
  - Evaluation of on-going training programs.

# Investigational Device Exemption (IDE) and Real World Evidence (RWE)

# Research Design



# Research Design



# Patient Protections

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

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

# “Practice of Medicine” or Research?

- 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.

- 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.

# IDE and RWE

- 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.

- The FDA regulations 21 CFR 50, 56, and 812 apply to all clinical investigations of devices to determine safety and effectiveness, with limited exceptions.

# Conclusions

- Contact us with Questions!
  - CDRHClinicalEvidence@fda.hhs.gov

- CDRH is committed to ensuring that patients have access to safe and effective medical devices.
- High-quality clinical evidence is central to our regulatory decision-making.
- The Real World Evidence Guidance Document is one part of the Center's efforts to support innovation in medical devices while ensuring adequate protection of patients and study subjects.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