U.S. FOOD & DRUG ADMINISTRATION

Evidence from Clinical Experience in CDRH

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Office of Product Evaluation & Quality
Center for Devices and Radiological Health
April 26, 2023

2012 to Current State

2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022

2012 to Current State

2012

FDA proposed development of a national system

2013

CDRH Priority [Strengthen Clinical Trial Enterprise & National Medical Device System]

2014

Established a Clinical Trials Program and Director

2015

NEST envisioned as community driven data network of collaborators

2016

FDA awarded funding for NEST

2017

Guidance on RWE for Regulatory Decision Making

2018

NESTcc Data Network formed & test cases initiated

2019

CDRH Re-Org Creation of OPEQ and OCEA

2020

NEST issued Data Quality & Methods Frameworks

2021

90 examples of RWE used in regulatory submissions

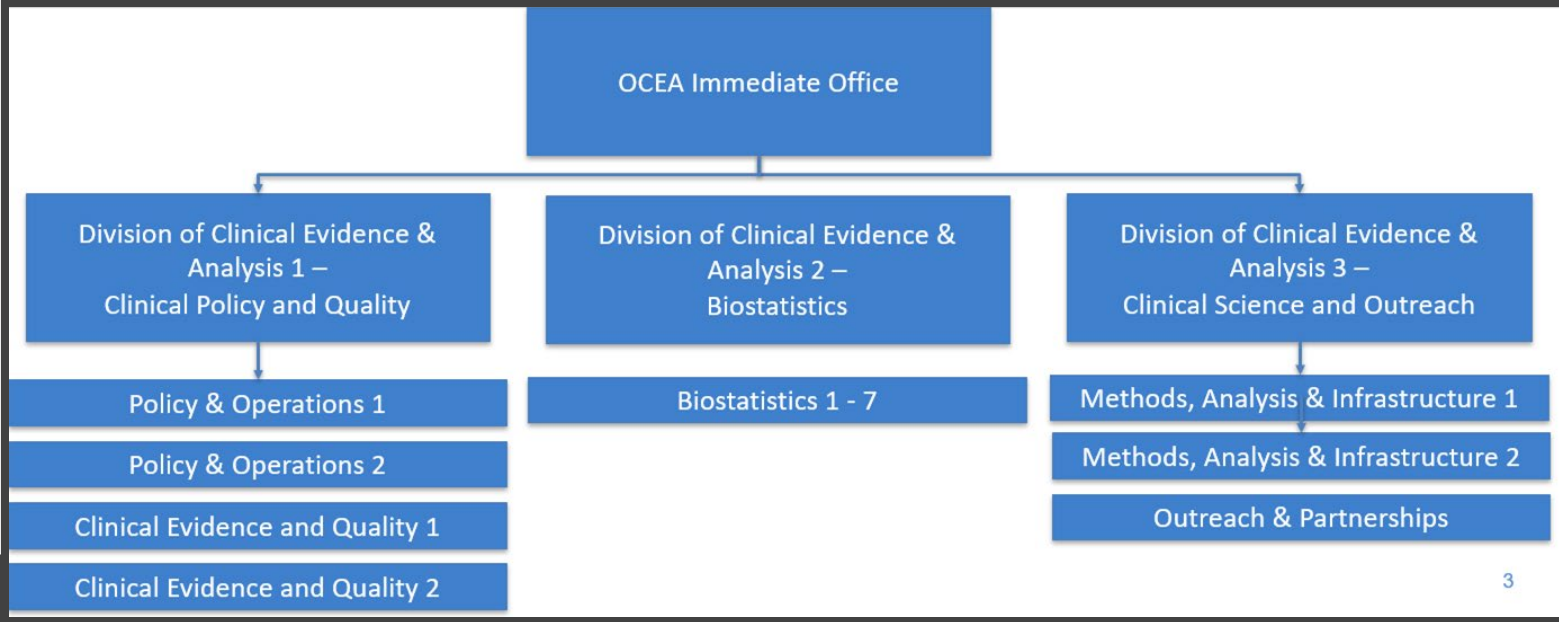
2022

Adverse Event Reporting in RWE Studies

Optimizing Infrastructure for Clinical Evidence

- Policy and program support of clinical trials and expedited access programs,
- Human subject protection and Good clinical and laboratory practice,
- Biostatistics,
- Real-world evidence,
- Epidemiological analysis, and
- Outreach and collaboration with hospitals and other external stakeholders.

