Harnessing Real-World Data (RWD) for and from *in vitro* Diagnostics (IVDs)

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Food and Drug Administration (FDA)

ISPOR – Baltimore, MD 5/23/2018

SHIELD$_x$ *Systemic Harmonization and Interoperability Enhancement for Lab Data*

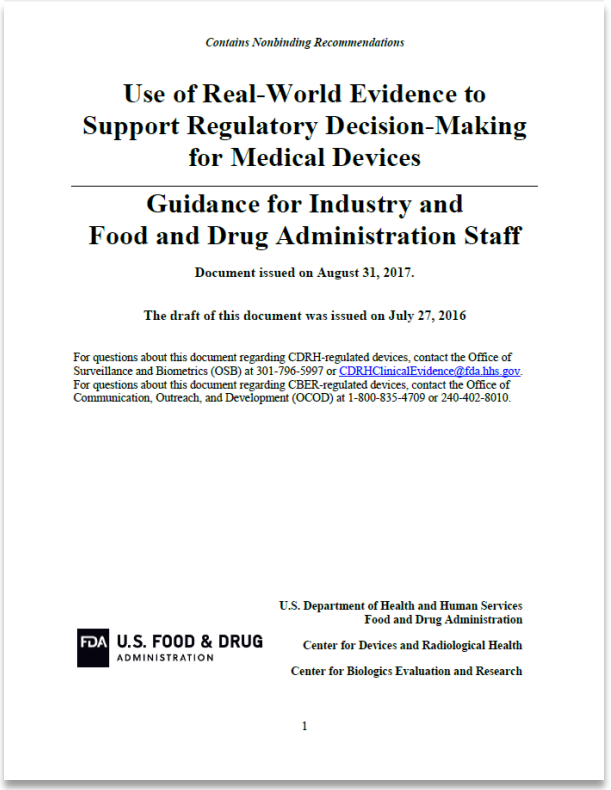
Context for RWE Guidance

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



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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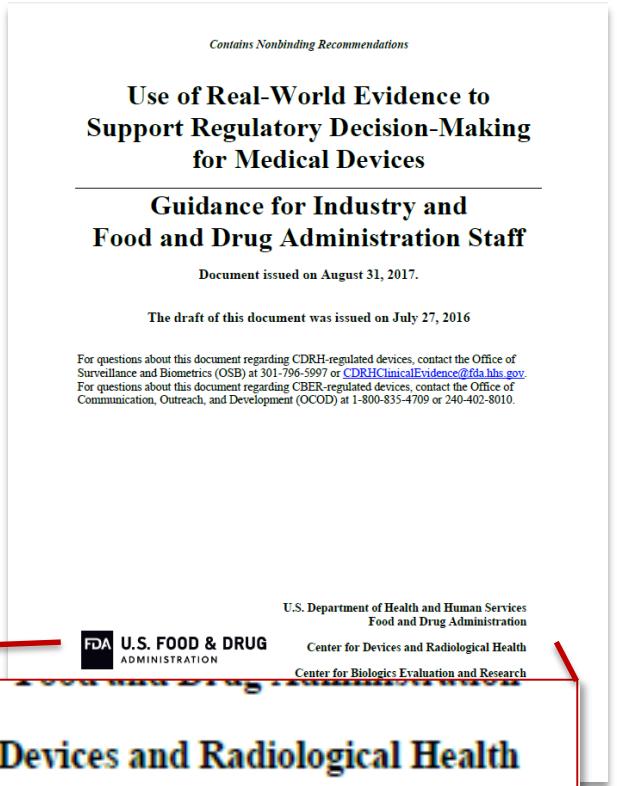

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What IVDs Do?

- *In vitro* diagnostics (IVDs) products are… intended for use in diagnosis of disease or other conditions...

  [21 CFR 809.3]

- Fundamentally, IVDs ‘ask’ a question of a specimen taken from a human body.

