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

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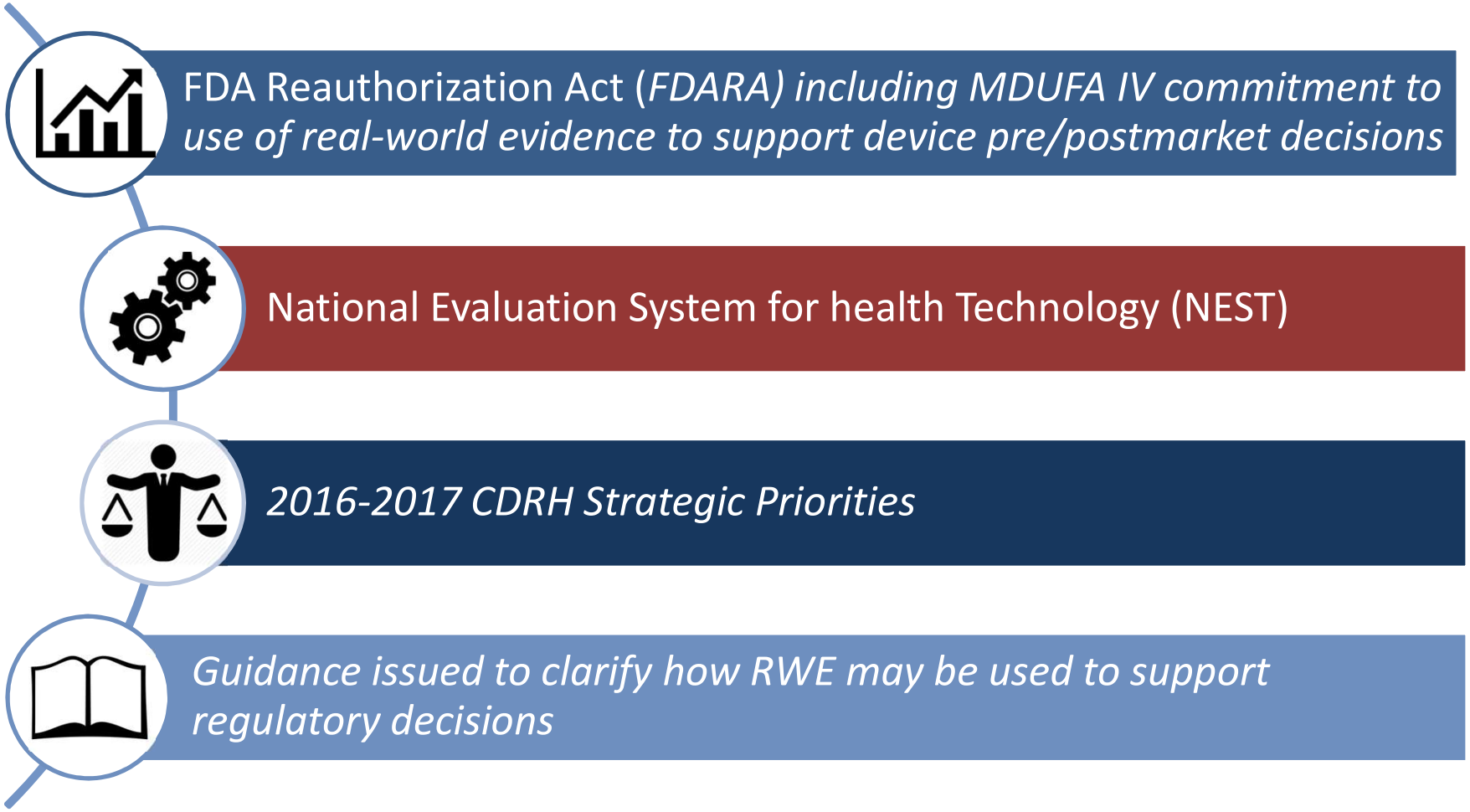
Patients are at the Heart of What We Do

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

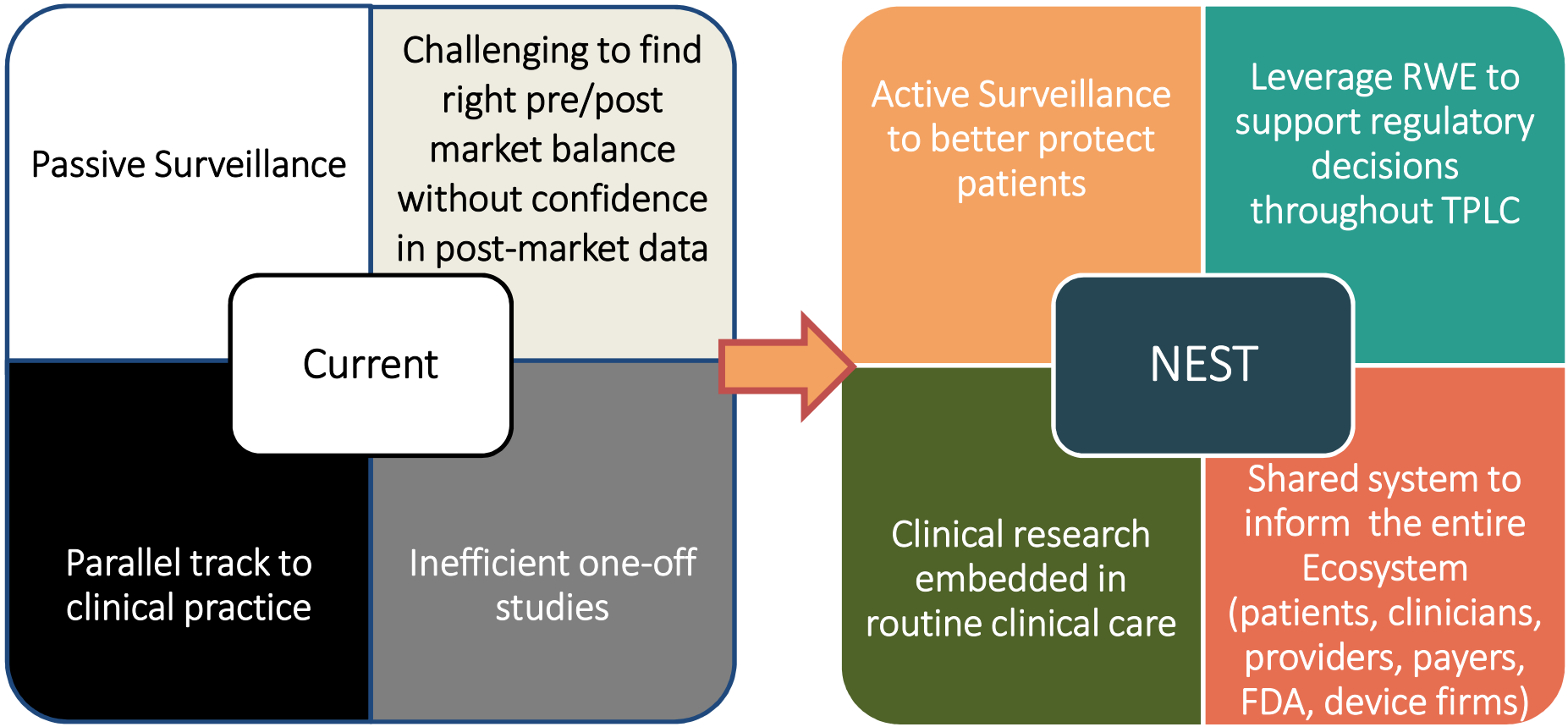
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592694.pdf
https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm301912.htm

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.