Office of Clinical Evidence & Analysis



Office of Product Evaluation and Quality

OPEQ Immediate Office

Office of Regulatory Programs	Office of Clinical Evidence & Analysis	Office of Health Technology 1 (Ophthalmic, Anesthesia, Respiratory, ENT & Dental Devices)	Office of Health Technology 2 (Cardiovascular Devices)	Office of Health Technology 3 (Reproductive, Gastro-Renal, Urological, General Hospital Device & Human Factors)	Office of Health Technology 4 (Surgical & Infection Control Devices)	Office of Health Technology 5 (Neurological & Physical Medicine Devices)	Office of Health Technology 6 (Orthopedic Devices)	Office of Health Technology 7 (In Vitro Diagnostics)	Office of Health Technology 8 (Radiological Health)

CDRH Foundations for Clinical Evidence

1. Training

- ✓ Rounds on RWE resources
- ✓ Training series on Real World Data (RWD) sources
- ✓ OHT-specific training for RWE relevance and reliability

2. Measuring

- ✓ Tracking marketing authorizations based on RWE
- ✓ Developing automated identification of RWE in submissions

3. Establishing Expertise

- ✓ Focal Point Program
- ✓ OCEA epidemiologists, biostatisticians, data scientists, and policy experts

4. Improving Science & Policy

- ✓ Updating RWE Guidance
- ✓ National Evaluation System for Health Technology (NEST)

RWE Challenge

- MDR Regulations (21CFR 803) require that device manufacturers submit a report to FDA when they become aware of:
  - serious adverse events,
  - deaths, and
  - certain device malfunctions.
- Each event reported in one MDR.
- Device manufacturers have indicated there is a lack of clarity regarding MDR reporting requirements that might be triggered.
- Not informative or efficient for manufacturers to submit or for FDA to review a bolus of individual events without context of RWE analysis.
- In some cases, a holistic report that groups events and provides context for the reported events may increase the quality of information available to inform post-market decisions.

Current Solution

- Manufacturers planning to analyze RWD could submit a request to report events discovered within certain RWD sources differently from the requirements of 21CFR 803.

- Requests should be submitted and approved ***before*** submitting a report that deviates from reporting requirements outlined in 21CFR 803.

- Recently updated the Exemptions, Variances, and Alternative Forms of Adverse Event Reporting for Medical Devices | FDA webpage
  - Communicates that CDRH has granted exemptions and variances from the requirements of 21CFR 803 for events identified in RWD sources such as registries
  - Lists the scope of exemptions, variances or alternatives for RWD sources that include
    - registries,
    - electronic health records, and
    - medical claims
  - Identifies information that should be submitted in a request for exemption, variance or alternative form of reporting.

NEST – Infrastructure

Customers

NEST Coordinating Center

Analytic Core (s)

Common Data Model

Data Connector (s)

Data Platforms & Sources

CVS Health · Mayo Clinic · MDEpiNet · Mercy · NWEH Discover-NOW · DukeHealth · HealthCore · INSIGHT Clinical Research Network · Lahey Hospital & Medical Center · Vanderbilt University Medical Center · Weill Cornell Medicine · Yale NewHaven Health · MedStar Health · Regenstrief Institute · OneFlorida Clinical Research Consortium · PEDSnet · STAR

+ Commercially Available Data Sources

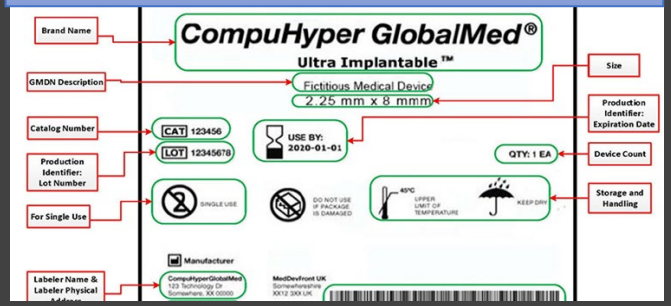
www.fda.gov

Full Integration of Clinical Evidence Sources

Electronic Health Records

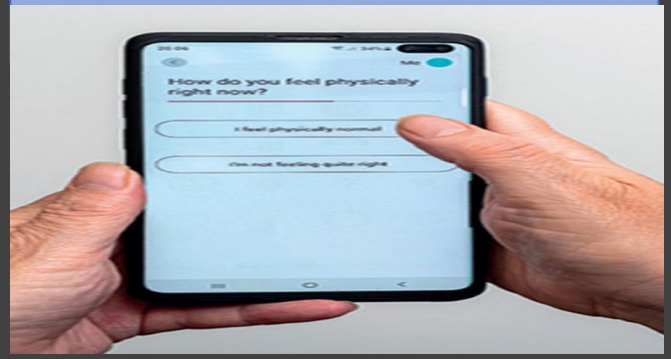
Administrative Claims

Device/Patient Registries



Diagnostic lab and imaging

Patient Generated Health



Device Generated Data

www.fda.gov

Increasing Use of Evidence from Clinical Experience

- Monitoring impact through tracking RWE use in premarket regulatory decisions
- Advancing RWE Adoption and Use for Regulatory Purposes
  - Through policy and
  - Internal trainings
- Optimizing Infrastructure to Develop RWE:
  - Internally aligned to maximize support for TPLC use of evidence from clinical experience
  - Developing infrastructure, including NEST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& Device
s

