Use of Real-World Evidence during EU Submissions

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Back to basics – what is RWD and RWE?

- **Real-world data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources[1,2]:
  - Electronic health records (EHRs)
  - Sponsor and national device registries
  - Administrative claims database
  - Patient-generated data
  - Active surveillance systems
  - Data platforms

- **Real-world evidence (RWE)** is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD[1]

[1] See US FDA's guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices

[2] Olivia McDermott & Breda Kearney (02 Dec 2023): The value of using real-world evidence as a source of clinical evidence in the European medical device regulations: a mixed methods study, Expert Review of Medical Devices, DOI: 10.1080/17434440.2023.2291454

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Objectives for the next half-hour

- Why care about RWD/RWE?
- How does it apply to EU?
- Review current guidance on how to construct scientifically valid studies using RWD
- EU-specific case study – PMCF using EHR data

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Why bother with RWD/RWE?

- Traditional clinical studies are typically narrow in scope to control sources of error and bias, whereas RWD studies may provide **more accurate insights from larger more heterogeneous populations**[1,2]
- Heterogeneity is often seen as a limitation of RWD; however, in the context of representation, RWD can provide a **more comprehensive understanding** of how medical product perform in clinical practice[3]
  - Monitor selection bias
- Traditional clinical studies may be **impractical or unethical** to conduct (e.g. in treatment assignments, rare diseases or certain populations)[1,2]

[1] See US FDA's draft guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-use-real-world-evidence-support-regulatory-decision-making-medical-devices

[2] See Heath Canada's "Guidance on clinical evidence requirements for medical devices" available at https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/clinical-evidence-requirements-medical-devices.html

[3] Jay Erturan, M.D. (15 Jan 2024): Building the Pathway to Successful Use of RWE, Bonezone. Publication available at https://bonezonepub.com/2024/01/15/building-the-pathway-to-successful-use-of-rwe/

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Why bother with RWD/RWE, ctd.?

- RWD may allow for assessment of **longer-term outcomes**[1]
  - Practical method for assessing device safety and performance over its **expected lifetime**
- Traditional clinical studies can be time and resource intensive
  - RWE can provide a **sustainable approach** for supporting both regulatory submissions and surveillance[2]
- RWE can expedite both regulatory decision making and identification of safety signals (both short and long-term)[1,2]
- RWD informs device benefit-risk profiles from **real-world environments**[1]
- Manufacturers may be required to **justify not considering RWD as part of the clinical evaluation**[1,3]

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[2] Jay Erturan, M.D. (15 Jan 2024): Building the Pathway to Successful Use of RWE, Bonezone. Publication available at https://bonezonepub.com/2024/01/15/building-the-pathway-to-successful-use-of-rwe/

[3] Fink M, et al. Clinical evidence under the EU MDR: A notified body perspective. RF Quarterly. 2023; 3(4): 24-31. Published online 8 December 2023. https://www.raps.org/News-and-Articles/News-Articles/2023/12/Clinical-evidence-under-the-EU-MDR-A-notified-body

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How can RWE support regulatory submissions?

Per 21 CFR 860.7(c)(1), “although a manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only **valid scientific evidence** to determine whether there is reasonable assurance that the device is safe and effective.”

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RWE can constitute valid scientific evidence

- Current (US FDA) guidance states that data derived from real-world sources can be used to support regulatory decisions, and **RWE may constitute valid scientific evidence** depending on the characteristics of the data, study question, and the design and analysis of the data[1]
- RWD may support uses across the medical device **total product life cycle** including[1]
  - Generating **primary clinical evidence** to support marketing authorization
  - Generating evidence directly by the subject device to provide **new information on safety or effectiveness**
  - Generating evidence for **expanding the labeling** of a device to include additional indications for use or to update the labeling to include new information on safety and effectiveness
  - Generating evidence for post-market surveillance to **identify signals that may suggest there is a safety issue** with a medical device
  - Providing post-market data **in lieu of some premarket data**

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[1] See FDA's draft guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-use-real-world-evidence-support-regulatory-decision-making-medical-devices

CAVEAT! Europe is different

- The EU MDR does not explicitly reference RWD or RWE, and MDCG guidance rarely refers to them
- Presently, RWE is not accepted by notified bodies as **primary evidence** for pre-market data
- **HOWEVER,** EU MDR allows for the use of multiple clinical data sources if **scientifically valid** methodologies used to generate clinical data are **reliable and robust**
- MDCG 2020-6 *Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC* states that "indirect clinical benefits may be demonstrable by other evidence such as **real-world data**"
- **AND** MDCG 2020-7 *Post-market clinical follow-up (PMCF) Plan Template A guide for manufacturers and notified bodies* references **RWE analyses as a type PMCF strategy**, and the RWD "from which these analyses are based on **should be of sufficient quality and come from reliable data sources**"

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What constitutes “sufficient quality” and “reliable”?