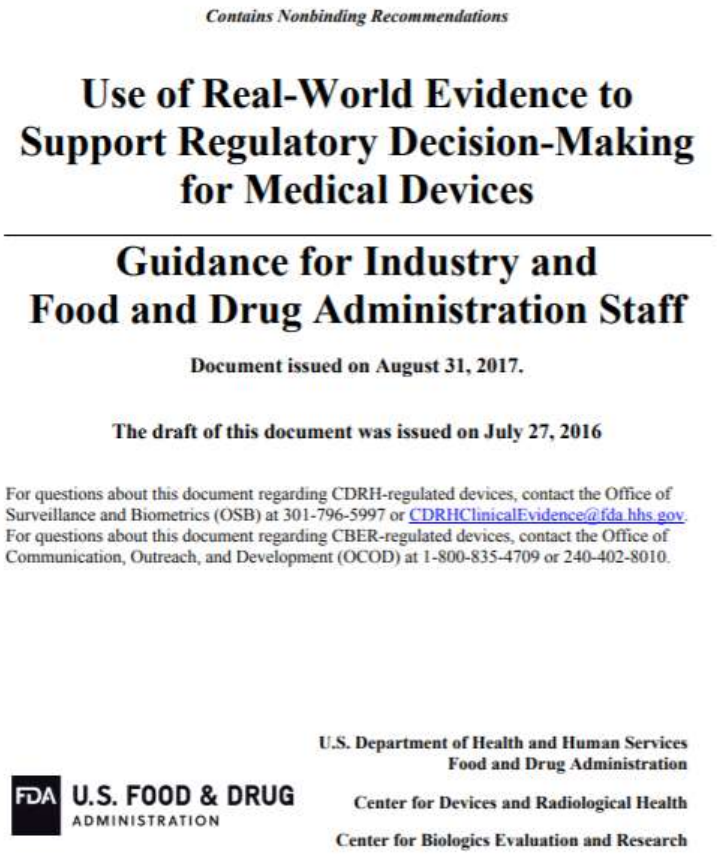
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592694.pdf

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

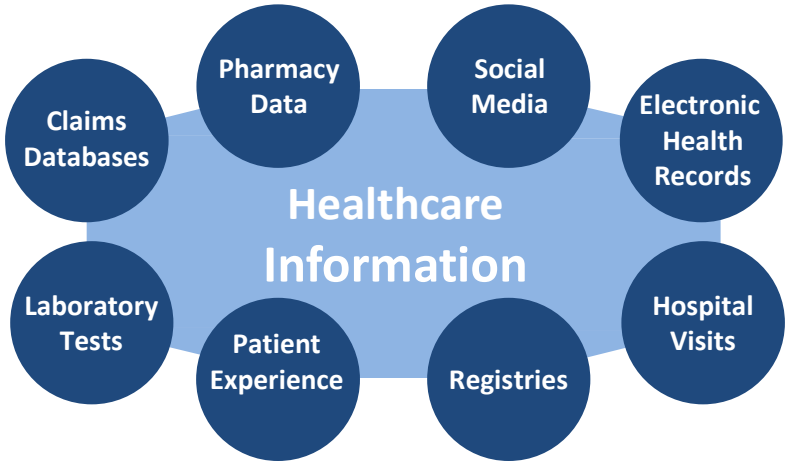
Guidance addresses issues related to processes of:

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

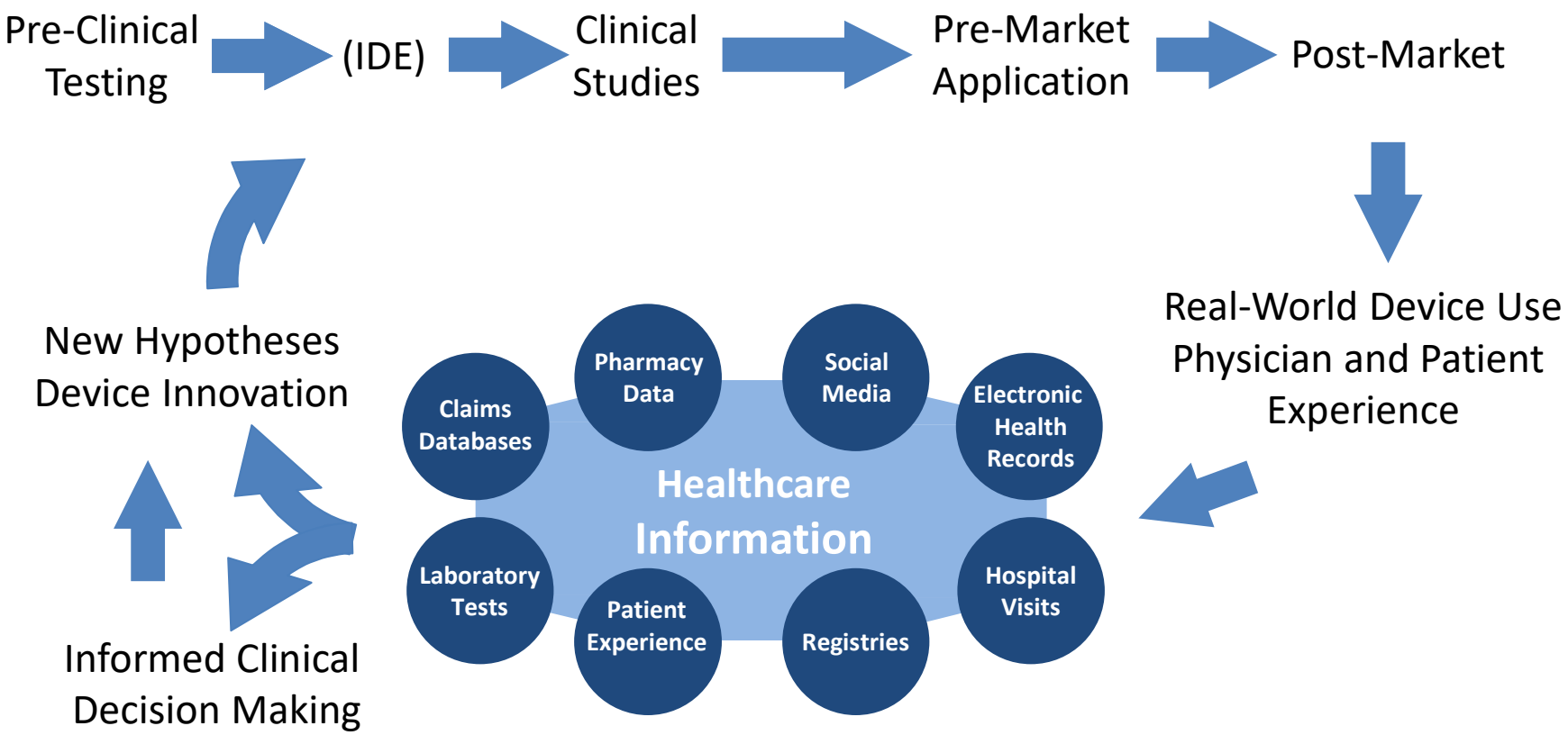
Bringing a Device to Market

Electronic Databases

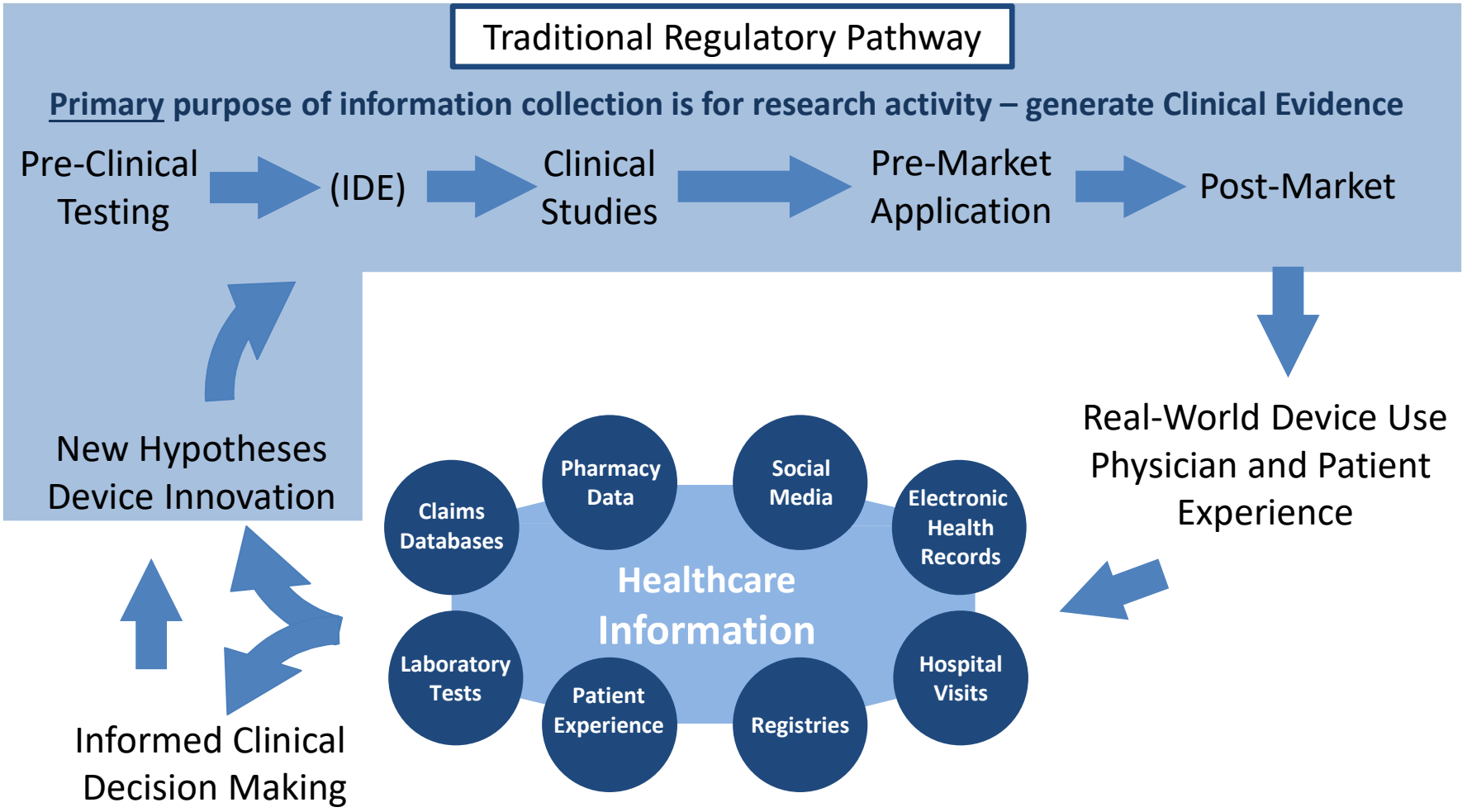
Pre-Clinical Testing → (IDE) → Clinical Studies → Pre-Market Application → Post-Market