NEST
Coordinating Center
An initiative of MDIC

Overview

Simon Mason | President

April 26, 2023

The **National Evaluation System for health Technology (NEST)** was established as a national system developed to efficiently generate better evidence for medical device evaluation and regulatory decision-making.

The idea behind NEST was first conceived by the FDA in 2012 and further refined by various planning committees through 2016.

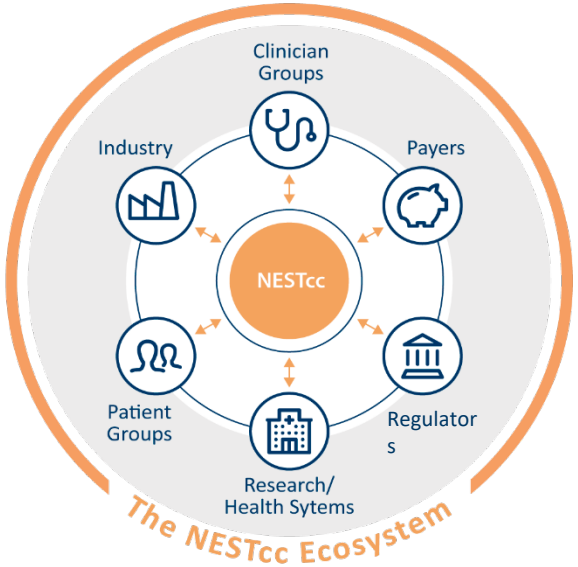
In 2016, MDIC was awarded a U01 Cooperative Grant from the FDA to establish the **NEST Coordinating Center (NESTcc)** as an operational business unit within MDIC that provides:

- Governance for the NEST ecosystem
- Development AND maintenance of the research infrastructure
- Guidelines for methodology and data quality
- Insight into the strengths and limitations of RWD data sources
- Work towards self-sustainability

CORE INITIATIVES

1. EVIDENCE GENERATION

NESTcc is a coordinating center that delivers high-quality evidence in the evaluation of medical devices and health technologies throughout the total product life cycle.
Regulatory, Reimbursement and Clinical Decision-making



2. COLLABORATIVE COMMUNITY

NESTcc has been recognized by FDA as a Collaborative Community, working to bring together diverse stakeholders to address common medical device ecosystem needs and initiatives.
UDI Adoption as Initial Focus

A Network of Collaborators and Strategic Partnerships

Governance | Research Infrastructure | Research Methods Framework | Data Quality Framework
Data Privacy | Device Identification | CDM | Data Curation | Data Linkage | Data Aggregation | Data Analytics

Quality *Evidence* by Design™

Leveraging our unique position, we combine real-world evidence with unparalleled expertise to accelerate patients' access to safe and effective medical technology

Curating the right data sources & research expertise to meet specific objectives – across device types and disease areas

Catalyzing transparent, traceable RWD provenance, leading to actionable evidence for clinical, regulatory or reimbursement decision-making

Creating a central, scalable system architecture for interoperability as a neutral, nonprofit organization informed by diverse stakeholders

