Basic Approach in Utilizing RWD for Regulatory Decision-Making

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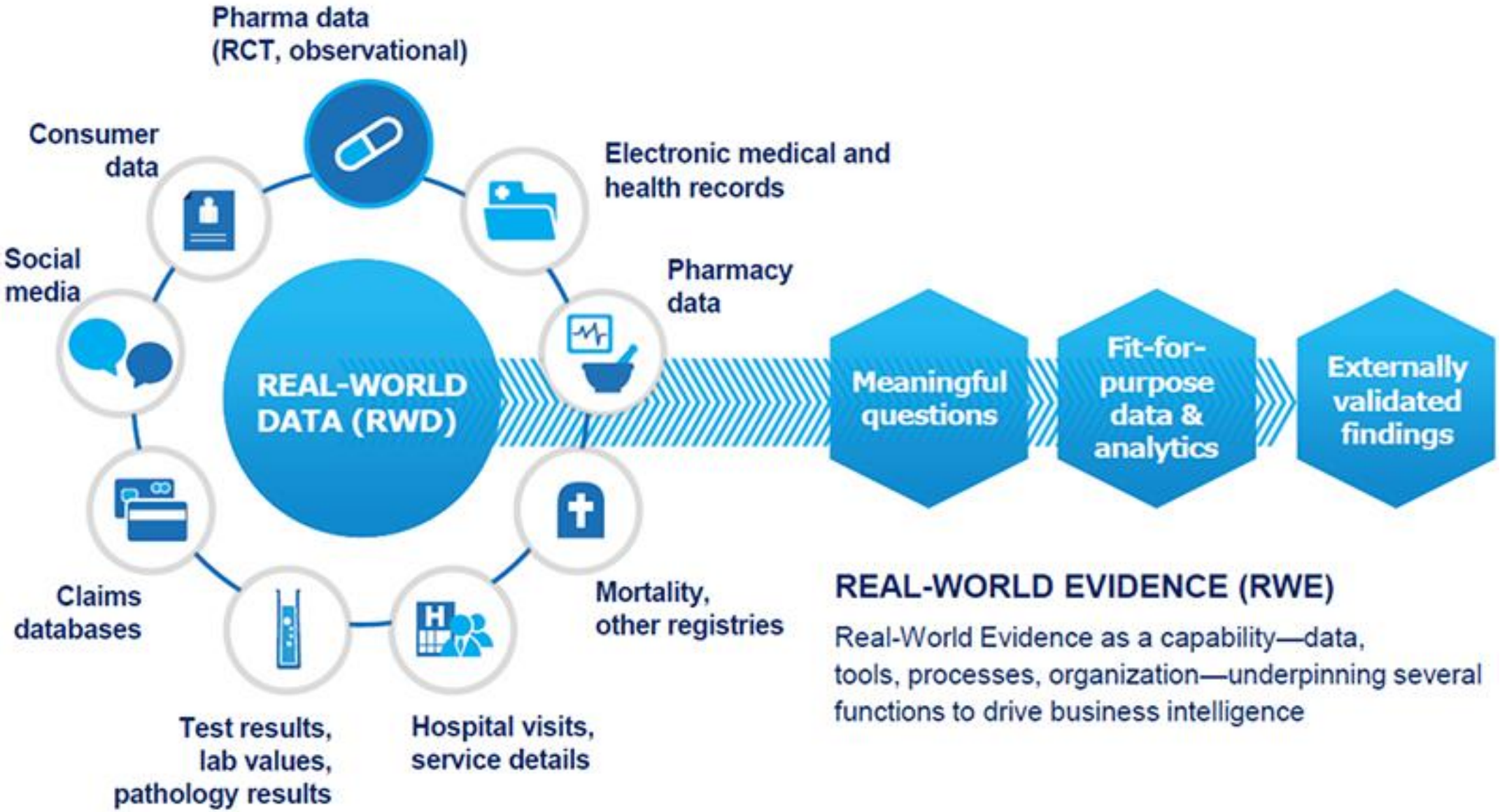


REAL-WORLD EVIDENCE (RWE)

Real-World Evidence as a capability—data, tools, processes, organization—underpinning several functions to drive business intelligence