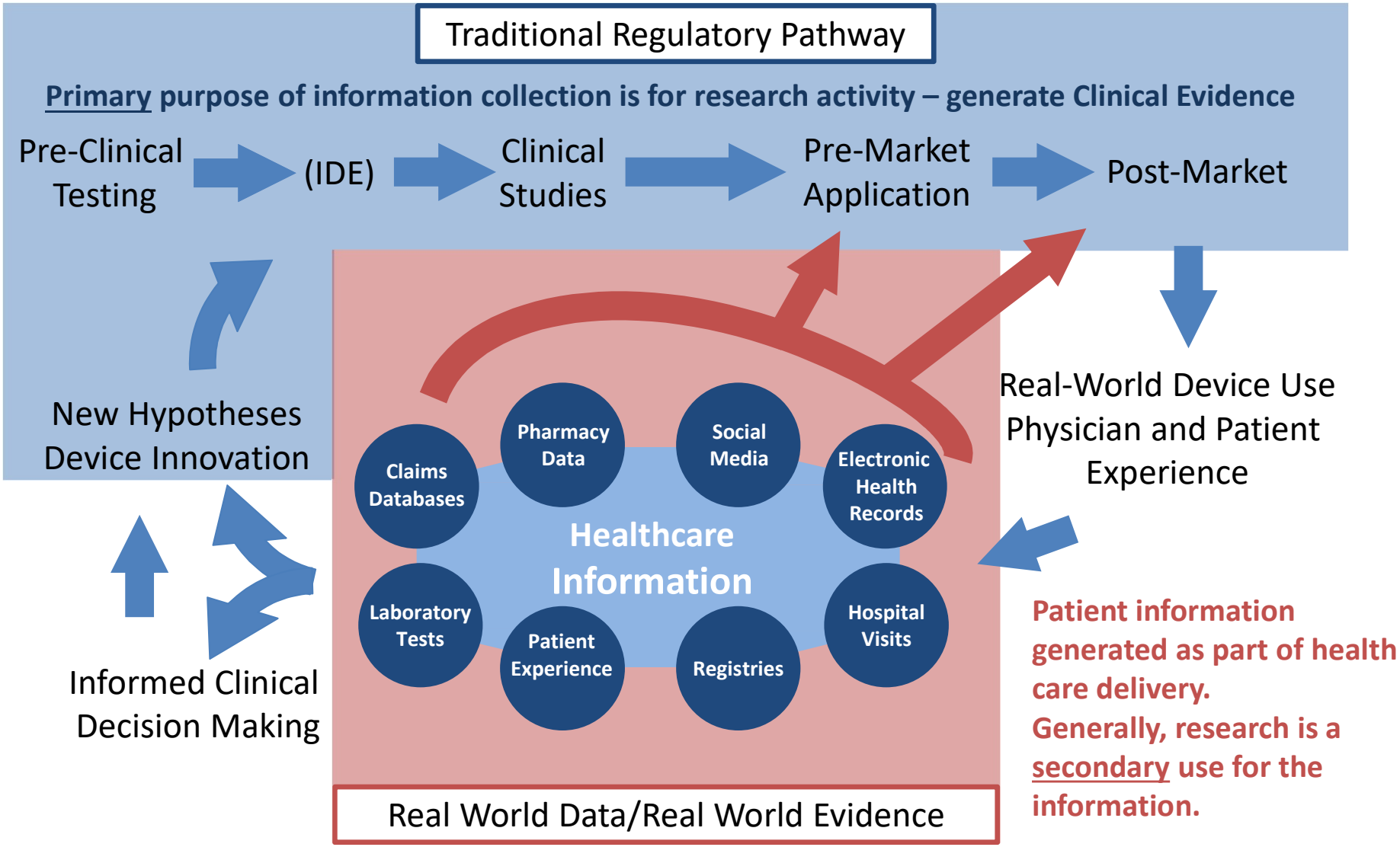
Device Cycles



Evidence for Regulatory Decisions

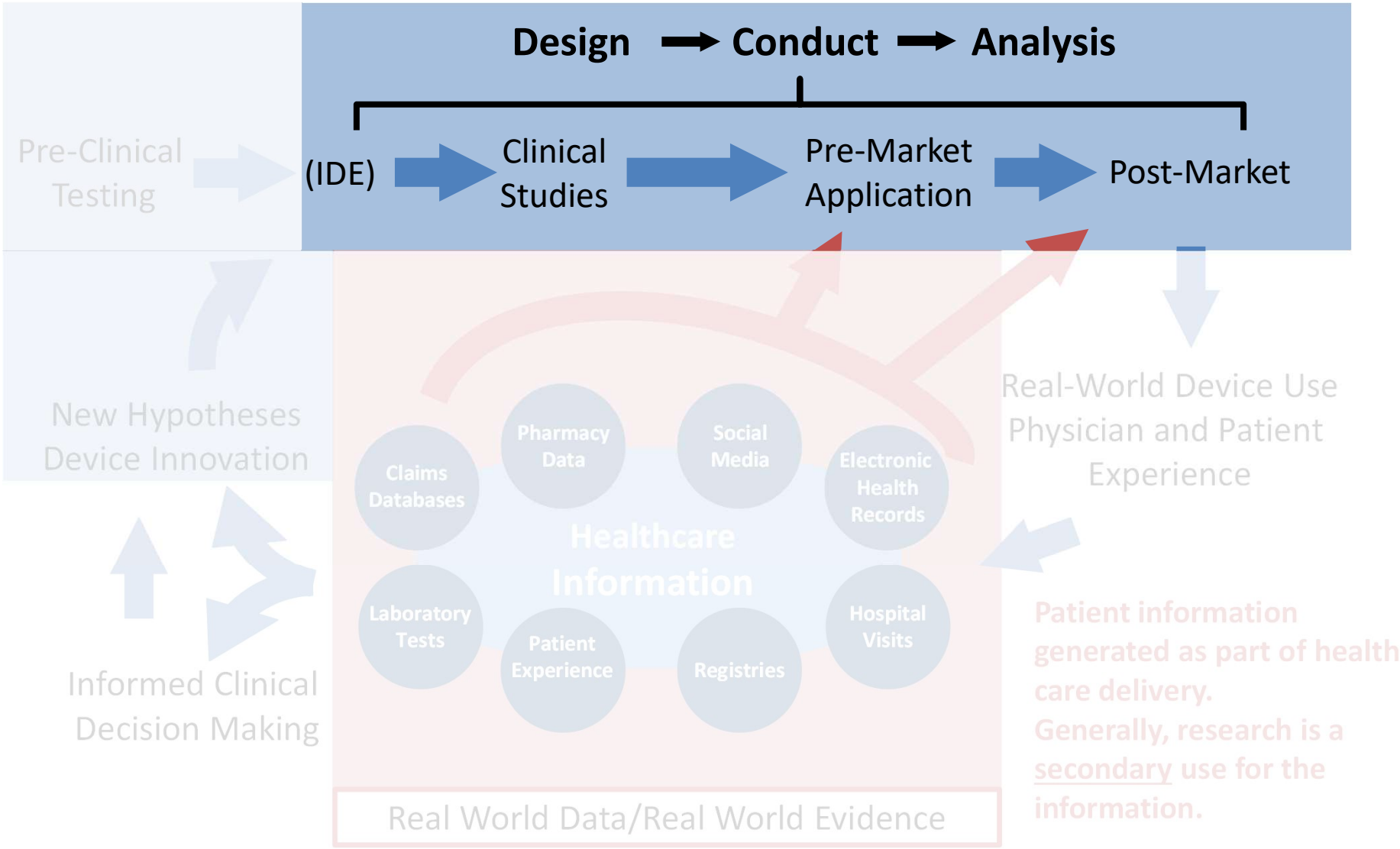


Real World Data

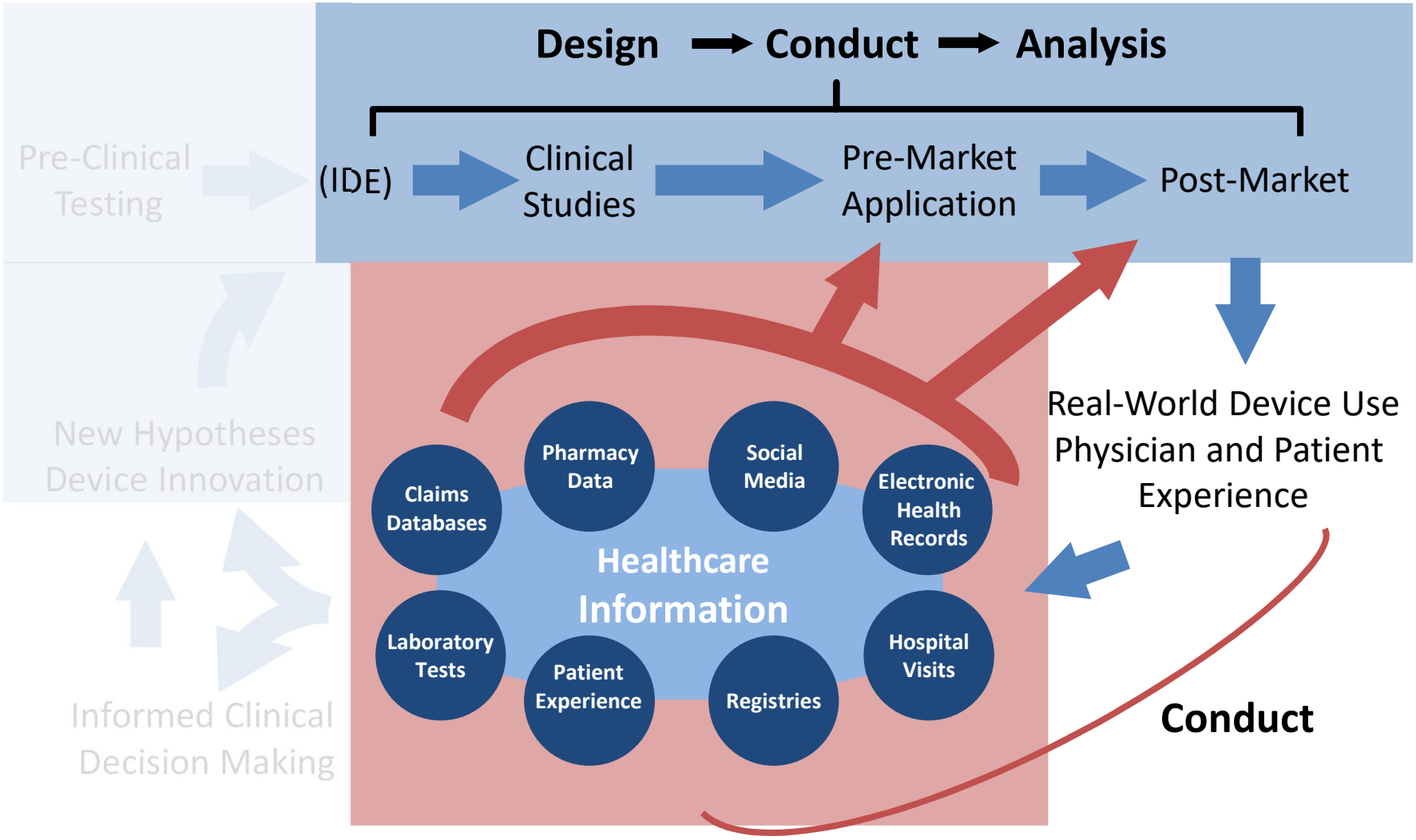


Patient information generated as part of health care delivery.