Where to go next?

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Utilization of RWE for regulatory decision making for medical devices is a world-wide movement following pharma's lead

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
FDA

NEST
Coordinating Center
An initiative of MDIC

National Evaluation System for health Technology Coordinating Center (NESTcc) Data Quality Framework

Health Canada | Santé Canada

Guidance on clinical evidence requirements for medical devices

Government of Canada | Gouvernement du Canada

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Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle

Updated: March 5 2019

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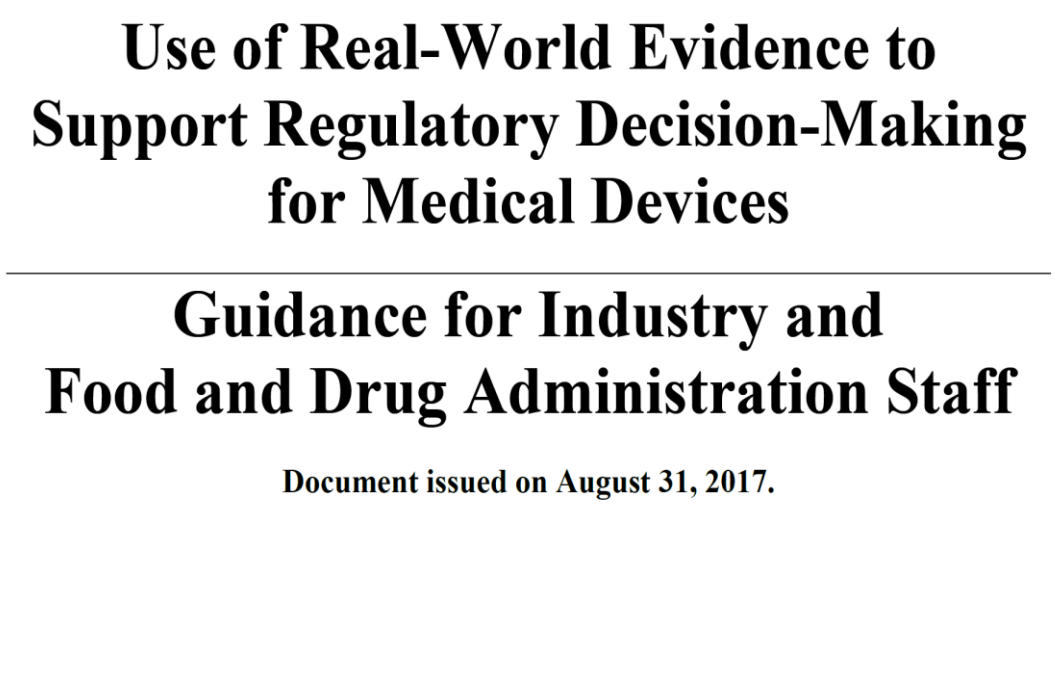
pmda
独立行政法人
医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

