U.S. FOOD & DRUG ADMINISTRATION

Examples of Real-World Evidence Used in Medical Device Regulatory Decisions

(Fiscal Years 2020–2025)

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Executive Summary

This report presents 73 examples of market authorizations from fiscal years (FY) 2020-2025 building on the foundational work presented in the 2021 publication "Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions," which documented 90 examples from FY 2012-2019, and demonstrated the continued evolution and expansion of real-world evidence (RWE) use in medical device regulatory decision-making across the Center for Devices and Radiological Health (CDRH).

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. Examples of RWD sources include electronic health records (EHRs), registries, administrative claims data, device-generated data, public health surveillance data, clinically annotated biobanks, medical device data repositories, and chargemaster and/or billing data. These data offer opportunities to generate evidence and better understand clinical outcomes using routinely collected, extant data outside of traditional clinical studies. In support of CDRH's mission to protect and promote public health by ensuring the safety and effectiveness of medical devices, while assuring patients have timely access to them, CDRH aims to foster the use of RWE to support regulatory decision-making throughout the medical device total product lifecycle. One way CDRH advances this goal is by systematically reviewing and sharing examples of how RWD have been incorporated into regulatory submissions and supported final regulatory decisions.

To document the growing utilization of RWE and highlight emerging and innovative applications, CDRH reviewed public-facing documentation of regulatory decisions from FY 2020-2025 and identified examples that illustrate the breadth of RWD sources, study designs, and analytical approaches sponsors have used to generate RWE in medical device submissions. The examples span a wide breadth of clinical and device areas throughout all 8 Offices of Health Technology in CDRH. These examples represent:

- 44 premarket notification (510(k)) submissions
- 7 De Novo classification requests
- 1 humanitarian device exemption (HDE) application
- 9 premarket approval applications (PMA)
- 12 PMA supplements

While this report focuses primarily on the use of RWD in premarket submissions, 3 examples reflect the use of RWE across the total product lifecycle, supporting both premarket clinical evidence and post-approval studies.

This report is organized into 9 sections separated by device type (therapeutic devices and in vitro diagnostics) and RWD source for therapeutic devices (medical records; administrative claims data; registries; device-generated data; public health surveillance data; combined registries and administrative claims data; combined medical records and registries; and other combinations of sources). Sections for device-generated data and public health surveillance data were newly added for this report. The inclusion of these sections reflects the expanded list of RWD source types described in the Food and Drug Administration (FDA) 2025 guidance, Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (the CDRH RWE guidance), and the evolving landscape of data sources used to generate RWE for medical devices.

[1]For the purposes of this document, we use the term "clinical studies" as a broad term to capture clinical research regarding the safety or effectiveness of a device, regardless of study design. We use the term "traditional clinical studies" to refer to clinical studies that do not utilize RWD.

The examples demonstrate a variety in the usage of RWE, including:

- RWE serving as the primary source of clinical evidence in submissions for new devices and expanded indications for currently marketed devices.
- RWE serving as supplementary clinical evidence to complement other clinical evidence.
- Use of RWD to generate external or historical control arms for evaluating device performance.
- Use of RWD to address both premarket and postmarket needs across the total product lifecycle.
- Linkage and combination of multiple RWD sources to generate more robust evidence.

This report also highlights innovative applications of RWE in areas where new device technologies continue to emerge, including:

- Multiple examples of artificial intelligence and machine learning-based medical devices that demonstrate the validation of device software functions using RWD.
- International biobank, registry, and medical record linkages that illustrate increasingly sophisticated data integration approaches.

The examples further demonstrate continued methodological advances in RWE approaches, including:

- Registry-claims data linkage as a maturing and increasingly common approach for long-term postmarket surveillance, enabling comprehensive assessment of healthcare utilization and clinical outcomes beyond traditional follow-up periods.
- Use of propensity score methods and other advanced statistical techniques to address confounding and selection bias in real-world studies.
- Hybrid study designs integrating prospective clinical trial data with real-world registry data to strengthen the evidentiary basis for regulatory decision-making.
- Generation of real-world external controls from administrative claims and registry data to support single-arm study designs.

Building on the trends established in the original 90 examples, these additional examples demonstrate both maturation of RWE methodologies and the expanding role of diverse RWD sources in generating valid scientific evidence across the device lifecycle. CDRH encourages the continued and expanded use of relevant and reliable RWD to generate RWE to provide new insights into the performance and clinical outcomes associated with medical device use. Successful applications of RWE are most often achieved when principles of relevance and reliability are considered, as detailed in the CDRH RWE guidance. Sponsors planning to seek marketing authorization are encouraged to consider, early in development, whether and how RWD may be appropriately incorporated into their evidence-generation strategies, and to engage with CDRH, as appropriate, to support alignment on the use of RWE for regulatory decision-making.

