U.S. FOOD & DRUG ADMINISTRATION

Relevant Infrastructure

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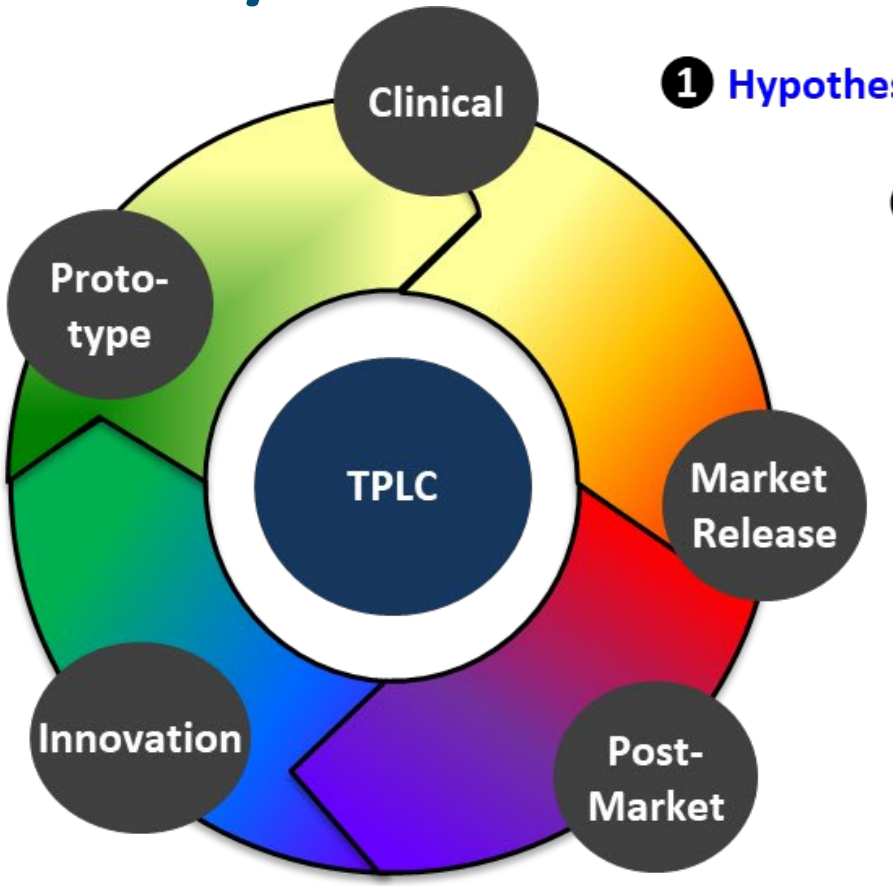
Agenda

- Introduction
- AAA Evolving Landscape
- RWE Case Studies
- AAA-Specific Source Characterization
- Considerations to using RWD/RWE
- Key Take-Aways

Potential Usages of RWE for Total-Product Life-Cycle Device Evaluation



1. Hypothesis Generation (e.g. treatment effect estimation for comparative studies)
2. Inform prospective trial design
3. RWE as a control arm for a clinical trial
4. Real-world data source as a platform to support a clinical trial (data collection / randomization)
5. Data collection framework for postmarket evidence generation (e.g. post-approval studies)
6. Public health surveillance
7. Generate evidence to support indication expansions and future innovation

AAA Evolving Landscape

- EVAR disadvantages are long-term (>1 yr)
  - Higher re-intervention rates
  - Higher risk of aneurysm-related death post-procedure
  - Endoleaks occur in ~33% of all EVARs
- Current Realities for Real World Use (in published literature)
  - Liberal use of EVAR outside of IFU
  - Surveillance Imaging Non-compliance ≈ 60% 3-4 years after EVAR

AAA RWD Challenges

- Limited Long-Term Follow-Up
- Inadequate Surveillance Mechanisms
- Identifying Core Outcomes
- Maintaining Patient Privacy Protection
- Data Use Agreements

