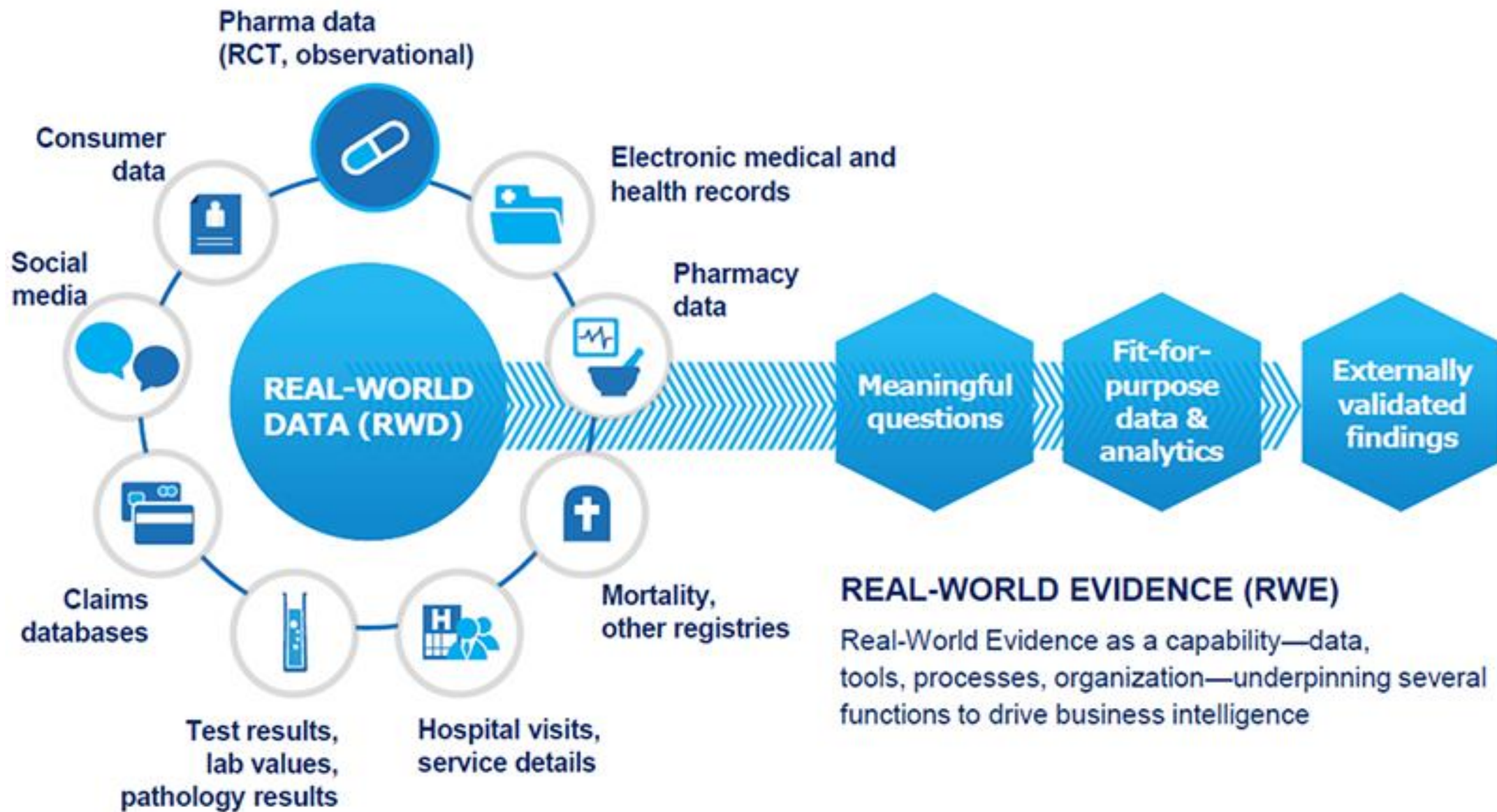


Basic Approach in Utilizing RWD for Regulatory Decision-Making

Misti Malone, PhD

Assistant Director, Office of Cardiovascular Devices

US FDA/CDRH



Traditional Clinical Trial

- Well-defined (but limited) patient population
- Prospective and interventional
- Controlled environment
- High quality, monitored data
- Bias minimized, clinical equipoise