NESTcc is Building a Platform for RWE Generation & Utilization

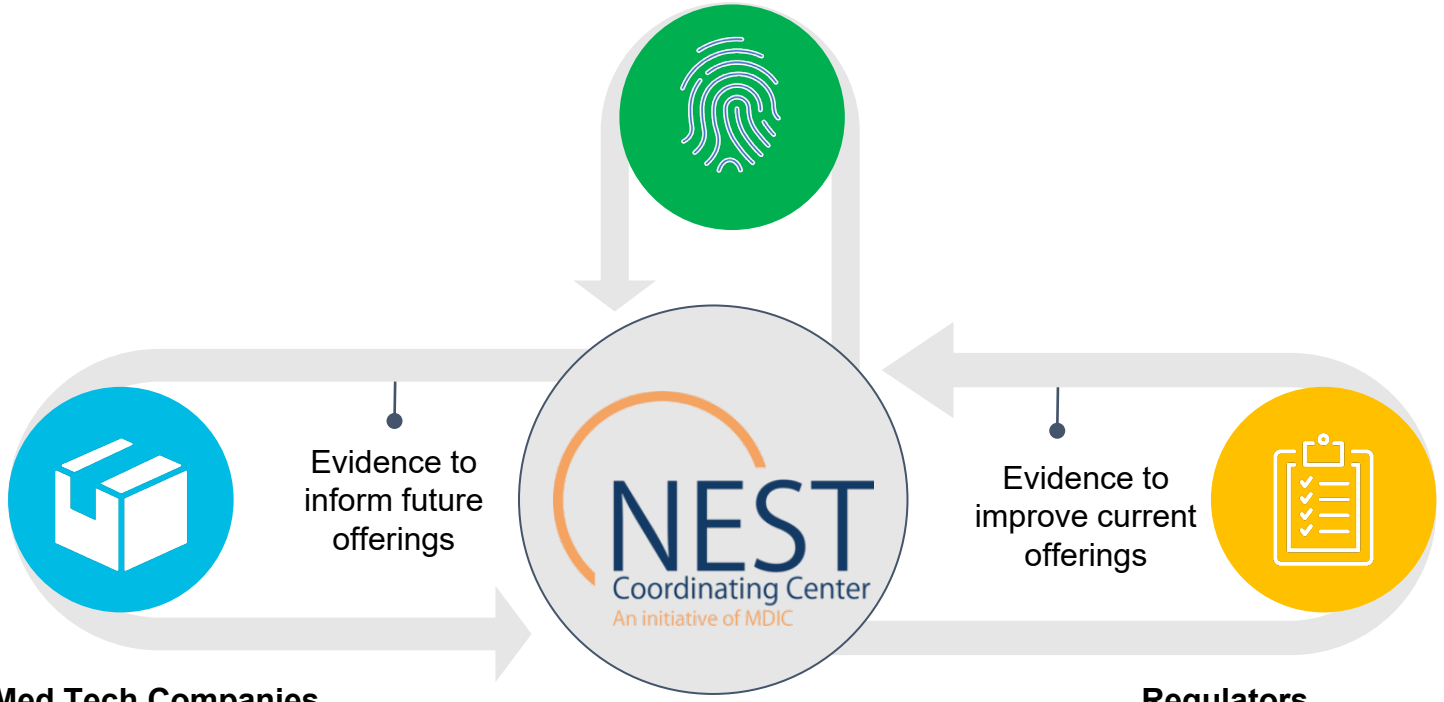
NESTcc is facilitating the generation of high-quality evidence while providing value between:

- **Producers** of Real-World Evidence
- **Consumers** and Evaluators of Real-World Evidence

NESTcc operates as a Neutral Ecosystem initially focusing on the pre-market regulatory space

RWE Data Services & Technology Providers

want to **produce** RWE to inform meaningful regulatory decisions



Med Tech Companies

want to **consume** RWE to increase **confidence** and **produce** RWE to inform meaningful regulatory filings

NESTcc

provides:

+ RWE Strategy Development
+ Data Services
+ RWE Study Contracting and Execution
+ Collaborative Ecosystems

Regulators

want **predictability** around use of RWE to increase industry confidence and **consume** RWE to make meaningful regulatory decisions