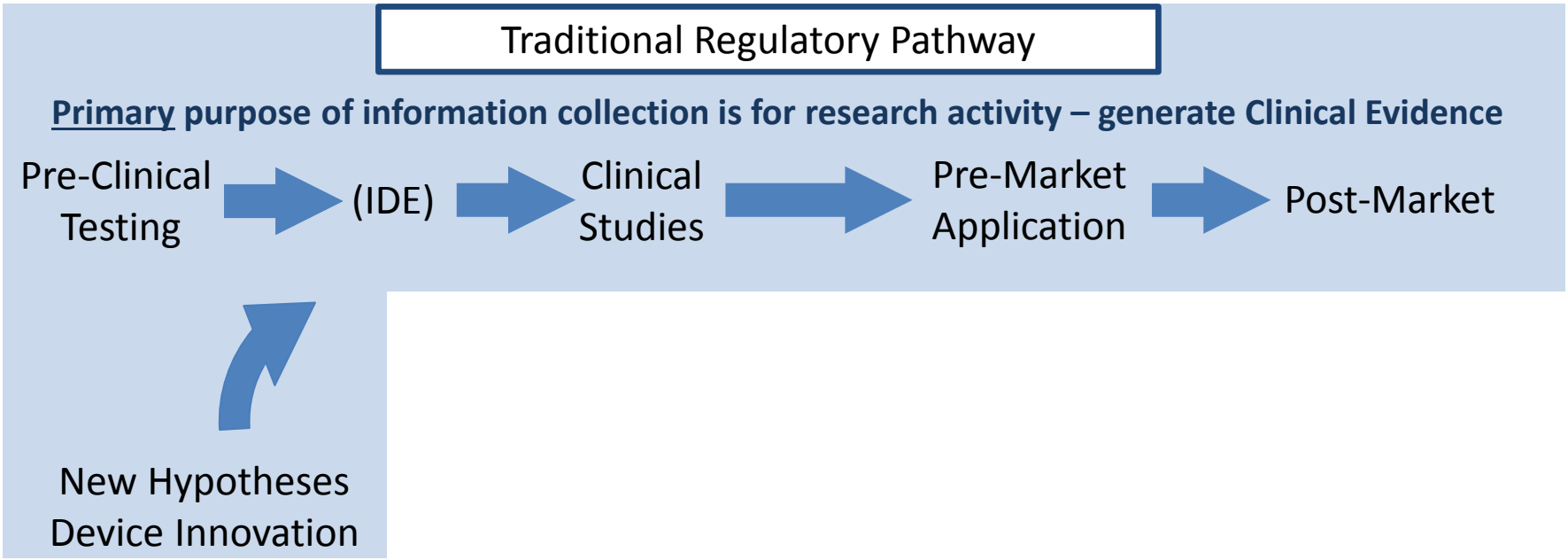
- The result that follows is the ‘answer’ to that question.

- Each individual device is ‘who’s asking.’

Some Nuances Unique to IVDs

- Labs operate under the Clinical Laboratory Improvement Amendments (CLIA) regulations
- CMS oversees labs through the College of American Pathologists (CAP) lab accreditation program Labs regularly conduct proficiency testing of CAP panels and submit results to CAP *(for most tests)*
- Labs conform to Good Laboratory Practices (GLP) *(21 CFR 58 & 42 CFR 493)*
- Labs have to validate off-label use and Laboratory Developed Tests (LDTs)