Introduction

The FDA currently defines RWD as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD are playing an increasingly important role in how medical devices are evaluated across the total product lifecycle, offering opportunities to understand device performance and clinical outcomes outside of traditional clinical studies. RWE is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD. When appropriate for the regulatory question at hand, relevant and reliable RWD can be used to generate RWE that deepens the understanding of device safety and effectiveness in real-world use.

To support broader use of RWE in regulatory decision-making, CDRH previously conducted a retrospective review of medical device regulatory decisions from FY 2012-2019. That effort identified 90 examples of RWE use across the device lifecycle and was published in 2021 as Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions.

Building upon this foundation, CDRH conducted an additional retrospective review of public-facing documentation covering submissions with final decision dates from FY 2020-2025. Submissions with final decisions in the specified timeframe were triaged to identify those utilizing RWD, with detailed review conducted of the public-facing documentation where RWD was considered important in supporting the final regulatory decision. This effort identified 73 additional premarket authorized examples, of which 3 also leveraged RWE in the postmarket approach, that demonstrate continued evolution and increasing sophistication in RWE applications, which are presented in this report. The examples included in this report are not inclusive of all submissions or regulatory decisions that used RWE between FY 2020-2025, but represent a curated selection that showcases the various uses of RWE as valid scientific evidence.

The structure of the report reflects both well established and emerging RWD sources. In addition to familiar sources such as medical records, registries, and administrative claims data, this report includes newly added sections for device-generated data and public health surveillance data. Consistent with the expanded list of RWD sources described in the CDRH RWE guidance, the examples also include uses of clinically annotated biobanks, medical device data repositories, and chargemaster and/or billing data, highlighting the increasingly diverse data landscape available to support evidence generation for medical devices.

Together, these examples offer insights into the evolving use of RWD and RWE to support regulatory decision-making for medical devices. They provide context for how RWD have been applied in practice and help shape continued use of relevant and reliable RWD to generate meaningful evidence across the total product lifecycle.

How to Read the Example Tables

Each example is presented in a structured table formatted to highlight key elements of how RWD were incorporated into the regulatory submission. The example tables summarize information drawn exclusively from public-facing documentation and include only publicly available information associated with the regulatory decision, resulting in variable levels of detail across examples. All clinical evidence described in the public-facing documentation is included for each example, including evidence that was non-RWE (e.g., traditional clinical studies). The examples are intended to support learning and discussion, and should not be interpreted as prescriptive or as representing preferred approaches.

Each example consists of a Submission Summary Table, a “Premarket Clinical Evidence” table, and, where applicable, a “Post-approval Study Requirement Using an RWD Source” table. Within each table, elements (e.g., Study Design, Population, Comparator) are identified by column headers, and some columns include multiple sub-elements (e.g., Follow-up/Duration, Study Period, Sample Size). When specific sub-elements were not available or sufficiently described in publicly available documentation, they were omitted. If an entire

element was not applicable or available, this was noted within the corresponding column as not applicable or not available.

Table Elements and Sub-Elements Descriptions

Submission Summary Table

1. **Submission Number** – Marketing submission number under which the device was approved, cleared, or granted by FDA.
2. **Authorization Date** – Date of official correspondence from the FDA authorizing the device for marketing in the United States (U.S.).
3. **Device** – Name(s) of the authorized device and its components, if applicable.
4. **Sponsor** – Name of the applicant who acquired authorization for the device, as stated in the public decision summaries.
5. **RWD Source(s)** – Identifies all RWD sources described in publicly available documentation as being used to generate clinical evidence in support of the device's authorization. When an RWD source is referenced by a specific or proper name, that name is also included within this field.
6. **RWE Use Summary** – Provides a narrative description of the clinical evidence considered during regulatory review. For all included examples, this section includes a "Premarket" narrative supported by the corresponding "Premarket Clinical Evidence" table. When a post-approval study was required as a condition of approval for a PMA or HDE and incorporated RWD, a "Postmarket" narrative is also included, supported by the corresponding "Post-approval Study Requirement Using an RWD Source" table. The narrative describes the submission type and regulatory purpose (e.g., new device, device modification, or expanded indications for use), and, where applicable, describes the specific indication or labeling change supported by the evidence. The section additionally summarizes the totality of clinical evidence considered in the regulatory decision and explains how RWE was used within the broader evidentiary context.
7. **Key Tags** – A predefined set of terms (see list and definitions below) that capture special areas of interest applicable to each example, including the types of RWD sources used, inclusion of specific populations (e.g., pediatric populations or subjects outside the U.S.), and the clinical area associated with the authorized device.