Generally, research is a secondary use for the information.

Quality Built In



Retrospective Analysis



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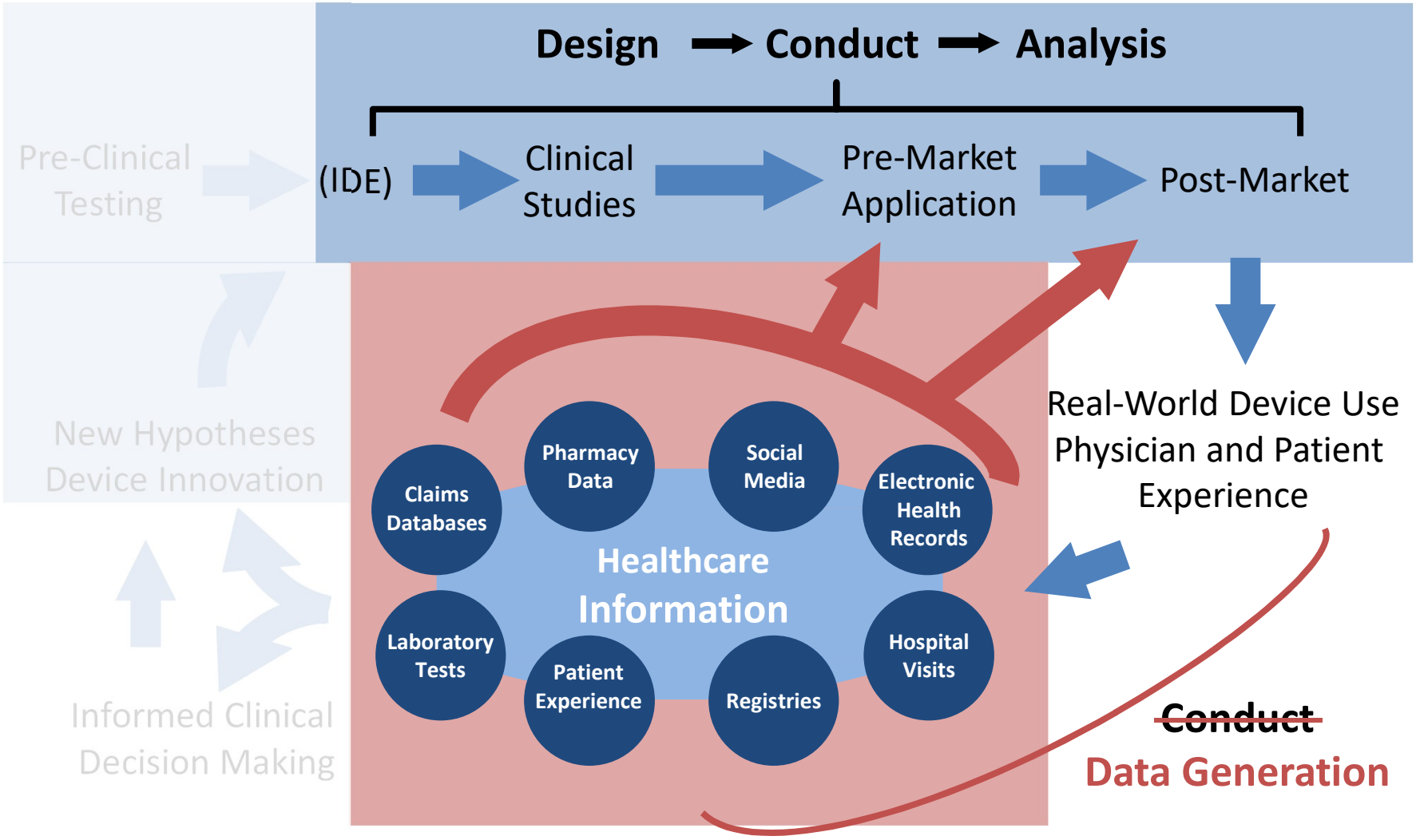