Evidence for Regulatory Decisions



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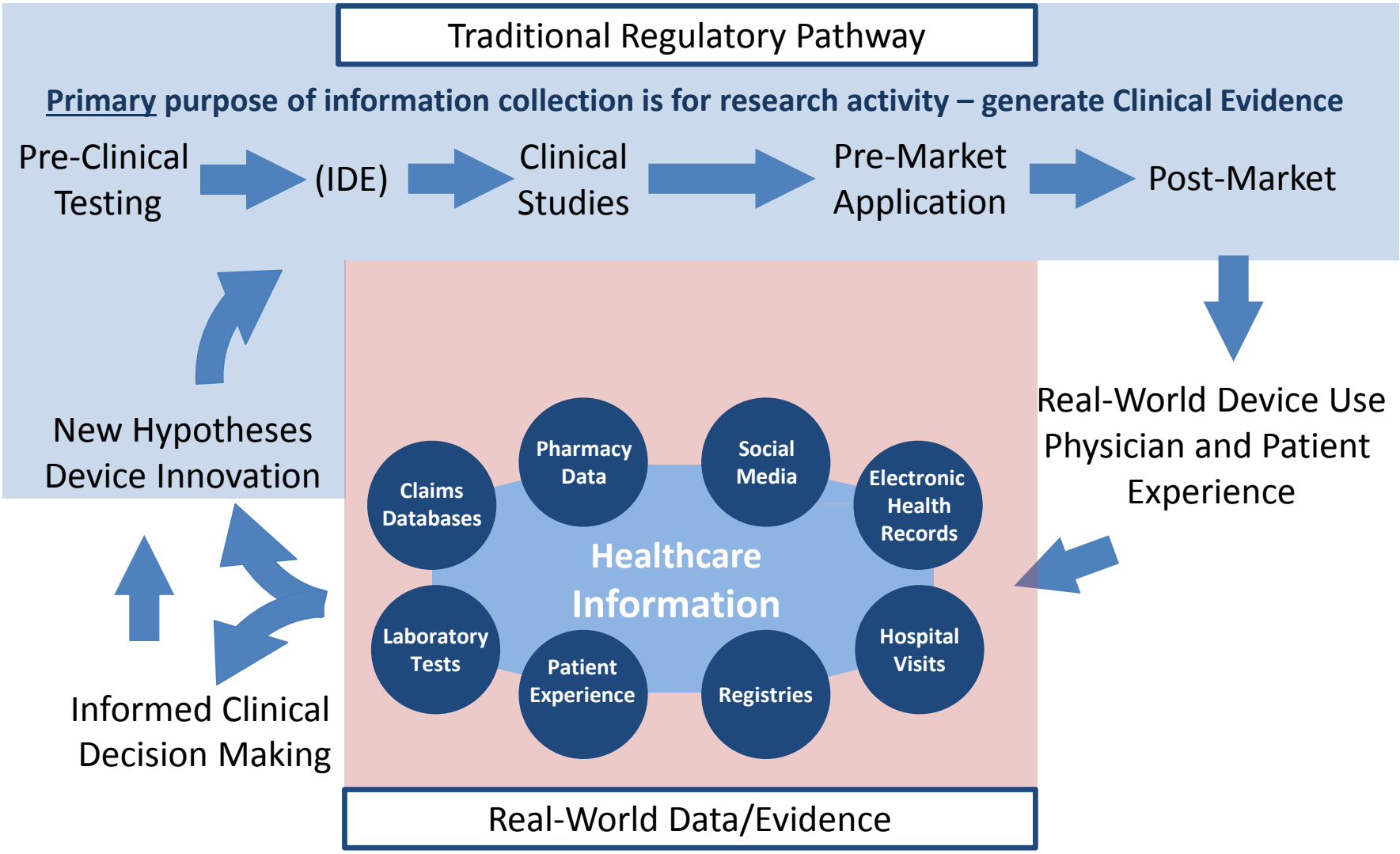
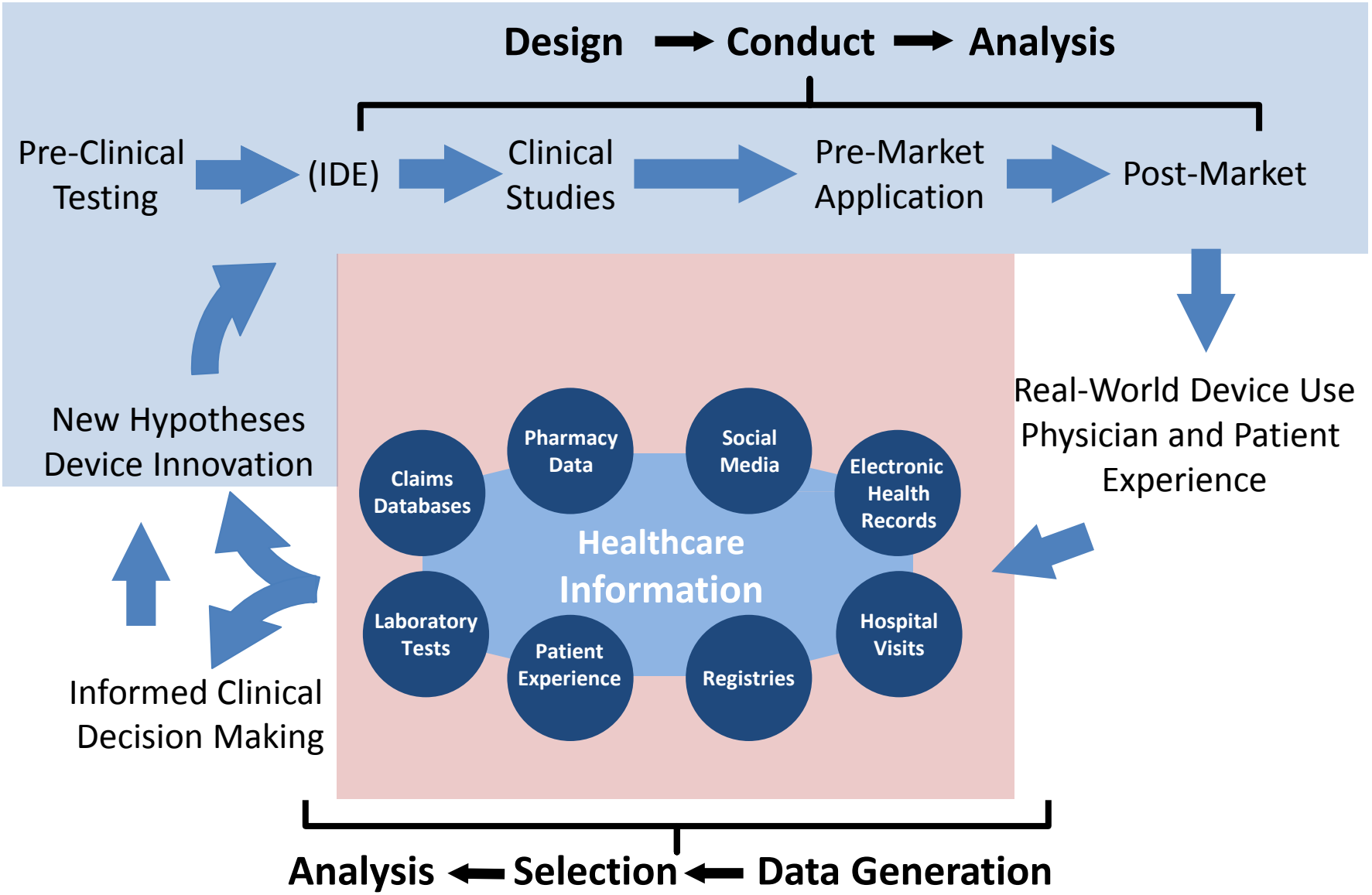