Key Tag Definitions

The tag definitions below are used for all examples and are not mutually exclusive:

1. **Administrative claims data** – Example includes (or will use) data from administrative claims.
2. **Biobank data** – Example includes (or will use) clinically annotated data from a biobank.
3. **Chargemaster and/or billing data** – Example includes (or will use) chargemaster and/or billing data.
4. **Comparator is, or is derived from, RWD** – Example includes (or will use) a comparator that is RWD or is derived from RWD.
5. **Device-generated data** – Example includes (or will use) RWD from the device during commercial use.
6. **Digital Health** – Example is for a digital health device.
7. **Linkage** – Example includes (or will use) linkage between multiple sources, including RWD sources.

[2] This definition is provided for the purposes of this document and is distinct from the regulatory definition. See, for example, 21 CFR 56.102(j).

8. **Medical records (EHR, EMR, or chart review)** – Example includes (or will use) data from medical records (includes EHRs, electronical medical records (EMRs), and medical chart reviews).
9. **Outside-the-US** – Example includes RWD from outside the U.S. (OUS).
10. **Patient-generated or patient-entered data** – Example includes (or will use) patient-generated or patient-entered RWD, such as through a mobile application.
11. **Pediatric** – Example includes (or will use) RWD from a pediatric population.
12. **PRO derived from RWD** – Example includes (or will use) patient-reported outcomes (PROs) derived from RWD.
13. **Professional society registry** – Example includes (or will use) data from a registry owned by a professional society, consortium, or other organization.
14. **Public health surveillance data** – Example includes (or will use) data from public health surveillance, such as, COVID-19 case surveillance, Medical Device Reporting (MDR), product complaint data.
15. **Registry** – Example includes (or will use) registry data. This key tag is utilized when the registry is not specified as being a professional society registry or a sponsor registry.
16. **RWE as a primary source of clinical evidence** – Example includes RWE used as the primary or sole source of clinical evidence for a premarket submission.
17. **Sponsor registry** – Example includes (or will use) data from a registry owned by the sponsor.
18. **Total-Product Lifecycle** – Example includes RWE for both premarket decision-making and to support a post-approval study.
19. **Validation** – Example includes (or will use) RWD for validation purposes.
20. The clinical area of the medical device is listed last in the Key Tags column. These are listed as stated in the Medical Device Databases for each submission. Clinical areas in this report include: Anesthesiology; Cardiovascular; Clinical Chemistry; Dental; Ear, Nose, And Throat; Gastroenterology/ Urology; General & Plastic Surgery; General Hospital; Microbiology; Molecular Genetics; Neurology; Ophthalmic; Orthopedics; Pathology; and Radiology.

Premarket Clinical Evidence/Post-approval Study Requirement Tables

These tables provide additional detail on the clinical studies and data sources referenced in the RWE Use Summary narrative. All information presented reflects what is described in publicly available documentation cited for each example. The elements and sub-elements below describe the information included for each study, when publicly available, along with important notes to consider when reviewing the tables.

1. **Study Design**
    a. **Study Title** – Title of the study, as provided by the sponsor or described in public-facing documentation, along with an indication of whether the evidence was classified RWE or non-RWE. In some cases, publicly available information was insufficient to confirm whether a component of the clinical evidence was RWE; such components are labeled as “Non-RWE.”
    b. **Study Design** – Describes the overall design of the study. Unless otherwise specified, studies are assumed to be 2 arms. Please note, only RWE used for validation studies is described; test or training data is not highlighted in the applicable examples.
    c. **Follow-up/Duration** – Length of follow-up or study duration, if reported.
    d. **Study Period** – Timeframe during which data were collected or the study was conducted, if reported.

e. **Database(s)** – For systematic literature reviews, identifies the database(s) searched.

f. **Publication Date Period** – For systematic literature reviews, specifies the publication data range covered.

g. **Methods of Note** – Highlights advanced or noteworthy methodological approaches (e.g. techniques used to address bias, data linkage, or other advanced analytical considerations). This field is not intended to provide a comprehensive description of all statistical methods used in the study.