Real-world Data Source

- Real-world environment and patients
 - diverse patient populations and subgroups
 - larger data sets to assess rare but important events
- Retrospective and observational
- Data may or may not be highly monitored
- Potential for increased biases, missingness and confounders

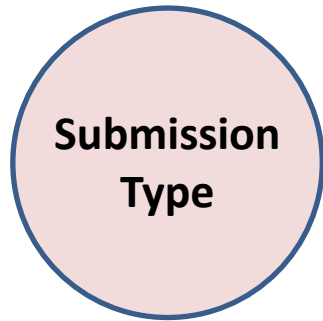
Key to both is a prospective statistical analysis plan!

RWE Successes

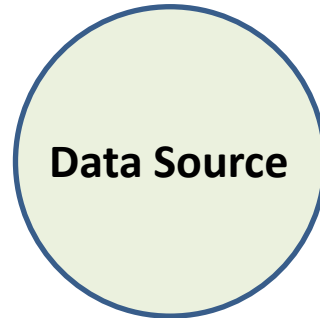
In March 2021, CDRH published 90 Examples of RWE used in medical device regulatory submissions.



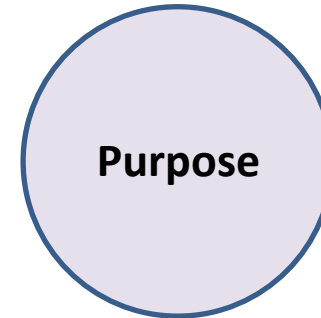
Cardiovascular
Diagnostics
General Hospital
Neurological
Ophthalmic
Orthopedics
Surgical