Example #1: RWD/RWE Regulatory Usage - Pre-Market

Medtronic Endurant II/IIs

- Objective: Premarket approval and post-approval study for expansion of indication
  - No primary safety endpoint, but supportive data collected on morbidity/mortality
  - Primary Effectiveness: Technical success rate, Type 1a endoleak rate 1/12 months, re-intervention rate through 12 months
- ANCHOR Registry
  - multi-center, post-market, non-interventional, non-randomized prospective study, follow-up up to 5 years post-procedure
- Also used for post-approval study

Example #1: RWD/RWE Regulatory Usage - Pre-Market

Why a Success?

- Sole source of clinical information for pre-market approval
- Data source used for capturing clinical and imaging outcomes
- Central governance of patient data.
- Concurrently used for post-approval study

Example #2: RWD/RWE Regulatory Usage - Post-Market

Transcatheter Valve Therapy (TVT) Post-Approval Studies

- Objective: Long-term safety evaluation for post-approval studies for TAVR devices using linked RWD sources:
  - TVT Registry (up to 1 year)
  - Center for Medicare Services (CMS) Medicare Data (1-5 years)
- Supported 25 regulatory decisions

Example #2: RWD/RWE Regulatory Usage - Post-Market

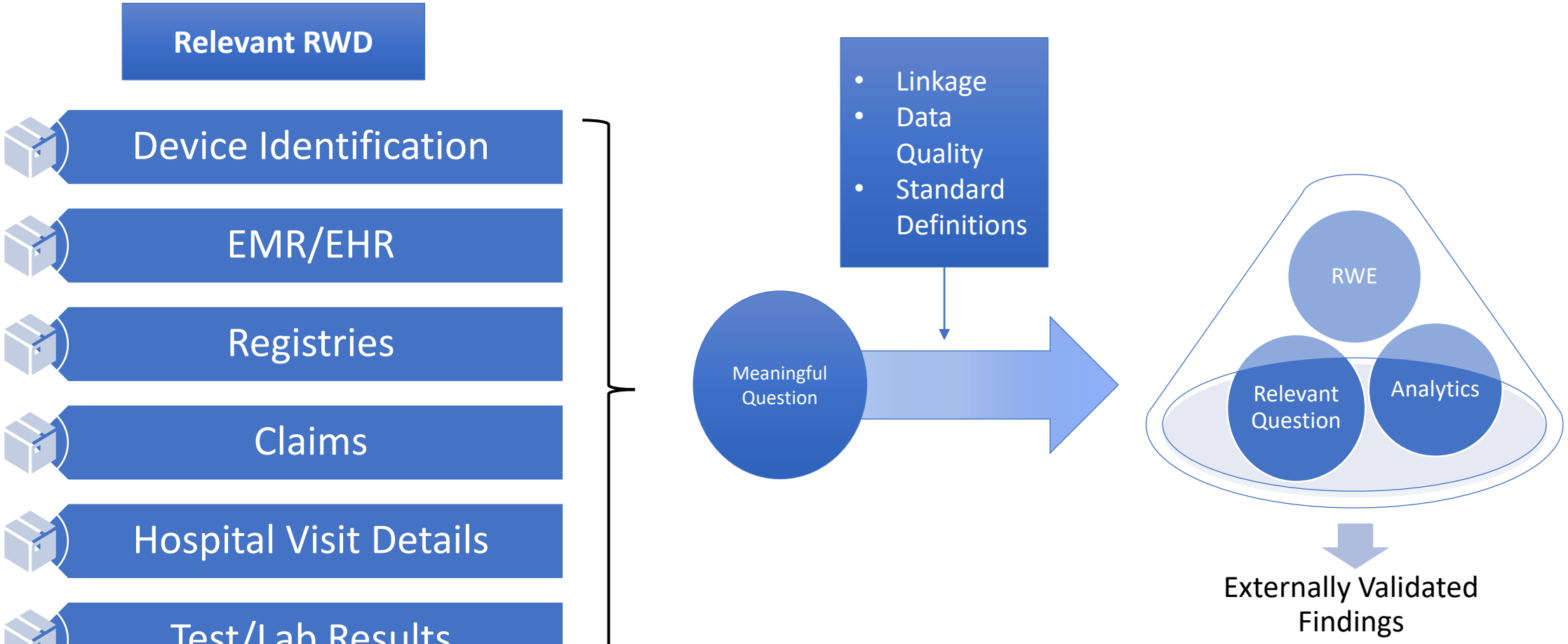
Why a Success?