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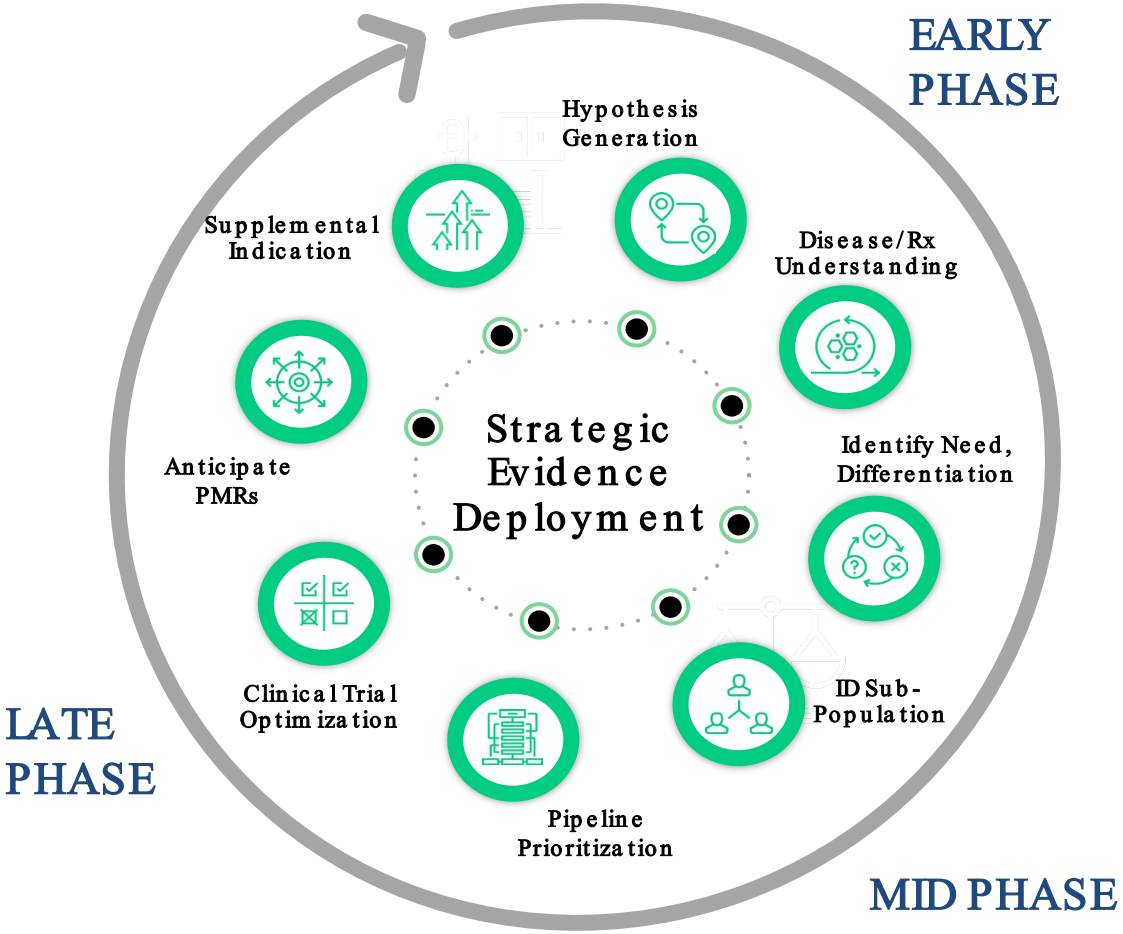
Integrating Evidence from Clinical Experience

Kathleen Troeger, MPH
Real World Evidence Solutions for Medical Device and Diagnostics
Aetion