Retrospective Analysis



Data Quality

‘Fit for Purpose’

Data must be complete, consistent, accurate, and *contain all critical data elements needed* to evaluate a medical device and its claims.

Relevant & Reliable

Benefit

Risk

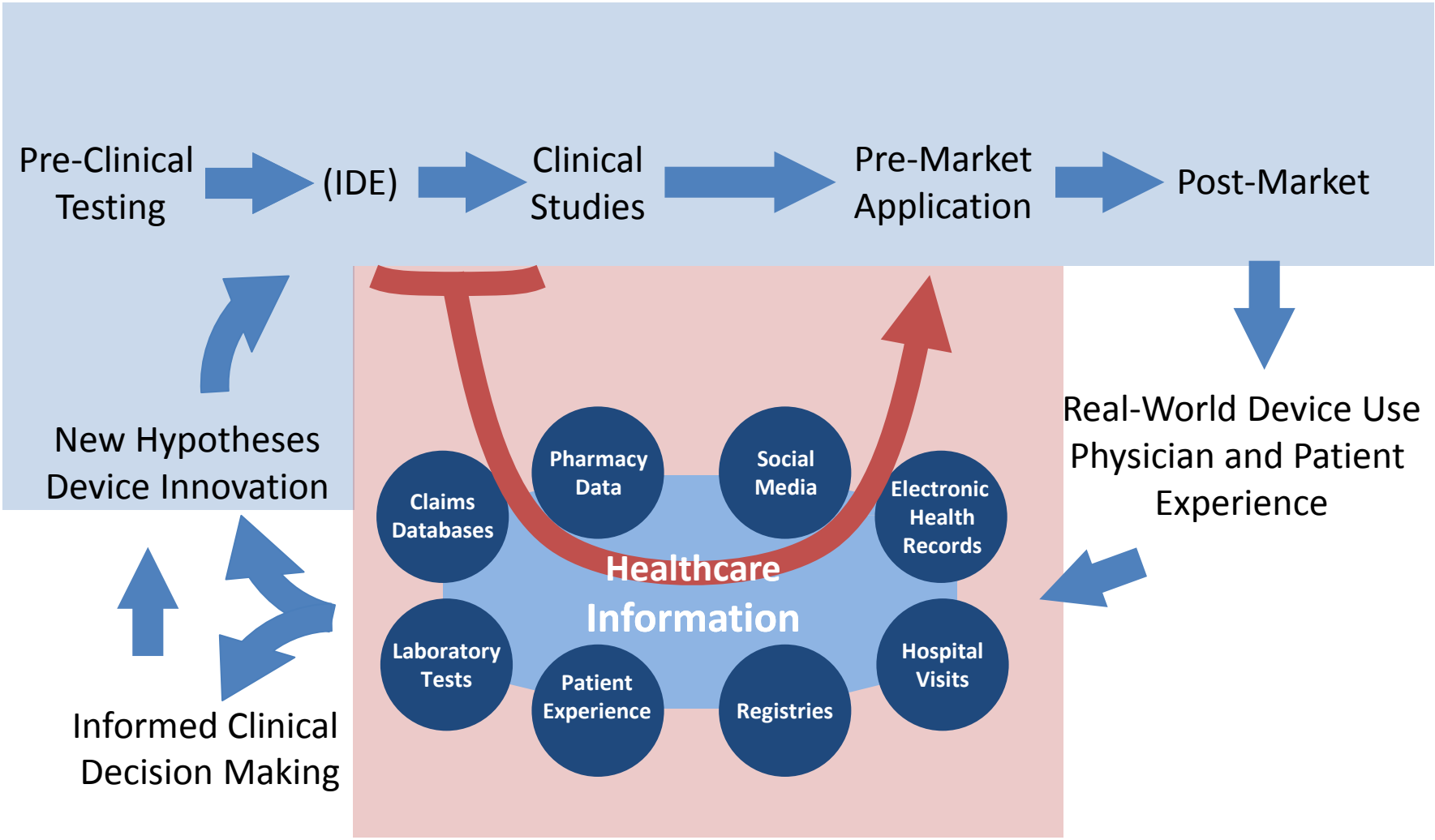
Safety

…probable *benefits to health* from use of the device *outweigh any probable risks* *[21 CFR 860.7(d)(1)]*

Effectiveness

…use of the device in the *target population* will provide *clinically significant results* *[21 CFR 860.7(e)(1)]*

Embedded Clinical Study



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.