2. **Population**

a. **Population** – Describes the population evaluated in the study. For studies with multiple arms, this section reflects the population of the treatment arm only.

b. **Sample Size** – Number of subjects included in the treatment arm. For systematic literature reviews, this reflects the number of publications included in the review.

c. **Number of Publications** – For systematic literature reviews, this reflects the number of publications included in the review.

d. **Number of Sites** – Number and country of study sites contributing data for the treatment population, if specified.

3. **Comparator**

a. **Type** – Describes the type of comparator used in the study, if applicable (e.g. historical control, concurrent control, within-subject comparator, performance goal, or other comparator approach).

b. **Population** – Describes the comparator population evaluated in the study.

c. **Sample Size** – Number of subjects included in the comparator arm.

d. **Number of Sites** – Number and country of study sites contributing data for the comparator population, if specified.

4. **Key Endpoints**

a. **Primary Safety Endpoint(s)** – Describes the primary safety endpoint(s) evaluated in the study. Included in the Premarket Clinical Evidence table for all submission types, when reported.

b. **Primary Effectiveness Endpoint(s)** – Describes the primary effectiveness endpoint(s) evaluated in the study. Included in the Premarket Clinical Evidence table for PMA, 510(k), and De Novo submissions, when reported.

c. **Probable Benefit Endpoint(s)** – Describes the primary endpoint(s) used to assess the probable benefit for HDE submissions, in lieu of effectiveness endpoints. Included in the Premarket Clinical Evidence table, when reported.

d. **Validation Study Endpoint(s)** – Describes the endpoint(s) used in validation studies in the Premarket Clinical Evidence table, when reported.

e. **Safety and Effectiveness Endpoint(s)** – Describes the endpoint(s) required to be evaluated in postmarket studies, including post-approval studies ordered as a Condition of Approval for an approved PMA. Included in the Post-approval Study Requirement Using an RWD Source table, as applicable and when reported.

Use of Literature and Systematic Literature Reviews

Literature alone is not considered RWE for the purposes of these examples. However, when published literature incorporated RWE (e.g., evidence derived from medical records, registries, or administrative claims) and were relied upon in the regulatory decision, those studies were identified as RWE. In such cases, the

"RWD Source(s)" column reflects the underlying RWD described in the literature rather than the literature itself.

For systematic literature reviews, the tables indicate whether any of the included studies incorporated RWE. Readers seeking additional detail on the specific studies included in a systematic literature review are encouraged to consult the publicly available decision summaries, as noted in the "Methods of Note" sub-element of these examples.

Section I. Examples Leveraging Medical Records as a Real-World Data Source

Example 1. PMA – Approval of a New PMA for a Selective Internal Radiation Therapy Using Medical Records [1, 2]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P200029 3/17/2021	TheraSphere	Boston Scientific Corporation	Medical records (EHR, EMR, or chart review) Public health surveillance data	**Premarket:** Medical record data was a primary source of clinical evidence to support the approval of this conversion of an HDE to a PMA. The sponsor conducted a retrospective, single-arm, multi-center study using medical records from consecutive patients with unresectable hepatocellular carcinoma treated with TheraSphere at U.S. sites. The sponsor also submitted supplemental clinical evidence which included adverse events the sponsor has received since U.S. commercial distribution of the HDE device. Postmarket surveillance data included adverse events reported as product complaints or identified in the published medical literature.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Outside-the-US Public health surveillance data Radiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
LEGACY Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** According to the site clinical practice (expected for month 3 or month 4 after initial post-TheraSphere treatment visit, and thereafter at 3-month intervals (depending on institutional clinical practice) through 12 months, at 6-month intervals at 18 and 24 months, and at 12-month intervals after 24 months) **Study Period:** 2/13/2014 – 12/31/2018	**Population:** Consecutively treated patients with unresectable hepatocellular carcinoma. **Sample Size:** 162 patients **Number of Sites:** 3 U.S. sites	**Type:** Performance criteria	**Co-primary Effectiveness Endpoint(s):** Confirmed objective response rate by localized modified Response Evaluation Criteria in Solid Tumors (mRECIST) >40%; and duration of response by localized mRECIST of ≥6 months in ≥60% of responders

Study Design	Population	Comparator	Key Endpoints
Postmarket Surveillance Analysis (RWE) **Study Design:** Retrospective Cohort (Single-Arm) Postmarket Surveillance **Study Period:** U.S.: Since 2000 OUS: 7/1/2012 – 12/31/2019	**Population:** Patients treated with the HDE device **Sample Size:** U.S.: Over 20,000 patients OUS: Over 10,000 patient administrations	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events