Traditional Clinical Trial

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

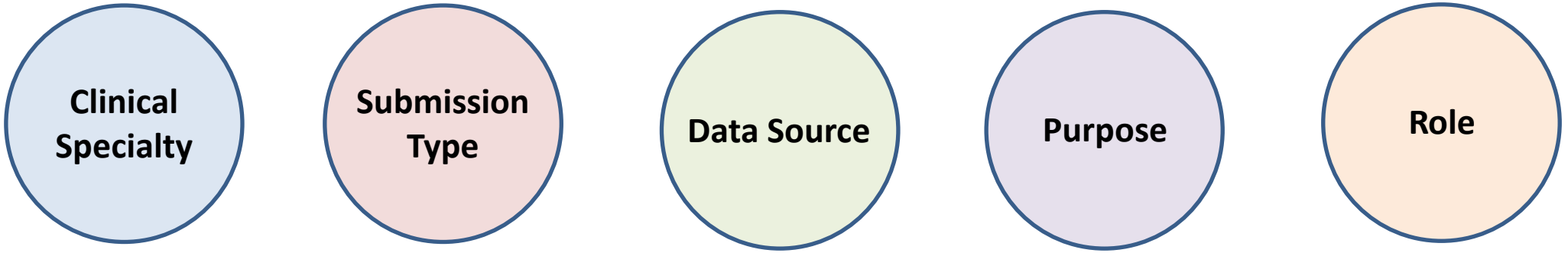
Real-world Data Source

- 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!