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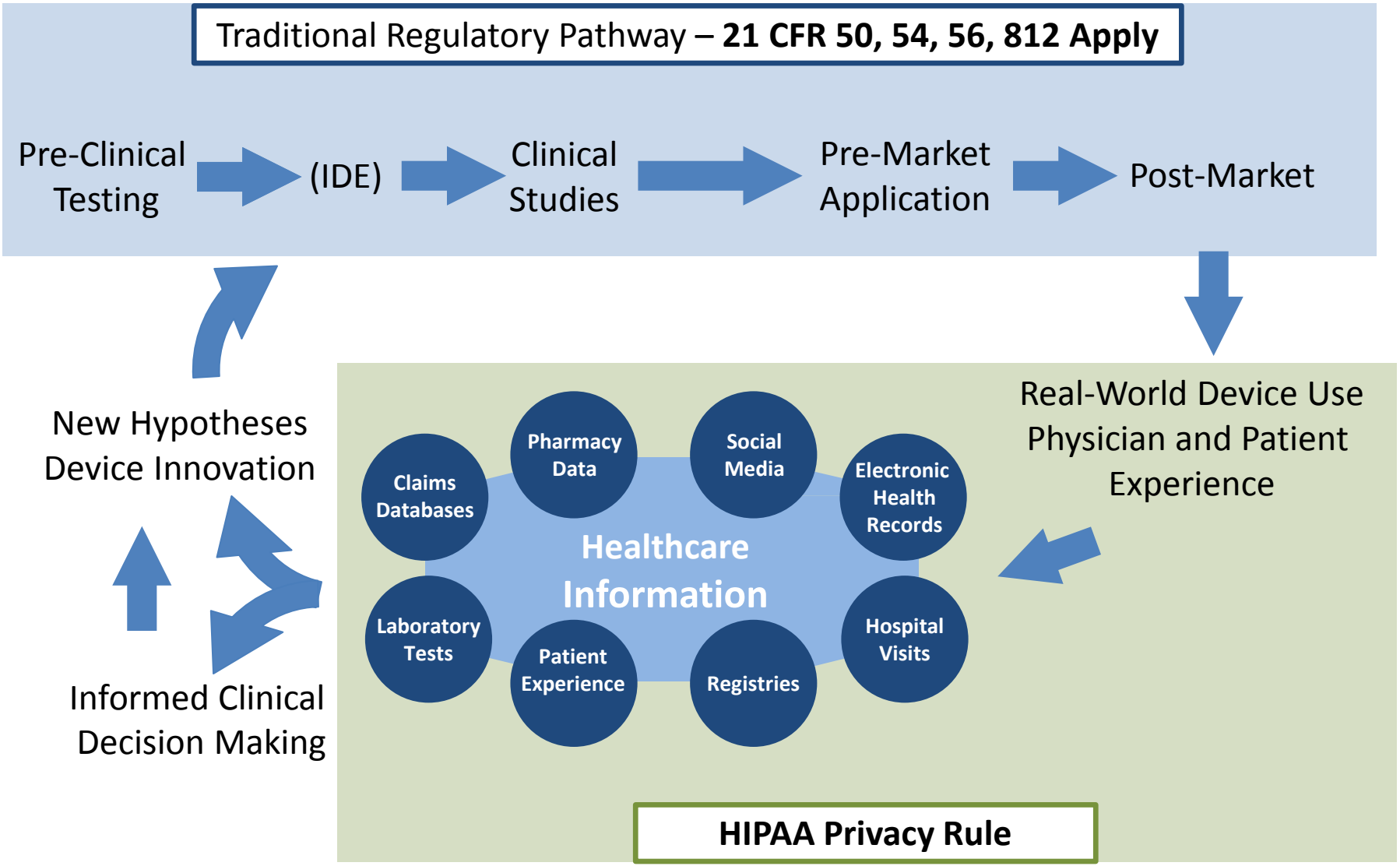
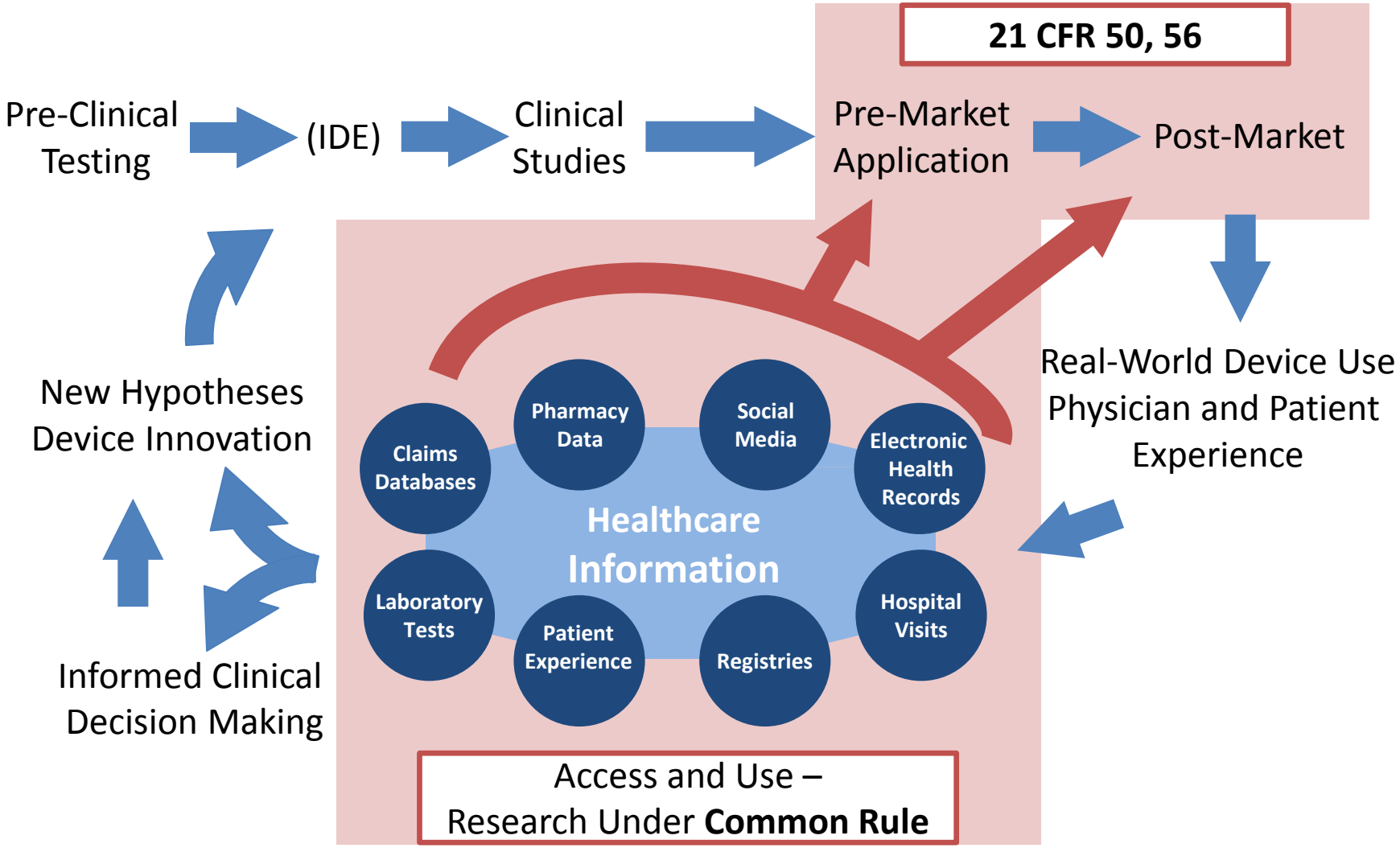