Example 2. PMA – Approval of a PMA for an Indication Expansion for a Cochlear Implant System Using Medical Records [3, 4]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P970051/S205 1/10/2022	Nucleus 24 Cochlear Implant System	Cochlear Americas	Administrative claims data Medical records (EHR, EMR, or chart review) Registry	**Premarket:** Medical record data was a primary source of clinical evidence for the approval of this PMA Supplement to expand the indication of the implant system to single-sided deafness (SSD)/unilateral hearing loss in children (≥5 years old) and adults. The clinical evidence included data from a feasibility study, which the sponsor pooled with RWD from 2 cochlear implant (CI) centers, and a systematic literature review that provided supplemental clinical evidence for safety and effectiveness in both adults and children. A subset of the literature reviewed in the systematic literature review incorporated RWD, including studies that utilized data from medical records, commercial insurance claims, and a registry.	RWE as a primary source of clinical evidence Administrative claims data Medical records (EHR, EMR, or chart review) Pediatric Registry Ear, Nose, And Throat

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
CI Feasibility + RWD Study (Non-RWE and RWE) **Study Design:** Pre-post Cohort Study **Follow-up/Duration:** 6, 12, and 24 months **Study Period:** Subjects implanted within the previous 10 years	**Population:** Patients ≥ 18 years old with moderate to profound sensorineural hearing loss who received a Nucleus cochlear implant (excluding the Hybrid L24 implant) for the treatment of SSD **Sample Size:** 42 patients total (10 feasibility study + 32 RWD) **Number of Sites:** Feasibility study: 4 U.S. sites; RWD: 2 of the 4 U.S. sites from the feasibility study	**Type:** Performance goal; within-subject comparator	**Primary Effectiveness Endpoint(s):** Improvement in noise scores post-activation in bimodal listening condition (CI + normal hearing) vs. pre-operative scores and improvement in noise scores post-activation in bimodal listening condition (CI + normal hearing) vs. normal hearing ear alone (CI off)

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Review (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** Embase and PubMed **Publication Date Period:** Effectiveness: 1/1/2015 – 9/3/2021 **Safety:** 1/1/2015 – 12/10/2021 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Effectiveness: Patients ≥6 months with SSD Safety: Patients ≥5 years old with cochlear implants **Number of Publications:** Effectiveness - Adults: 17 peer-reviewed publications, which included data from 296 adults with SSD Children: 10 peer-reviewed publications, which included data from 105 children with SSD Safety: 20 peer-reviewed publications	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** Speech perception in noise, localization ability, and patient reported outcomes

Example 3. PMA – Approval of a PMA for an Indication Expansion for a Venous Stent Using a Systematic Literature Review and Medical Records [5, 6]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P980033/S050 3/17/2020	VENOUS WALLSTENT	Boston Scientific Corporation	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary and supplemental source of clinical evidence for the approval of this PMA Supplement for an indication expansion for the treatment of symptomatic iliofemoral venous outflow obstruction. The primary clinical evidence was a systematic literature review, which included multiple studies using medical record data and provided a critical review of the published information relevant to safety and performance of the VENOUS WALLSTENT. The clinical evidence additionally included a supplemental investigator-sponsored research study, which utilized retrospective chart review to evaluate the procedure, patency rates, and clinical outcomes among patients who were treated with the VENOUS WALLSTENT.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Review (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** Databases representative of the U.S. and OUS literature **Publication Date Range:** Prior to 4/1/2019 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Patients receiving stents (including the WALLSTENT and competitors) for venous obstruction or pelvic obstruction (lower extremity, superior vena cava and central venous) **Number of Publications:** 38 publications total (29 publications from systematic search, 8 publications providing additional reports of adverse events, 1 meta-analysis added due to relevance to iliac venous stenting)	Not applicable for this study	**Primary Safety Endpoint(s):** Major adverse events and adverse events **Primary Effectiveness Endpoint(s):** Patency rate