AFDO RAPS HEALTHCARE PRODUCTS COLLABORATIVE

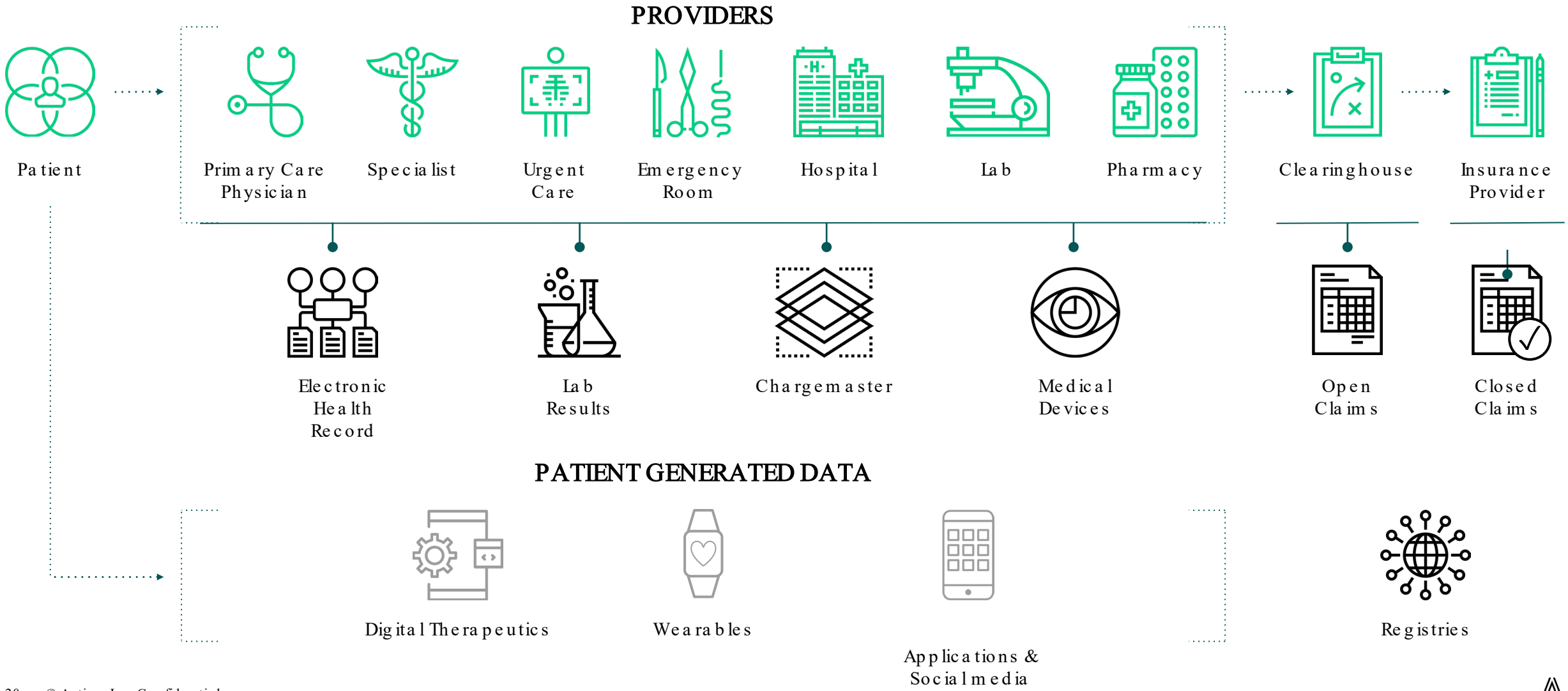
Looking ahead: integrated evidence



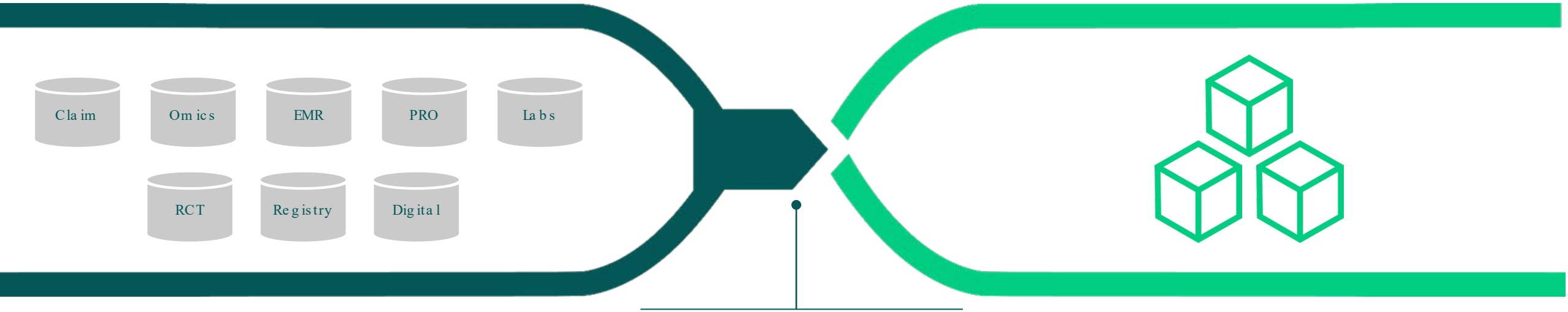
Why it matters

- Accelerate time to market
- Rapidly address regulatory requests
- Reduce risk and increase probability of trial success
- Lower costs through shorter and more targeted clinical trials
- Label expansions

Health data abounds, but...



… we need fit-for-purpose data



Real-world data

Data relating to patient health status and/or the delivery of healthcare routinely collected from electronic health records (EHRs), claims, registries, PROs and devices, etc.

- Fit-for-purpose (FFP) data must be **reliable** and **relevant** within the clinical context
- To identify FFP data, we conduct a **systematic assessment** of data sources using a structured process

Real-world evidence

Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD

Successful evidence integration and analysis requires an optimized environment

- Ready for analysis datasets
- Stacked with robust data synthesis and analytics
- Enable rigorous real world research

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Unlocking the Potential of RWE: NEST Test Case and Other Experience

Paul Coplan, ScD, MBA, FISPE

VP, MedTech Epidemiology & RWD Sciences, Johnson & Johnson

Co-Chair, NEST Data Quality Framework Group

Fellow, International Society for Pharmacoepidemiology

AFDO RAPS HEALTHCARE PRODUCTS COLLABORATIVE

Getting the right medical device/procedure to the right patient at the right time

- Clinical trial evidence is gold standard but has significant gaps
  - RWE needed to answer important questions for treating patients
- Real world evidence is better than no evidence or "eminence-based" evidence
- RWE working for post-approval studies and some label extensions
- Determining level of evidence that is needed for regulatory decisions is an evolving science in terms of data quality, study methodology and whether the results are fit for purpose to answer the research question