Research on Information



Example Case Studies

#	Device (Submission)	Data Source	Used	Action
1	Wearable (PMA/S)	*Wearable Device & Patient Reports*	Modification of claims from adjunctive to non-adjunctive to use diagnostic for treatment decisions	Indication Expansion
2	Computer assisted triage software (De Novo)	*Literature*	Peer reviewed literature Meta-analysis.	New Indications
3	Sequencing assay (510(k))	*Public NGS database*	Publicly-maintained database support clinical validity of the test in lieu of clinical trials	Indication Expansion
4	Screening assay (De Novo)	*State lab & surveillance databases*	Pivotal clinical trial was embedded in routine clinical practice (under an IDE) in lieu of a traditional pivotal trial.	New Indications
5	Implantable Cardioverter-Defibrillator (PAS)	*Multiple RWD data sources*	Monitor multiple aspects of real-world device safety and performance using data collected in routine care.	Condition of Approval

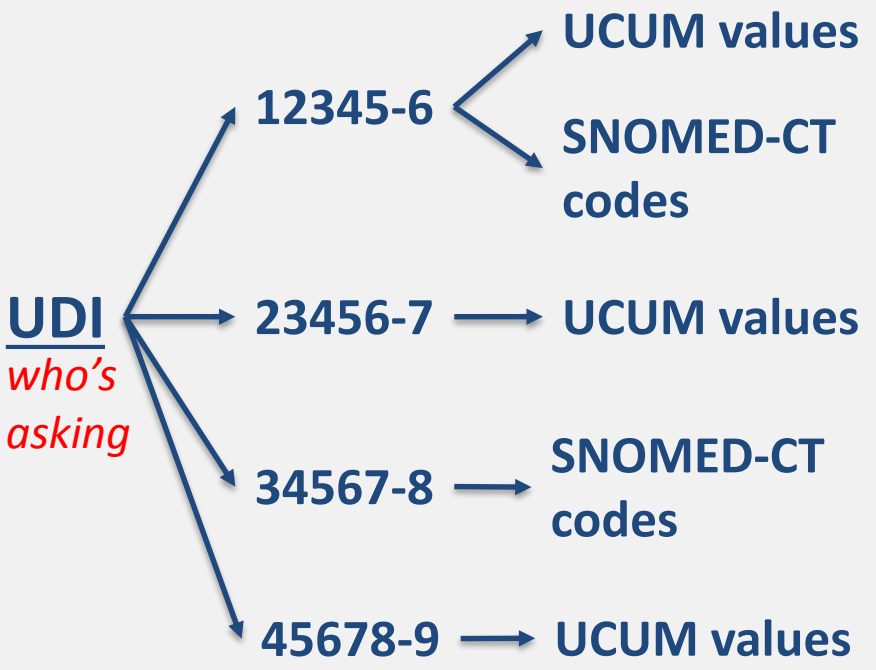
SHIELD: Empowering Tools for Lab Data

FDA

UDI	
Element	**Example**
Device Identifier	
Production Identifier	

LOINC	
Element	**Example**
Component	White Blood Cells
Property	Number Concentration
Timing	Point in Time
System	Cerebral Spinal Fluid
Scale	Quantitative
Method	Manual Count