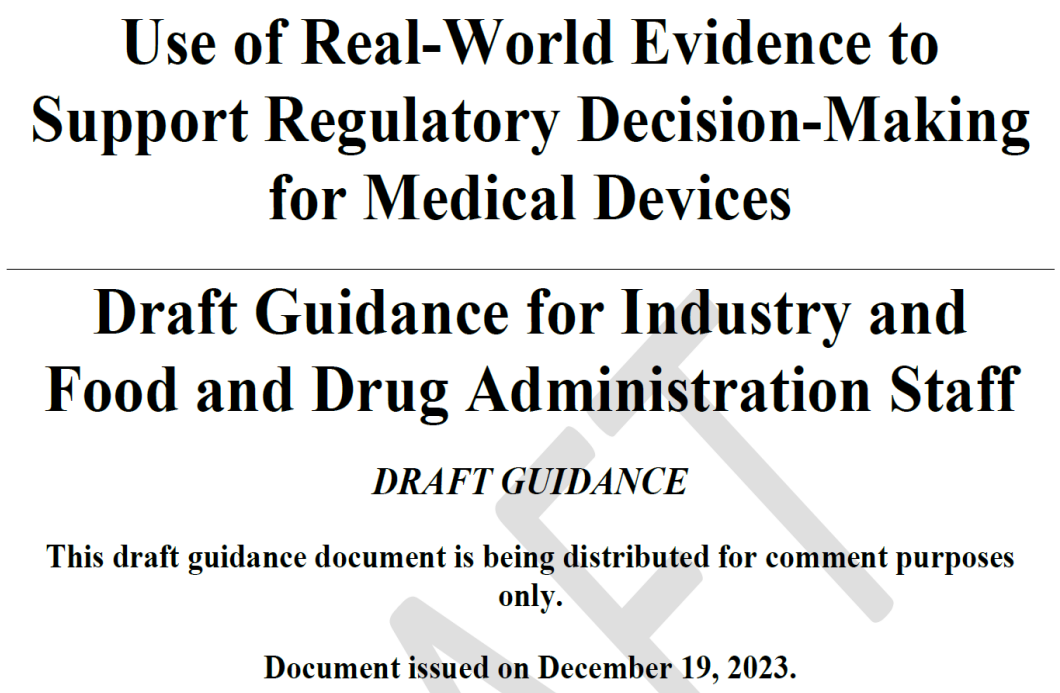
US FDA guidance is the most comprehensive resource currently available



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.



Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on December 19, 2023.

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Refer to US FDA's current recommendations for data relevance, reliability and methodology

- FDA has greatly expanded their recommendations for how to assess **data relevance, reliability, and methodologies for collection and analysis of RWE**
  - Fourteen pages on just these topics
  - Plus additional information on fit-for-purpose assessment, RWD study protocol, and study report
  - Appendix A is a checklist for recommended elements to include in regulatory documentation
  - Appendix B are examples of how RWE has been successfully used

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-use-real-world-evidence-support-regulatory-decision-making-medical-devices

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Start with your study question and purpose, and then perform a fit-for-purpose assessment

- To be scientifically valid, studies using RWD should assure the data are **fit-for-purpose**
  - Your study question and purpose should drive evidence generation
- When assessing **relevance** of the RWD, consider:
  - **Data availability**
    - Can you identify which device was used and is there enough detail to assess outcome(s) of interest?
      - Clinically relevant proxies may be okay
    - Are relevant covariates impacting outcomes available such as pre-existing conditions, labs, demographics, patient and family history, etc.?
      - Clinically relevant proxies may be okay
    - Can you longitudinally trace the patient across the continuum of care for the required timeline?
  - **Data linkages**
    - Are data from different sources obtained?
    - Are same individuals matched correctly following pre-defined methodology?
    - Are there strategies for correcting redundant data, resolving inconsistencies and assessing for missing data

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Start with your study question and purpose, and then perform a fit-for-purpose assessment, ctd.

- When assessing **relevance** of the RWD, consider:
  - **Timeliness**
    - Is the time between data collection and analysis reasonable, and does the RWD represent current clinical practice?
  - **Generalizability of RWD**
    - Is the RWD representative of the population of interest?
      - Is it transferable if collected in another country?
        - Consider the possible technical, regulatory, clinical and scientific barriers (e.g. unique patient or clinical practice characteristics)
- When assessing **reliability**, consider:
  - **Data accrual**
    - What is the data type, health care setting, and purpose of collection?
    - Are there data transformations, including modifications made for privacy protection?
    - What is the completeness of fields needed for most study questions?
    - What are the key technical and privacy information?

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Start with your study question and purpose, and then perform a fit-for-purpose assessment, ctd.