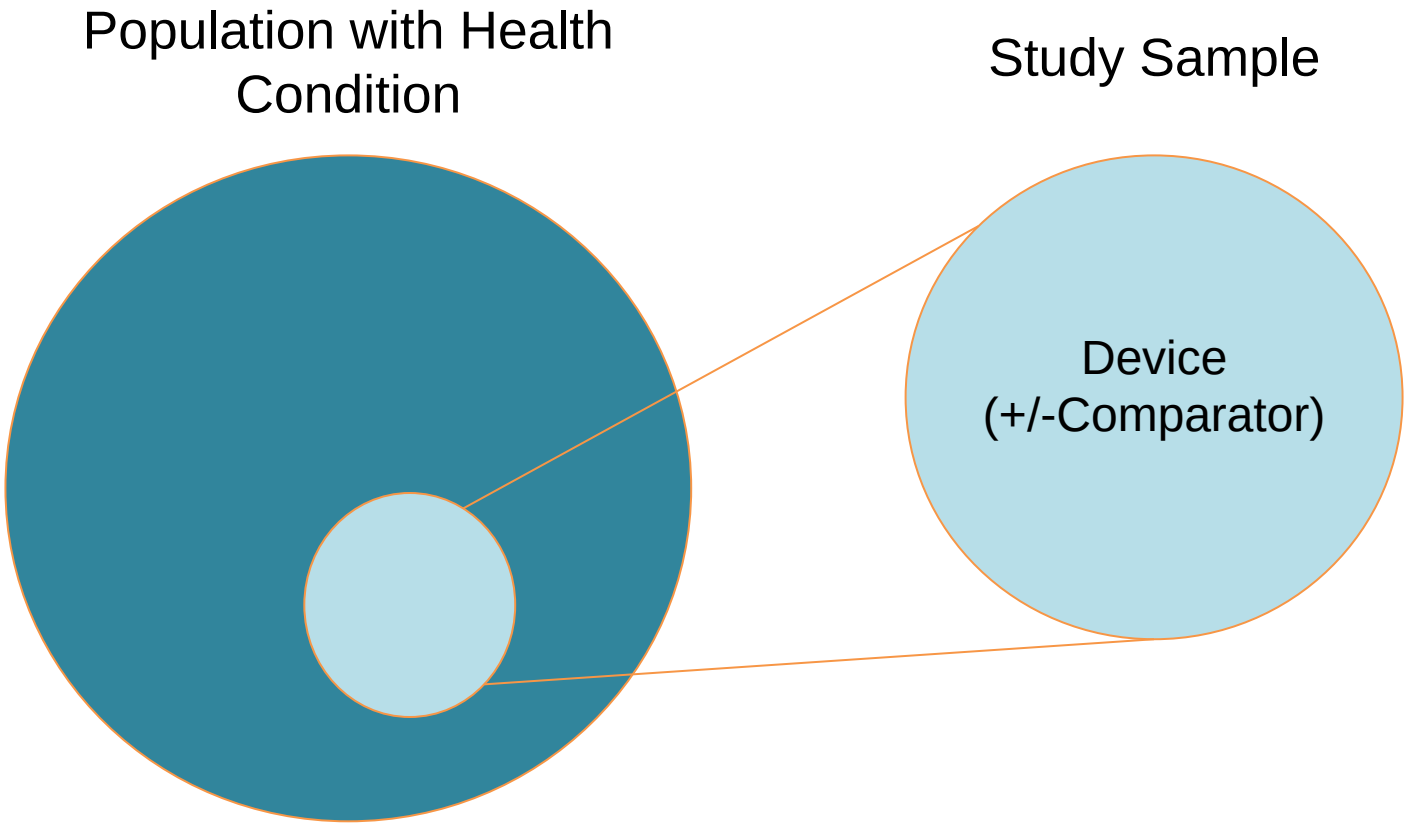
RWE Successes

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



Clinical Specialty	Submission Type	Data Source	Purpose	Role
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



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

↓

Conduct statistical analysis to assess safety and performance

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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:

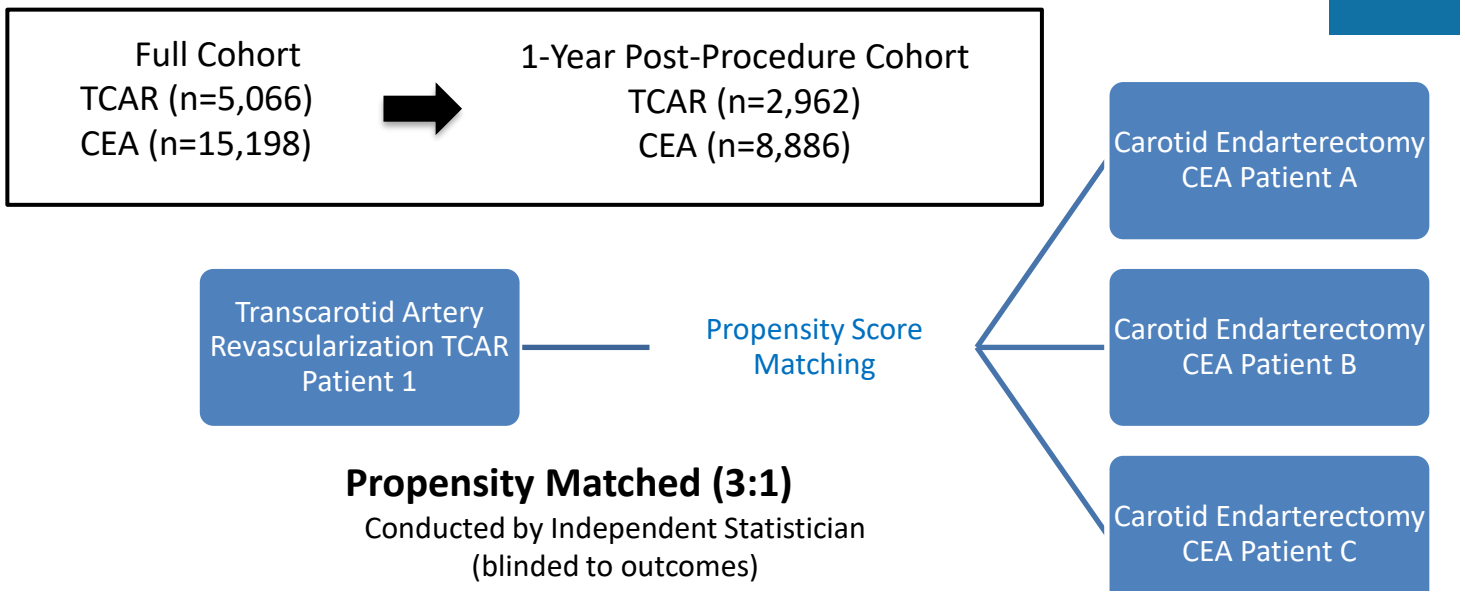
- Carotid Endarterectomy (CEA)
- Transcarotid Artery Revascularization w/stent (TCAR)

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



Propensity Matched (3:1)

Conducted by Independent Statistician (blinded to outcomes)