Use



LOINC is used throughout electronic healthcare messaging, from ordering → reporting

Projected Return On Investment (ROI)

GOAL: IVD Manufacturers Intend to Map and Send Codes for:

Question (e.g., LOINC)
Answer (e.g., SNOMED-CT)
Who's Asking (e.g., UDI)

→ Transmission (i.e., LIVD) → Clinical Information Sharing System (i.e., HL7 v2/FHIR) → Laboratory Information Systems (LIS)

RWD/RWE through TPLC
- Reliable/robust quality pre/postmarket RWD
- Access to meaningful RWE

Tracking
- Infectious disease outbreak monitoring
- Real-time epidemiology
- Public health reporting
- Signal detection

Savings
- Lab savings
- Reduced RWD costs

Patient Protection
- Adverse event reduction
- Clinical Decision Support (CDS)
- Healthcare research

SHIELD Stakeholders:

FDA, CDC, NIH, ONC, CMS, Industry, Labs, EHR Vendors, Standards Developers, more.

Get involved. Contact: Michael.Waters@fda.hhs.gov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Case Example: Leveraging RWE in a Pre-Market De Novo Application

FDA approved an indication expansion:

from: *adjunctive* use followed by an invasive monitoring procedure

to: *non-adjunctive* use—where Continuous Glucose Monitor CGM information can be used directly to make diabetes treatment decisions.

Patient & Healthcare Provider Experience; Wearable Device Data Logs :

- Panelist clinical experience w/ current off-label non-adjunctive use of the marketed device.
- Direct comments from current users regarding their experience with off-label non-adjunctive use of the marketed device including public comments from patients, caregivers and other members of the community impacted by the disease.
- Data was generated both by the device (through event logs) and by the patients (through a log of their experience).
- Additional safety endpoints around symptomatic (subject reported) or asymptomatic (device derived) hypoglycemia as well as severe hypoglycemic episodes were reported.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P120005S041

Case Example: Leveraging RWE in a Pre-Market De Novo Application

FDA granted a De Novo for computer-assisted triage and notification software intended to notify an on-call neurosurgeon specialist of a potential stroke in their patients.

Traditional Multi-Reader Multi-Case (MRMC) Study: MRMC study with hundreds of patient cases and 20 to 30 readers in multiple reading sessions (with and without device).

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Study with RWE– Published studies comparing the standard of care with and without computer-assisted triage software was used to supplement stand alone testing.

- Meta-analysis from peer reviewed literature recording the time to notification for an on call neurosurgeon.
- Stand alone testing to estimate the performance of the subject device to a test data set with known ground truth for sensitivity and specificity analysis.

https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170073.pdf

Case Example: Leveraging a RWD Database to Enable Pre-Market Claims

FDA cleared two 510(k)s for sequencing assays for variant/variant combinations associated with cystic fibrosis using a public next-generation sequencing (NGS) database.

Traditional Studies: Full clinical trials/summary of information available in peer-reviewed literature to provide evidence of the test's clinical validity.

https://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf
https://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm509837.pdf

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Study Using Public Database – An established publicly-maintained database hosted by the academic institution was used to support clinical validity of the test in lieu of clinical trials.

- Database used as a source of valid scientific evidence to establish which variants/ variant combinations were causal for the target disease.
- Additional relevant patient information, e.g. sweat chloride, lung function, pancreatic status, and *Pseudomonas* infection rate, associated with each variant/variant combination were included in the evaluation.

https://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf
https://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm509837.pdf

Case Example: Embedded Pivotal Trial in a RWD Source for a Pre-Market De Novo Application

FDA granted a De Novo for a newborn screening assay for enzymes associated with lysosomal storage disorder from dried blood spots.

Traditional Pivotal Trial: Full traditional pivotal trial to capture each of the endpoints that were captured in the embedded pivotal trial.

https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN150035.pdf ; Advisory panel meeting, 8/10/16

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Collection from RWD source – In lieu of a traditional pivotal trial, a pivotal clinical trial was embedded in routine clinical practice.

- Pivotal trial evaluated performance on all samples submitted to a state lab for routine screening in lieu of banked bio-specimens artificially enriched with known positives.
- Used a department of health surveillance program to check for false negatives reported to the state's contracted metabolic centers.
- This study was conducted under an Investigational Device Exemption (IDE).

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