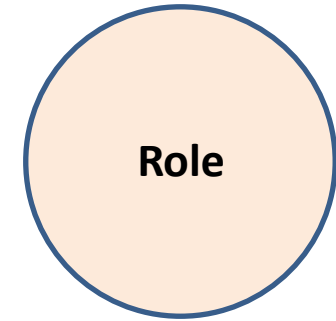
510(k)
De Novo
PMA
HDE



Medical Records
or Charts
Claims
Registry
S-I Studies
Literature



New Marketing
Submissions
Indication Expansion
Postmarket Study
Signal Detection

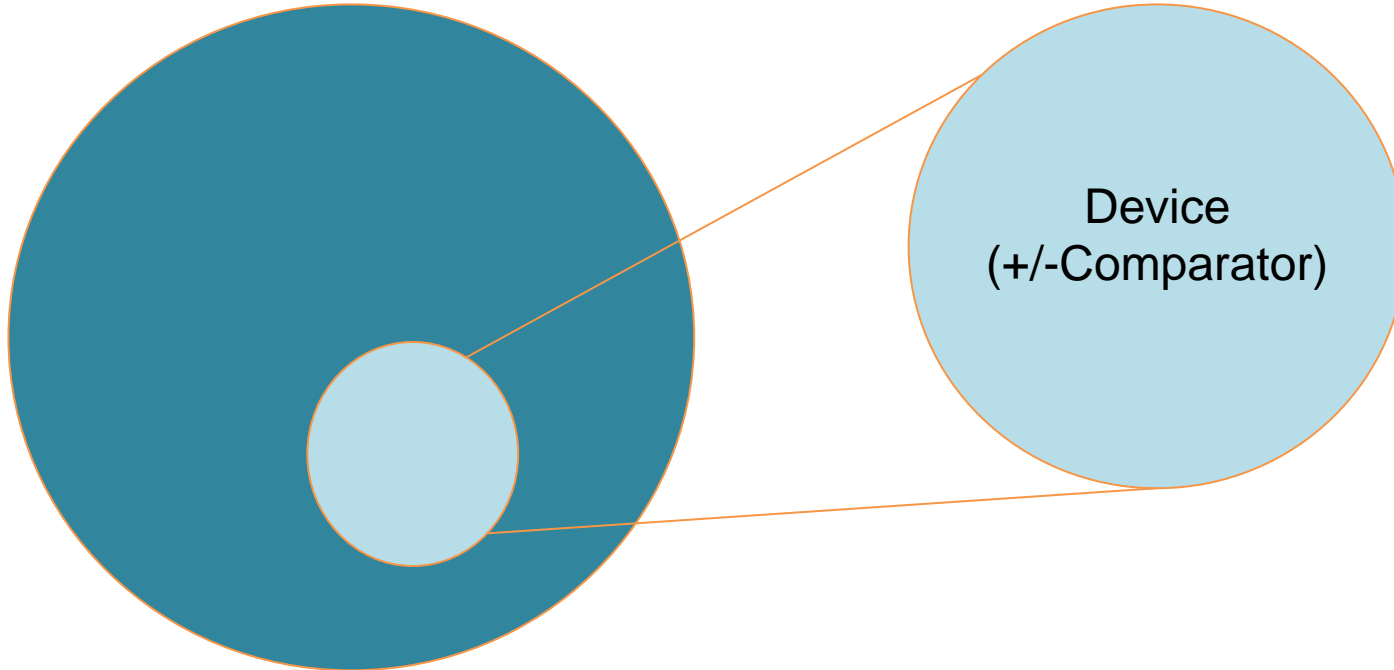


Primary
Supplementary
Partnering
Find patients

RWD Relevance and Reliability

Population with Health Condition

Study Sample



Real-world Data:
Timeliness, Definitions,
Completeness, Accuracy



Conduct statistical analysis
to assess safety and
performance



Interpret results

High Quality/Reliable: free from errors
Relevant: Sufficient information to answer
the questions at hand

Build confidence in data and minimize bias:
data quality, monitoring/auditing, linkages,
account for differences/covariates

PERIPHERAL VASCULAR EXAMPLES

ENROUTE Transcarotid Stent System

Expanded Indication



- **Device:** Transcarotid Stent System with Embolic Protection
- **Indication Expansion:**
 - From: patients at HIGH risk for adverse events from carotid endarterectomy
 - Expanded to include: patients at STANDARD risk for adverse events from carotid endarterectomy
- **Primary Data Source:** Registry Data from Society of Vascular Surgeons – Vascular Quality Initiative (VQI)
 - Transcarotid Artery Revascularization (TCAR) Surveillance Project
 - Carotid Artery Stent (CAS) Cohort
 - Carotid Artery Endarterectomy (CAE) Cohort

Photo Source: ENROUTE® Transcarotid Stent System | Silk Road Medical

Prespecified Study Design and Analysis Plan



Standard Surgical Risk Patients undergoing:

- Carotid Endarterectomy (CEA)
- Transcarotid Artery Revascularization w/stent (TCAR)

Endpoints – composite of:

- 30-day Composite: Death, Stroke, Myocardial Infarction
- Day 31 through 365: Ipsilateral Stroke