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

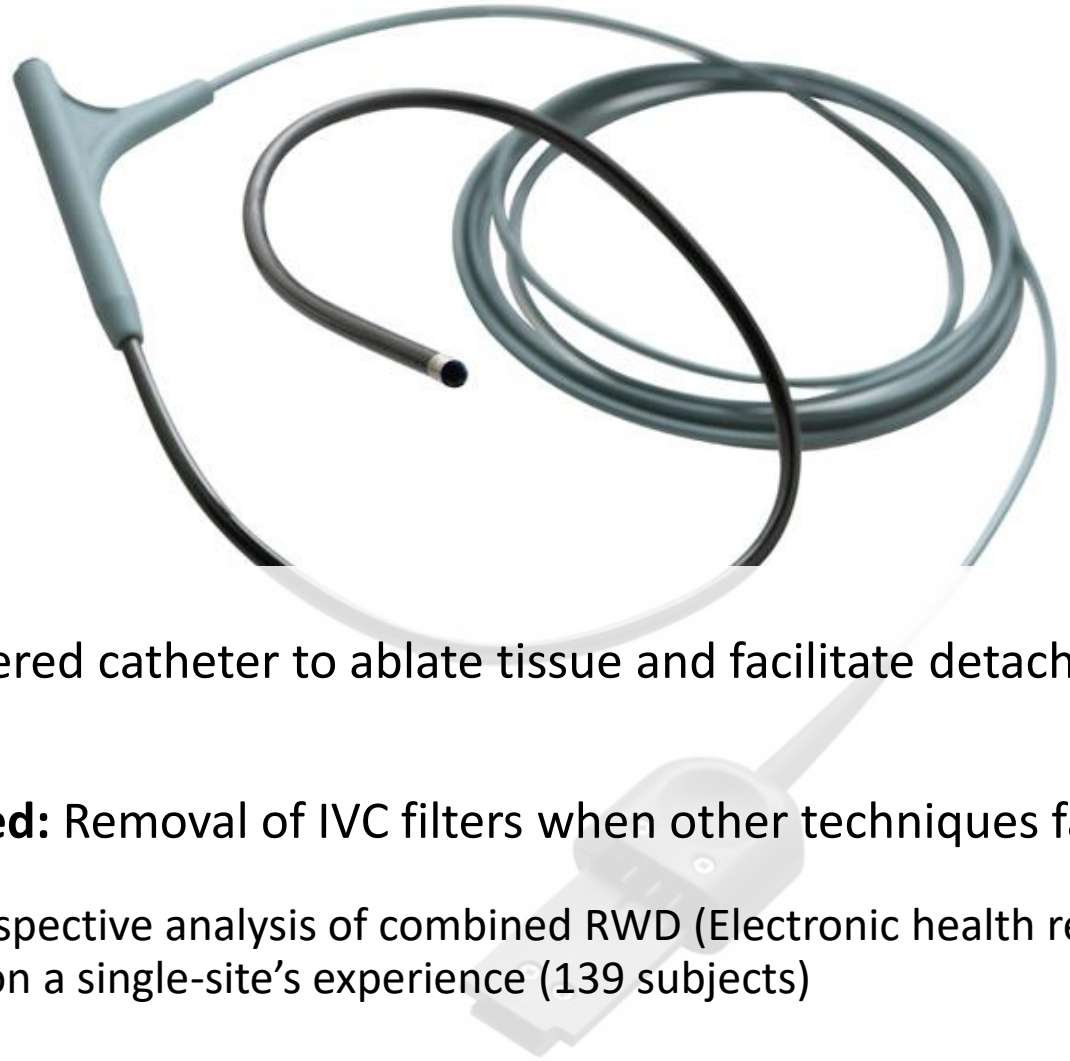
Outcome	KM Estimate for TCAR N=2962	KM Estimate for CEA N=8886	Bootstrap 95% Confidence interval (TCAR minus CEA)
30 Day Stroke	1.55%	1.13%	
30 Day Death	0.34%	0.41%	
30 Day Death/Stroke	1.79%	1.45%	
30 Day Death/Stroke/MI*	2.20%	2.05%	
Primary Endpoint: 30 Day Death/Stroke/MI* and 1-Year Ipsilateral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

Source: P140026/S016 SSED (fda.gov)

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)

Source: DEN210024 Summary

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

Source: DEN210024 Summary

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%]

Plan early and be flexible because RWD can be messy

Role of RWE:
- Primary
- Supplementary/Addititive
- 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!