- When assessing **reliability**, consider:
  - **Data accrual (continued)**
    - What are the site collection procedures?
    - Is there usage of common data capture forms?
    - What are the data cleaning and cross-referencing procedures?
    - What are the methods for data retrieval and data quality checks in the data captured at the point of care
  - **Data quality and integrity**
    - Quality control – are there site and data monitoring processes and audit programs?
    - How are completeness, accuracy and consistency assessed across sites and over time?
    - Is data reflective of patient experience?
    - Are the auditing rules, methods, and mitigation strategies to reduce error documented?
    - Is patient-level data available for each patient? If not, do regulators have access?
    - Are adequate patient protections in place and established in advance of the study?

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Summary so far…

- There are numerous benefits to embarking on a RWD study, and it may be required for your product
- Currently there is a lack of EU-specific guidance helping you ensure sufficient quality and scientific validity of RWE supporting your medical devices
- However, the principles laid out in the mentioned US FDA draft guidance can help you plan and assess the relevance and reliability of your RWD collection

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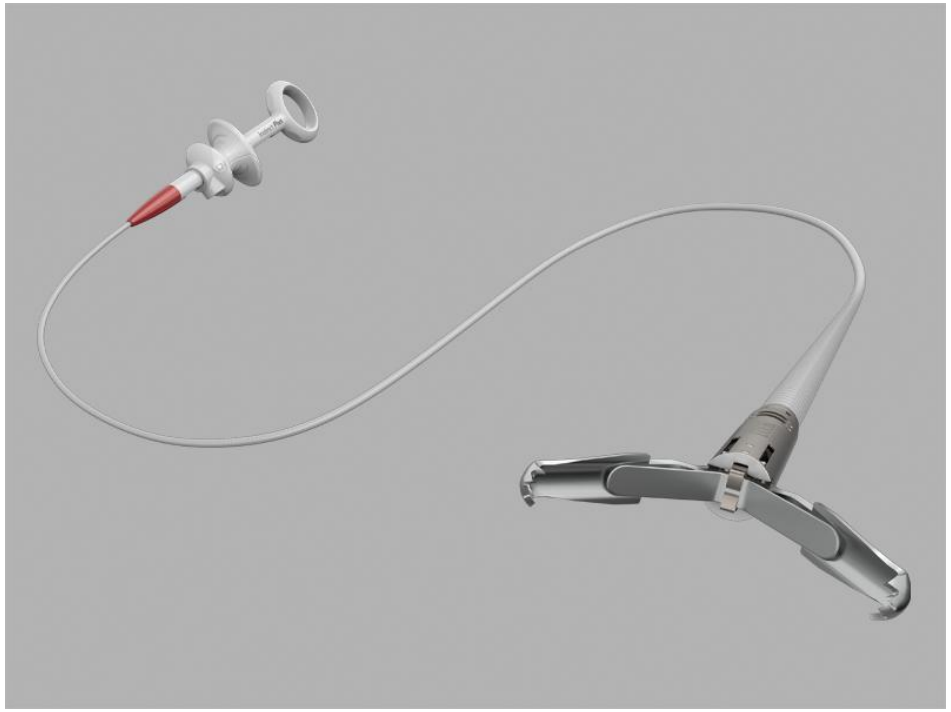
Case study – EHR data used to execute a PMCF study

- Class IIb implant
- This device is used for endoscopic clip placement within the gastrointestinal tract for the purpose of
  - Endoscopic marking,
  - Hemostasis,
  - Prophylactic clipping,
  - Anchoring to affix jejunal feeding tubes to the wall of the small bowel,
  - As a supplementary method for closure of GI tract luminal perforation less than 20mm
  - Anchoring to affix fully covered esophageal self-expanding metal stents to the wall of the esophagus