- Linkage of different data sources for long-term outcomes
- Real-world device use representation
- Efficiencies gained:
  - Time: reduced need for site selection and initiation
  - Site-level patient follow-up
- Registry development involved multiple stakeholders in the pre-competitive space

Safety Signal Endovascular Graft Efforts

- Surveillance
  - Kaiser Permanente Registry
    - Integrated Clinical Database
- Post-market safety studies
  - Harvard/Center for Medicare Services
    - Medicare claims

Real World Data Analytics



AAA RWD Sources

		RWD Source 1	RWD Source 2	RWD Source 3
Geographic Coverage	US Regional			
	US National			
	International			
Device Information	Device Class			
	Device Brand			
	Device UDI/Serial Number			
Demographics	Age			
	Sex			
	Race/Ethnicity			
Clinical Characteristics				
Anatomic Characteristics				
Follow-Up Duration	1-year Follow-up			
	3-year Follow-up			
	5-year Follow-up			
	10-year Follow-up			

Confidently Captured

Variably Captured

Not Captured

AAA RWD Sources

	Outcome	RWD Source 1				RWD Source 2				RWD Source 3			
		1Y	3Y	5Y	10Y	1Y	3Y	5Y	10Y	1Y	3Y	5Y	10Y
Clinical	All-cause mortality												
	Aneurysm-related mortality												
	EVAR Re-Intervention												
	Aneurysm Rupture												
	Conversion to Open Repair												
	Stenosis												
Imaging	Loss of Device Integrity												
	Device Occlusion												
	Device Migration												
	Aneurysm Enlargement												
	Endoleak												

Confidently Captured

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Not Captured

Challenges of AAA RWD Sources

- Identification of specific devices
- Long-term follow-up (>1 yr)
  - Aneurysm-related mortality
  - Stenosis
  - Endoleak types
  - Device-related outcomes
- Low imaging compliance

Elements of Success for Regulatory RWD Utilization

- Relevance and Reliability
  - 2017 FDA Guidance
- Data Governance
  - Process of managing the availability, usability, integrity and security of the data
- Data Flow
  - Data Harmonization
  - Data Interoperability
    - Standardized definitions

Overall Challenges for AAA RWD Utilization

- Maintaining Patient Privacy Protection
- Data Use Agreements
- Data Collection Compliance/Incentivization
  - Consistent Data Variable Collection (e.g., endoleak type)
  - Lack of longer, more reliable follow-up
- Imaging Compliance

Potential Solutions to Challenges

- Data Use Agreements
  - Establish contracts early
  - Utilize third-party entities with existing DUAs
- Data Collection/Longer-Term
  - Linking Multiple RWD
- Imaging Compliance
  - Focus on designated sites
- Multi-stakeholder cooperation

AAA RWD Take-Aways

- Strengths
  - Multiple modalities for data capture
  - Significant AAA infrastructure
  - Captures imaging & clinical outcomes
  - Real-world representation of device use
- Challenges
  - Data Use Agreements
  - Imaging compliance
  - Long-Term Follow-up
  - Maintaining Patient Privacy Protection

Panel Feedback

FDA seeking input on:

- What outcome data and duration of long-term follow-up should be collected
- Ways to overcome current challenges in AAA EVAR RWE infrastructure


THANK YOU

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Clarifying Questions from Panel for FDA

Circulatory Systems Devices Panel of the Medical Devices Advisory Committee Meeting

November 3, 2021