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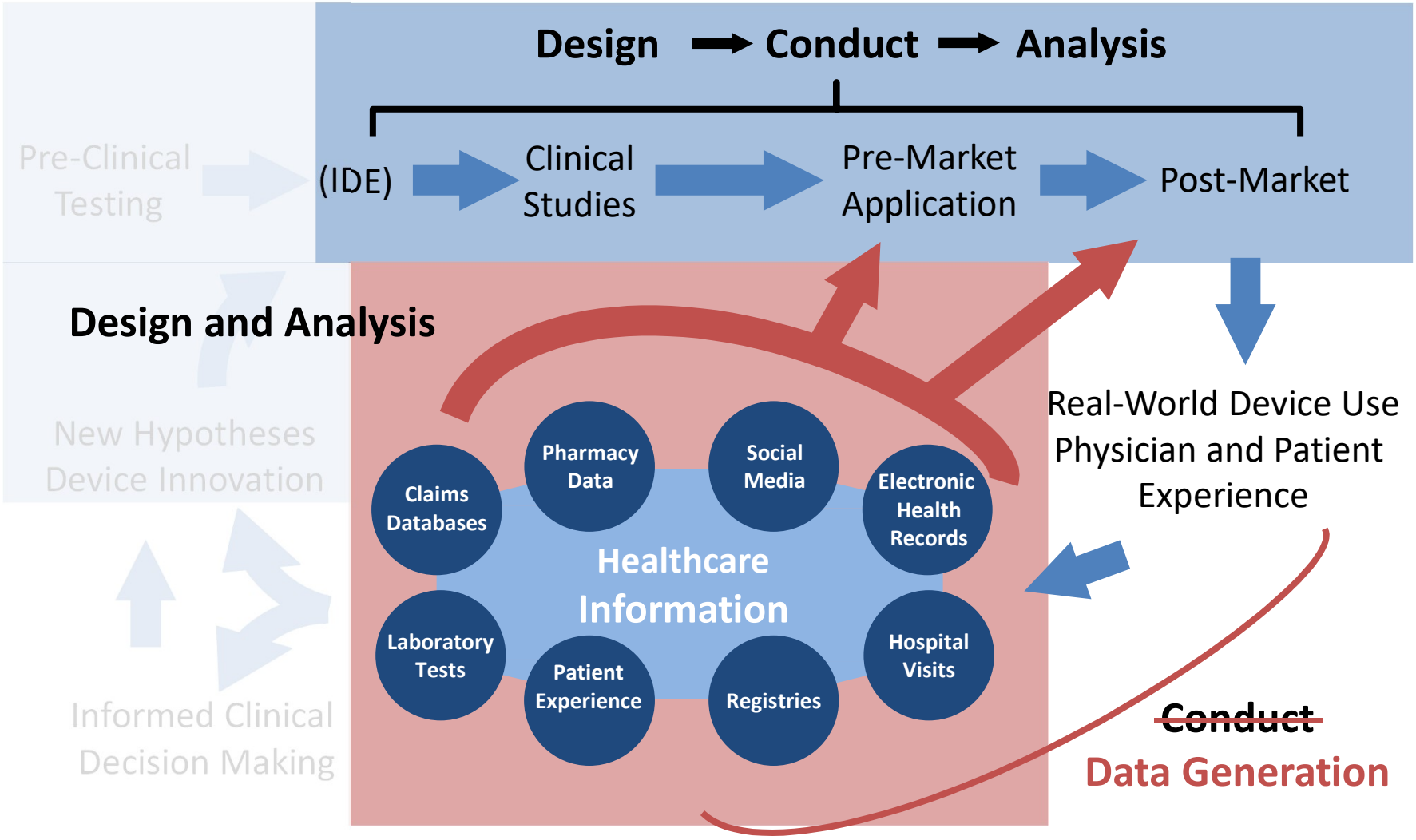