Result

- TCAR w/stent demonstrated similar safety and effectiveness as CEA

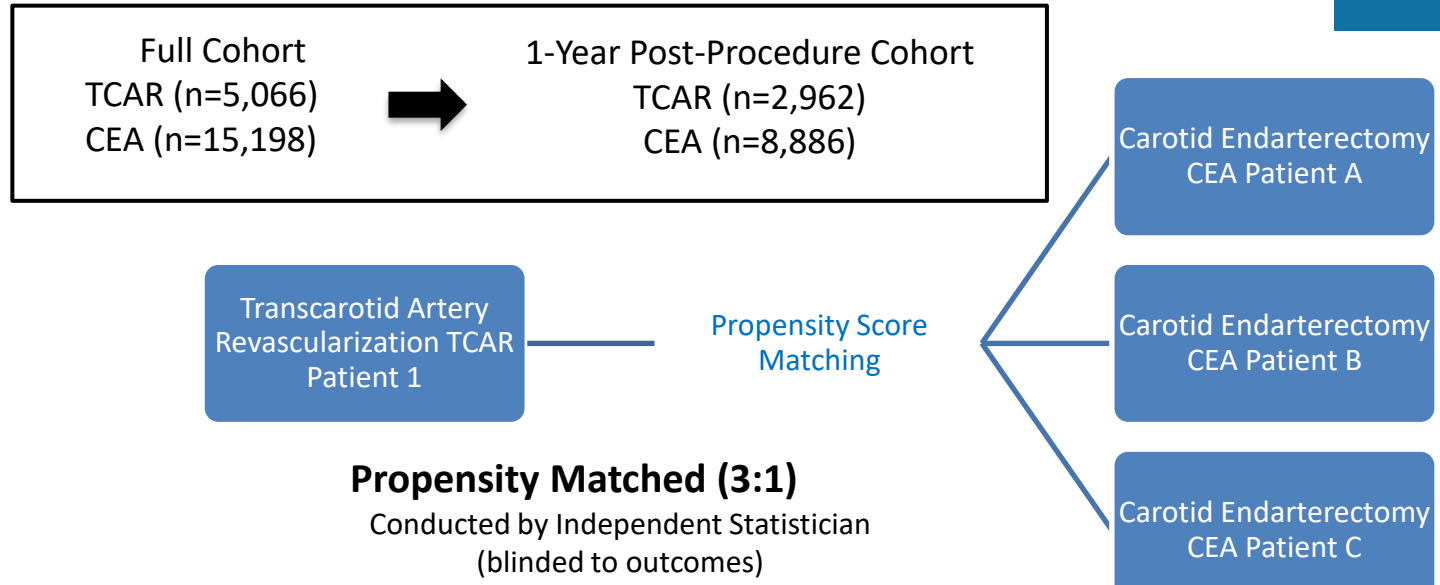


Table 11: Primary Endpoint Results for All Matched Patients in the Supplemental Analysis Population

Outcome	KM Estimate for TCAR N=2962	KM Estimate for CEA N=8886	Bootstrap 95% Confidence interval (TCAR minus CEA)
30 Day Stroke	1.55%	1.13%	
30 Day Death	0.34%	0.41%	
30 Day Death/Stroke	1.79%	1.45%	
30 Day Death/Stroke/MI*	2.20%	2.05%	
Primary Endpoint: 30 Day Death/Stroke/MI* and 1-Year Ipsilateral Stroke	2.96%	2.56%	-0.43%, 1.24%

*MI is reported as in-hospital. The CEA registry of the SVS VQI does not track MI past discharge whereas the CAS registry does.

Granting of DeNovo: CavaClear

Laser Sheath for Inferior Vena Cava (IVC) Filter Removal



Device: laser-powered catheter to ablate tissue and facilitate detachment and removal of IVC filter retrievals

Unmet clinical need: Removal of IVC filters when other techniques fail

Data Source: Retrospective analysis of combined RWD (Electronic health records) at 6 centers (126 subjects) and published data on a single-site's experience (139 subjects)

CavaClear – Laser Sheath for Inferior Vena Cava (IVC) Filter Removal



Endpoints:

- Safety: Device-related complications
- Effectiveness: Site-reported procedure technical success rate

Results:

- Primary safety endpoint met (Device-related major complication rate of 2.9% and 4.0%)
- Primary effectiveness endpoint met (Procedural technical success rate of 95.7% and 95.2%)

	Single-Center Experience	Multi-Center Experience
Patient Demographics		
Number of Subjects	139	126
Age (years)	52±16 (138)	52±16 (126)
Gender	Female: 56.1% (78/139) Male: 43.2% (60/139)	Female: 59.5% (75/126) Male: 40.5% (51/126)
Filter Dwell Time (months)	57.1±51.8 (136)	69.7±62.0 (110)
Prior failed retrieval attempts	100.0% (139/139)	42.1% (53/126)
Study Primary Endpoints		
Procedural Technical Success Rate	95.7% (133/139) [90.8%, 98.4%]	95.2% (120/126) [89.9%, 98.2%]
Device Related Major Complication Rate	2.9% (4/139) [0.8%, 7.2%]	4.0% (5/126) [1.3%, 9.0%]

Source: [DEN210024 Summary](#)

Plan early and be flexible because RWD can be messy

Role of RWE:

- Primary
- Supplementary/Additive
- Partnering (e.g., as control, prior, or otherwise combined with traditional clinical study data)

Statistical Methods:

- Pre-specified flexible SAP
- Methodology (eg, matching)
- Accounting for confounders and biases
- Handling missing data

Data Source:

- Patient Population
- Elements and definitions
- Outcomes
- Duration/Follow-up
- Accuracy/Missingness

Other considerations:

- Quality measures
- Multiple sources and linkages
- Other data (eg, imaging)
- Rationale for generalizability (e.g., international data)

Thank you!