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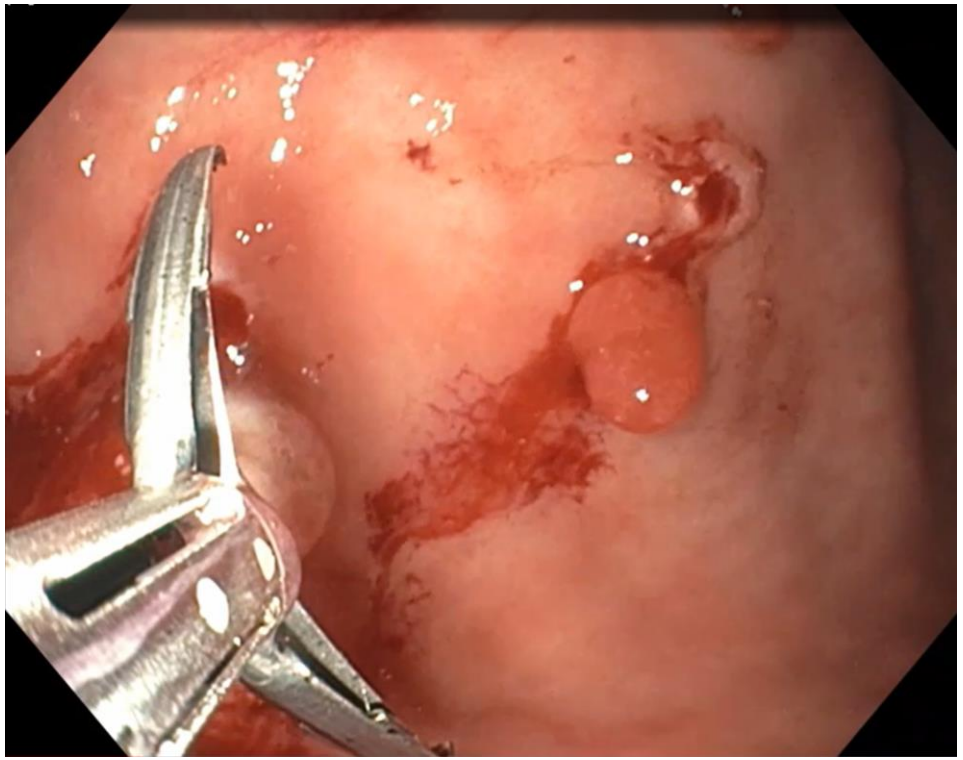
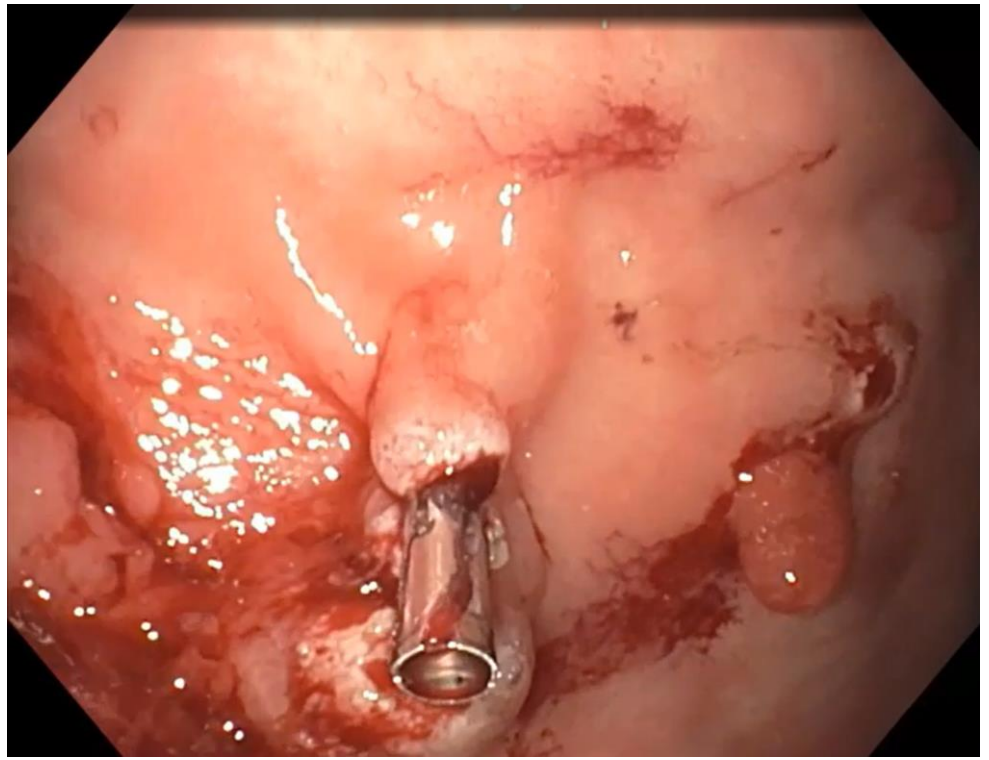
Endoscopic hemoclips are commonly used to prophylactically clip a post-polypectomy wound





Images courtesy of Dr. Shou Jiang Tang, The University of Mississippi Medical Center, Jackson, MS

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Case study – EHR data used to execute a PMCF study, ctd.