NESTcc Test Case Example: Comparative studies for label extensions using RWE

Label extension using RWE for 6-Hole catheter for persistent Afib

Impact

- Test Case funded by National Evaluation System for health Technology (NEST)
- Label extension (PMA) under review by FDA's CDRH
- If FDA approves, first label extension using comparative effectiveness RWE study from EHR databases
- First and only NEST test case of 21 test cases whose data submitted to FDA for label extension

Objective

- To evaluate if 6-Hole catheter not currently approved for persistent AF is non-inferior to 56-Hole catheter that is currently FDA-approved

Results: Primary Safety Endpoint

- Composite safety endpoint (14 safety endpoints) among persistent Afib patients
- ThermoCool ST and STSF groups balanced using propensity score weighting

Health Care System	Cardiac Ablation Catheter #1 (6-hole tip cooling)	Cardiac Ablation Catheter #2 (56-hole tip cooling)	Risk Difference	P-value for non-inferiority
	Cumulative Incidence (90% CI)	Cumulative Incidence (90% CI)		
	N = 337/186	N = 764/184		
Mayo Clinic	4.4% (1.9%, 6.9%)	3.1% (1.0%, 5.2%)	1.3% (-2.1%, 4.6%)	
Mercy	6.2% (4.0%, 8.4%)	10.1% (2.8%, 17.3%)	-3.8% (-11.4%, 3.7%)	
Weighted average			0.5% (-2.6%, 3.5%)	P = 0.002

JAMA Network Open

Dhruva et al JAMA Network 2022

Conclusions

Safety endpoint rate between ST and STSF groups was not inferior (upper 90% CI is less than 7%) and **met the prespecified criteria for label extension**

JAMIA OPEN

Jiang et al 2021

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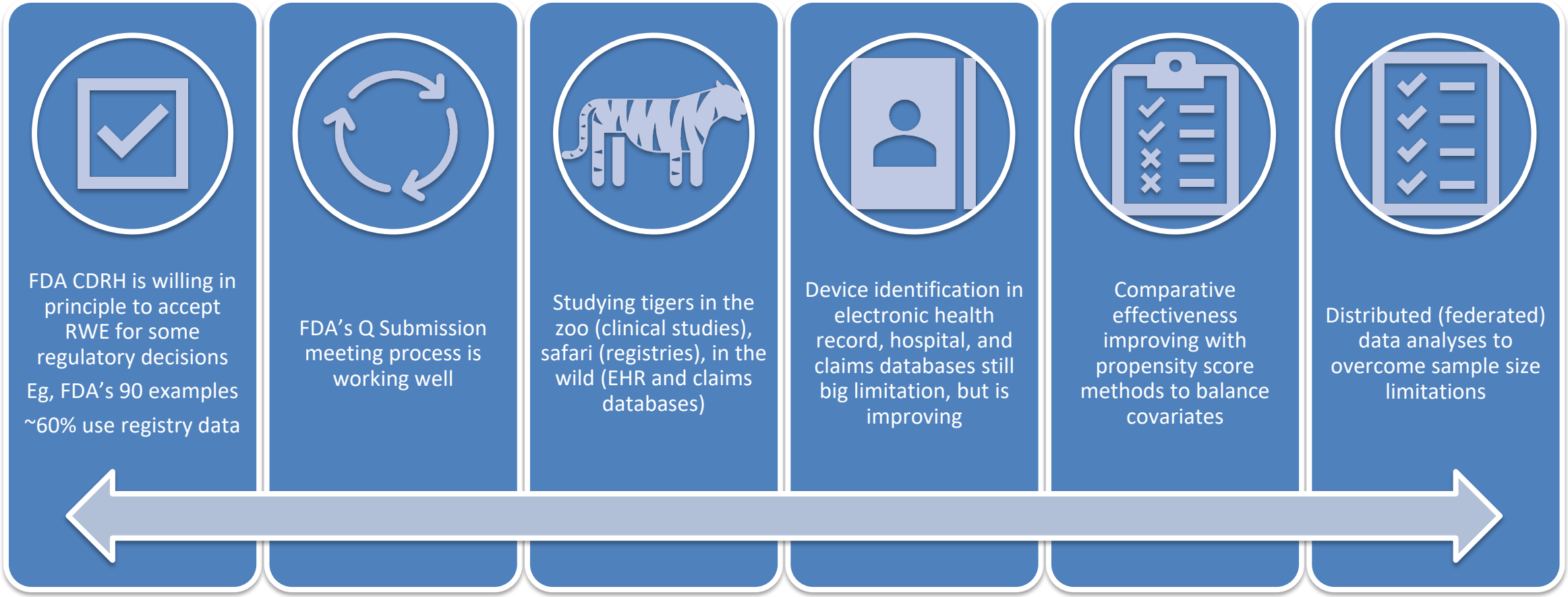
What's working well with RWE for patients, developers and regulators