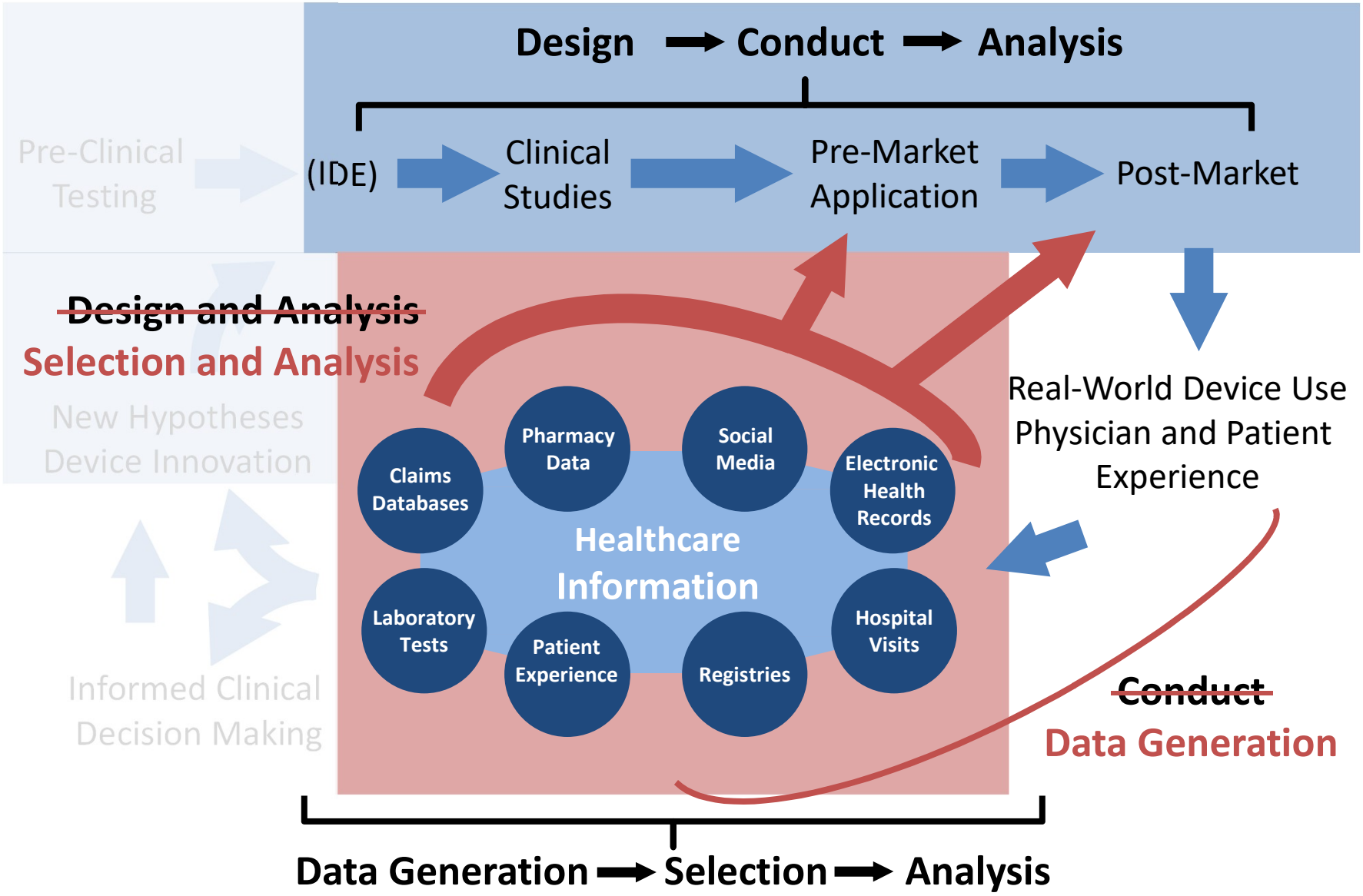
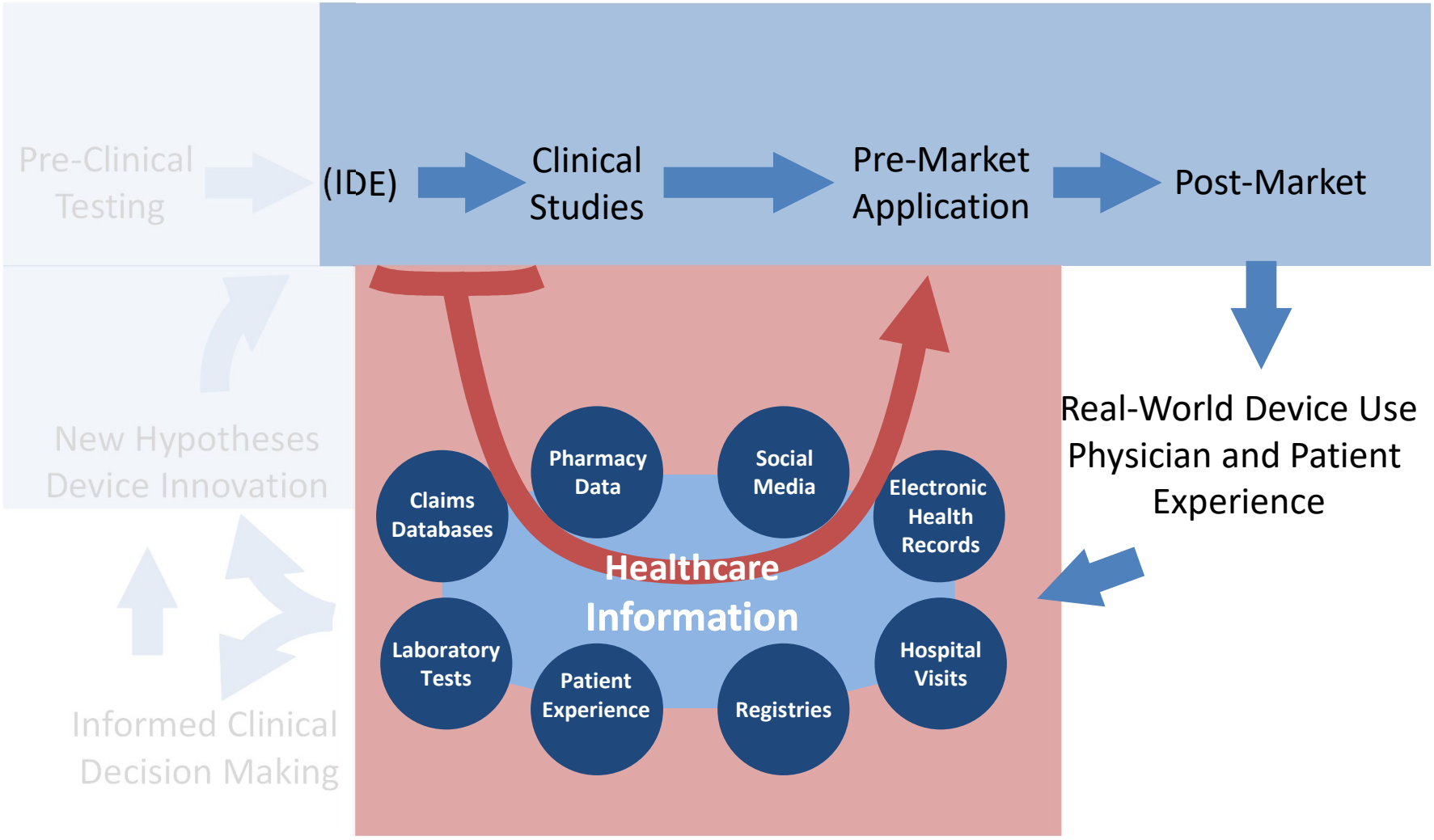