Study requirements were prospectively defined and assessed against the RWD source

- Data must be patient-level and specific to a catalog number
  - Manufacturer recently updated the device and needed data on that updated device
- Patient population must represent all indications – calculated minimum patient number for each indication
- Safety and performance measures must be available (next slide)

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Each indication consisted of separate clinical and safety definitions

Indication	Clinical success	Safety
Endoscopic marking	Clip retained at target	Adverse events associated with clip placement (injury/perforation/bleeding)
Hemostasis	Initial hemostasis successful	Rebleeding
Prophylactic clipping	Lack of delayed bleeding	Adverse events associated with clip placement (injury/perforation/bleeding)
Anchoring feeding tube	Lack of migration of feeding tube	Bleeding Tube stuck at removal Aspiration pneumonia at removal Bleeding PEG Perforation PEG
Supplementary method for luminal perforations	Closure of perforation	Small leaks due to inadequate sealing Premature dislodgement Mucosal injury Deployment malfunction
Anchoring metal stents	Lack of stent migration rate	Bleeding Perforation Recurrence of initial disease Intolerance of food intake

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Case study – EHR data used to execute a PMCF study, ctd.

Study requirements were prospectively defined and assessed against the RWD source

- Patient data must be longitudinally traceable for 30 days post-procedure
  - Product recently launched – next project to assess expected lifetime of 3 years
- Required data elements
  - Demographics and relevant medical history
  - Anatomic location of clip deployment
  - Successful delivery and deployment of the endoscopic clip (yes/no)
  - Number of clips used in procedure
  - Use of adjunctive/combination treatments (yes/no)
  - Procedural and post-procedural complications
  - Device malfunction or use error (yes/no)
- Important - assessment of reliability occurred (vendor qualification), and required details must be available to share in regulatory documentation

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Study using EHR data successfully met PMCF objectives with reduced time and effort

- PMCF objectives:
  - To ensure continued acceptability of the benefit-risk ratio
  - To confirm the safety and performance of the device throughout its *expected lifetime*
  - Identify and analyze emergent risks based on factual evidence
  - Identify previously unknown side-effects and monitoring the identified side-effects and contraindications
  - Identify possible systemic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct
- Manufacturer uncovered complications, adverse device effects and performance failures (outcomes in line with SOTA)
- Off-label use was assessed – **unique to RWD studies**

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Study using EHR data successfully met PMCF objectives with reduced time and effort, ctd.

- Overall study duration was **6 months**
- Level of effort by function:

Study Function	FTE hours
Clinical Project Management	42
Clinical Safety	85.5
Clinical Science	153
Data Management	11.5
Legal	0
Reimbursement	0
Statistics	103
Quality Assurance	3.5
Total	**398.5**

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Thank you!

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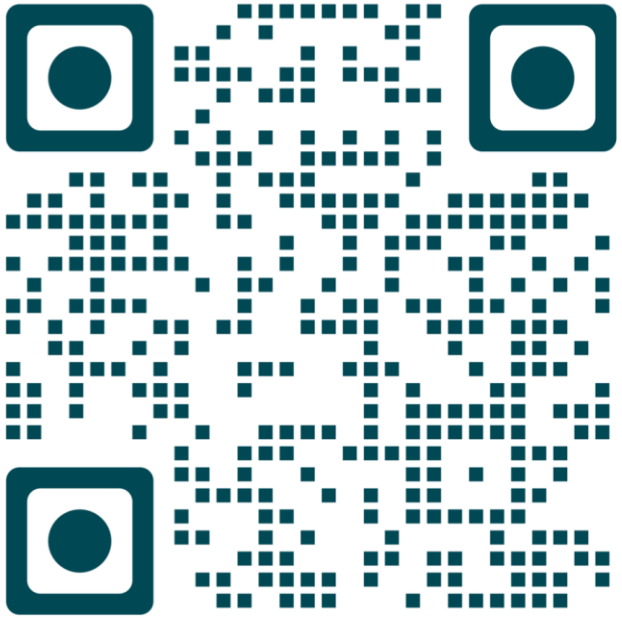

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