Common Obstacles with RWE Submissions

Required study variables not available in EHR, hospital or claims databases

- Eg, Orthopedic radiographic images for outcomes
- requires image database linkage to EHR/claims

Long time to finalize study protocol and analysis plan

Q Submission process takes 6 to 9 months to get Agency feedback for 1 data source/design; takes another 9 months for feedback on revised alternative

Validation of study endpoints using ICD-10 codes often required by physician chart review; lengthy, costly exercise and limits databases

Distributed data analyses are complex, require large team coordination across different research teams, and therefore expensive and slow

Long term follow up of acute invasive procedures often limited; loss to follow up can be high

Opportunities for Advancing RWE Use

Data quality issues identified early on

- Avoid rolling set of data quality issues that require new analyses
- Bindingness of Q Submission meetings

Processes for validating study endpoints and variables in EHR, hospital, and claims databases

For orthopedic data, can radiologist text notes of fusion/non-fusion be validated for use instead of actual image data

NEST Data Quality and Methodology frameworks and next generation RWE guidance

Acceptance of outside US orthopedic registry data

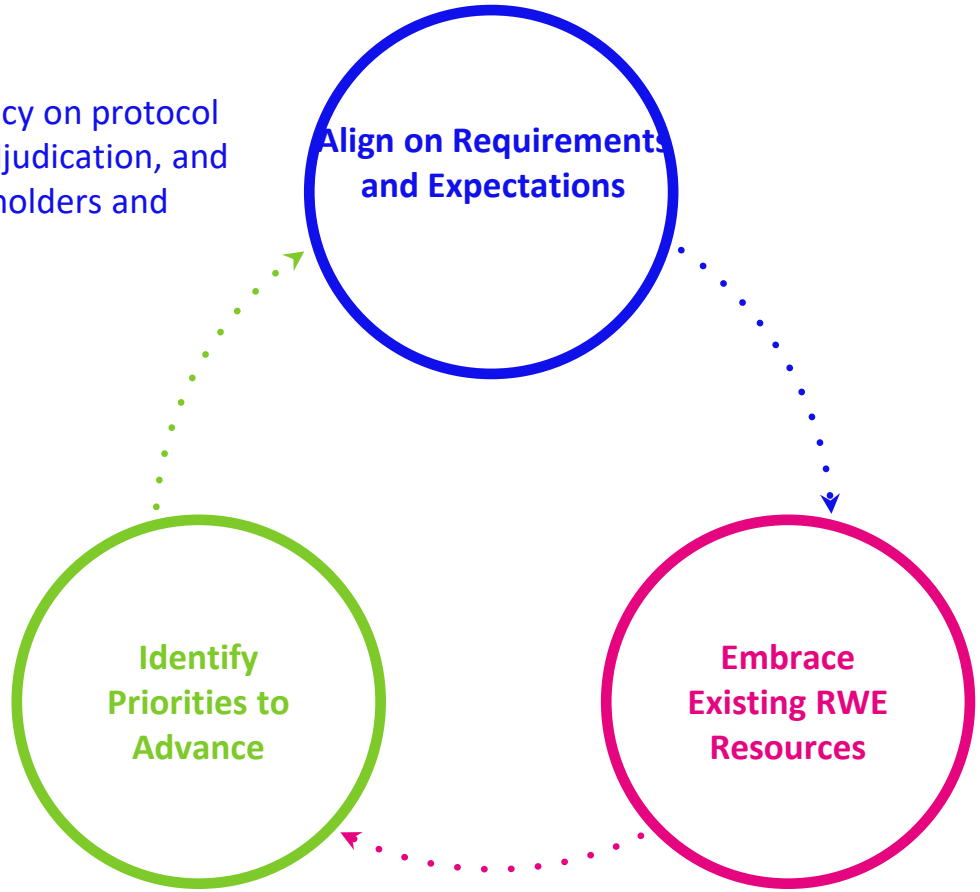
International harmonization of guidance for streamlined submissions

Discussion

Advancing Real-World Evidence (RWE) Through Effective Multi-Stakeholder Collaboration

Incentivizing collaboration and data sharing, research method development, and applications

Promote consistency and transparency on protocol development, data validation and adjudication, and study/data governance across stakeholders and applications



Identify high impact priorities to continue advancing use and applications of RWE for decision-making

Implement existing RWE frameworks and tools on transparency, research methods, and study conduct

Medtronic