Retrospective Analysis



Embedded Clinical Study



Examples of RWE USE

Some Regulatory Uses for RWE

Control arm for pivotal clinical study

Replacing post approval study

Supplementary Data

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

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

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.

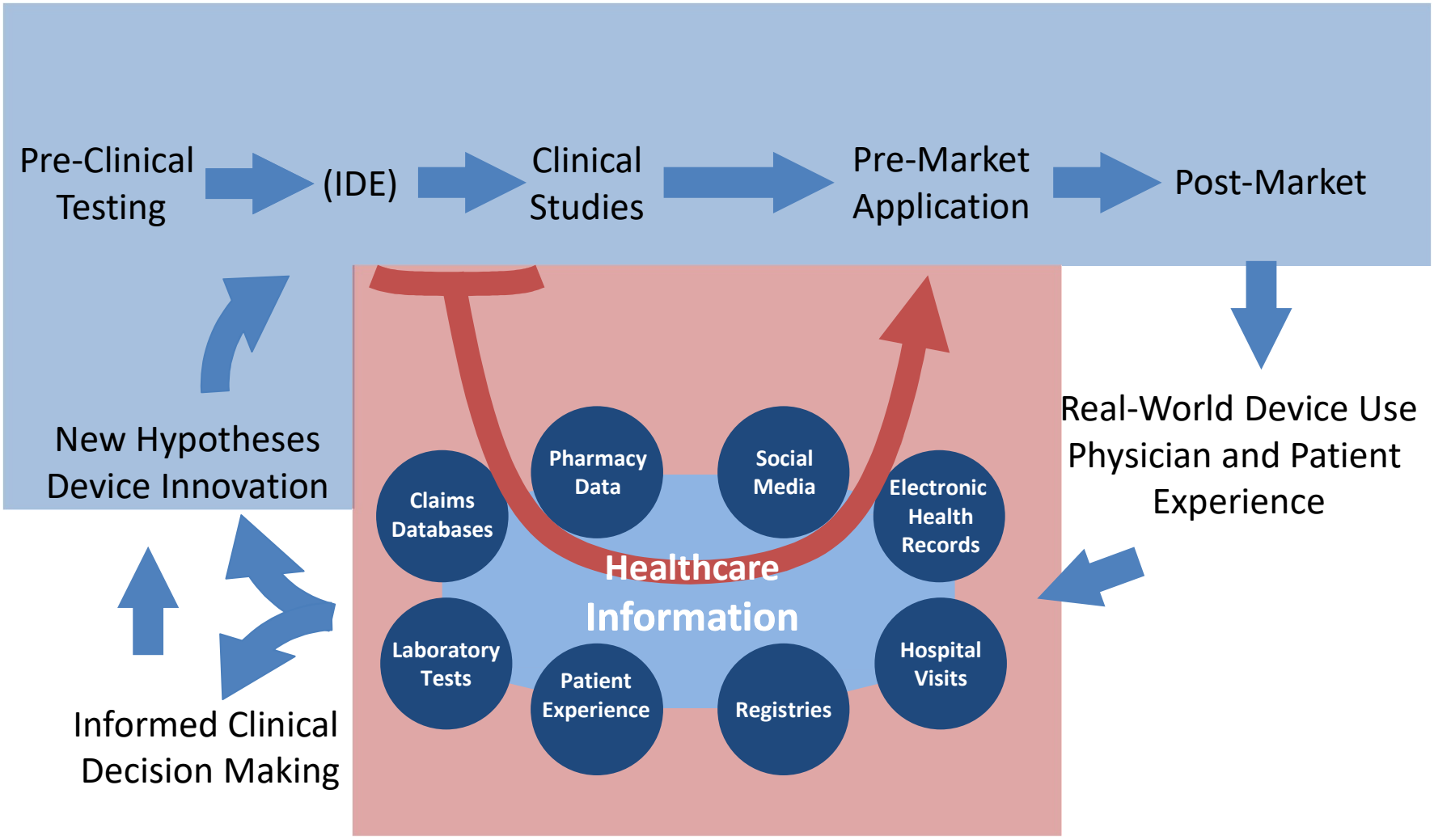
RWE Reliability Evaluation
Data Assurance - Quality Control

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

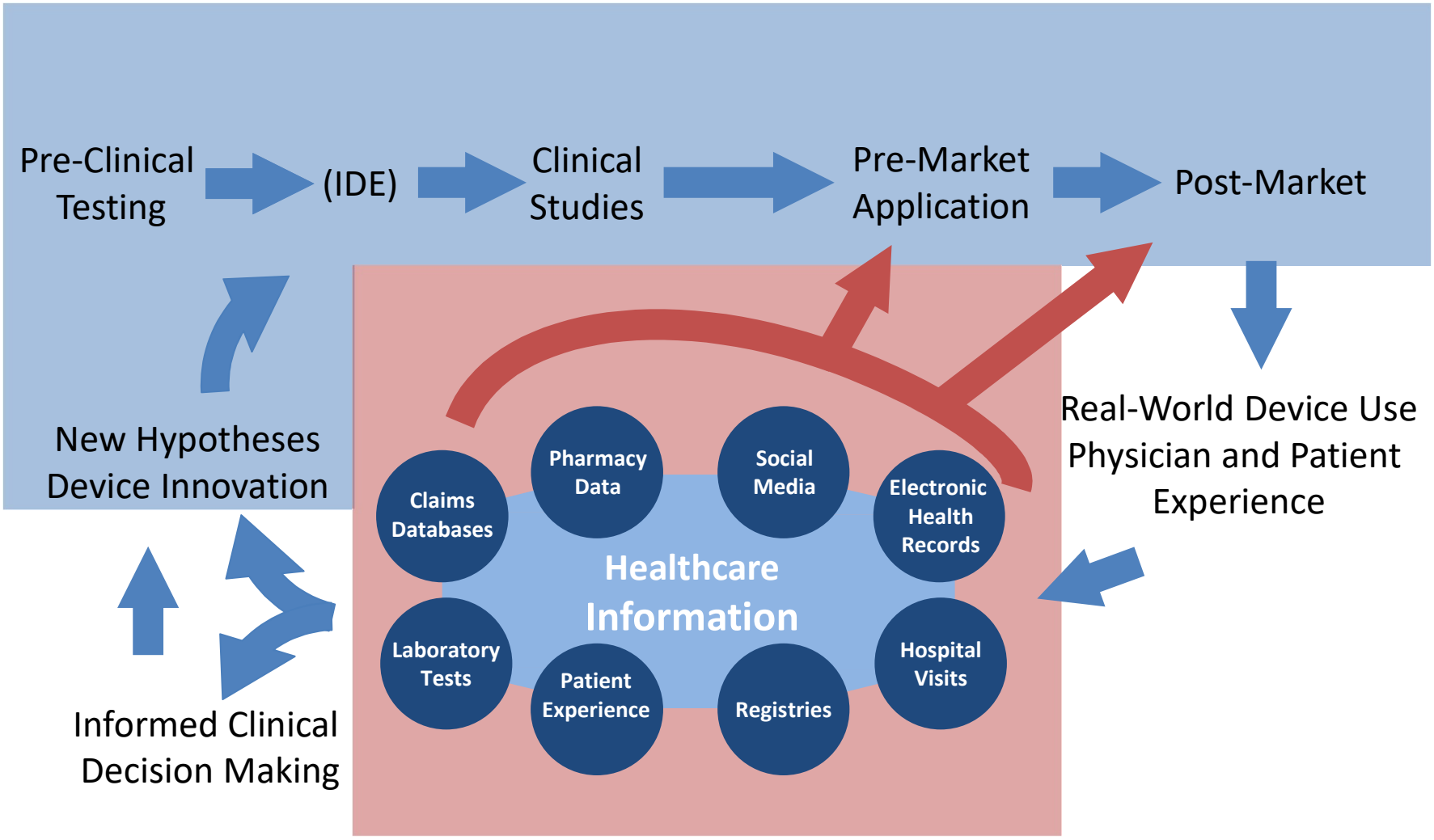
- Includes consideration of aspects such as:
  - How data elements were populated.
  - Data source verification procedures.
  - Data completeness including of confounding factors.
  - Data consistency across sites over time.
  - Evaluation of on-going training programs.

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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