Study Design	Population	Comparator	Key Endpoints
Investigator-Sponsored Chart Review (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 1 month, 6 months, 12 months, 24 months, 36 months **Study Period:** Patients operated on between 11/1/2007 – 10/31/2014, follow-up accrued through 3/31/2017	**Population:** Patients ≥18 years old with signs and symptoms consistent with chronic venous hypertension in the legs, not ascribed to superficial venous insufficiency, who underwent placement of an iliofemoral VENOUS WALLSTENT **Sample Size:** 67 patients (77 limbs, treated with a total of 126 VENOUS WALLSTENT devices) **Number of Sites:** 1 U.S. site	Not applicable for this study	**Primary Safety Endpoint(s):** Major adverse events (including device- or procedure related death, major bleeding event, device- or procedure-related arterial or venous injury, device- or procedure-related acute deep vein thrombosis, clinically significant pulmonary embolism, and embolization of stent) **Primary Effectiveness Endpoint(s):** Patency (primary, assisted primary, and secondary), and clinical improvement

Example 4. HDE – Approval of a New HDE for a Total Talus Replacement Metal Prosthesis Device Using Medical Records [7-9]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
H230003 11/17/2023	restor3d Total Talus Replacement	restor3d, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the approval of this HDE for a new total talus replacement (TTR) device. The sponsor conducted a retrospective chart review study, examining clinical and radiographic outcomes of patients who received a patient-specific restor3d TTR implant to treat talar dysfunction. The clinical evidence included this retrospective chart review study to determine probable benefit and safety outcomes.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Orthopedics

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Chart Review Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** < 1 year, 1–2 years, 2–3 years, 3+ years **Study Period:** 1/1/2019 – 1/6/2023	**Population:** Adult patients (≥ 22 years old) who underwent foot or ankle deformity correction with the restor3d TTR device **Sample Size:** 27 patients **Number of Sites:** 4 U.S. sites	**Type:** Within-subject comparator	**Primary Safety Endpoint(s):** Rate of adverse events, device- or procedure-related adverse events, and serious adverse events; rate of subsequent surgical intervention; and rate of implant survivorship **Probable Benefit Endpoint(s):** Improvement in pain (as measured by the Pain Numerical Rating Scale and PROMIS 1.0 – Pain Interference scale, at last follow-up from baseline)

Example 5. De Novo – Classification of a Portosystemic Pressure Gradient Measurement System Using Medical Records [10–12]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
DEN180062 11/20/2019	EchoTip® Insight™ Portosystemic Pressure Gradient Measurement System	Cook Ireland, Ltd	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data described in a peer-reviewed publication was a primary source of clinical evidence for the classification of this De Novo. The clinical evidence from the publication included a single-arm, single-center cohort study to provide confirmatory evidence that the device could safely measure endoscopic ultrasound (EUS) - portal pressure gradient (PPG).	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Gastroenterology/ Urology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
EUS-PPG Study – Huang et al. 2017 (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 48 hours	**Population:** Patients between 18–75 years old with a history of liver disease or suspected cirrhosis **Sample Size:** 28 patients **Number of Sites:** 1 U.S. site	Not applicable for this study	**Primary Safety Endpoint(s):** Intraprocedural or postprocedural adverse events **Primary Effectiveness Endpoint(s):** Technical success of PPG measurement and correlation with clinical parameters, including cirrhosis, varices, and gastropathy

Example 6. De Novo – Classification of an Adjunctive Hemodynamic Indicator with Decision Point Software Using Medical Records [13, 14]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
DEN200022 3/1/2021	Analytic for Hemodynamic Instability (AHI)	Fifth Eye Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Hospital data was a primary source of clinical evidence for the classification of this De Novo. The sponsor conducted a prospective validation study using data from consecutive patients from critical care and emergency room units at the University of Michigan Medical Center. The study evaluated the performance of the device's algorithm in identifying signs of hemodynamic instability by comparing the device output to a reference standard derived from continuous electrocardiogram (ECG) and continuous arterial line blood pressure measurements. Performance was assessed on a per-window basis using pre-specified sensitivity and specificity acceptance criteria.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Prospective Medical Records Study (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration**: 5 minutes of continuously recorded Lead II ECG data **Study Period:** 11/26/2019 – 1/29/2020	**Population:** Patients 19–92 years old with continuous ECG and continuous arterial line blood pressure monitoring **Sample Size:** 222 patients **Number of Sites:** 1 U.S. site	**Type:** Reference standard based on continuous ECG and continuous arterial line blood pressure monitoring	**Validation Study Endpoint(s):** Hemodynamic instability

Example 7. De Novo – Classification of a Laser Inferior Vena Cava Filter Retrieval Catheter Using Medical Records [15, 16]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
DEN210024 12/21/2021	CavaClear Laser Sheath	Spectranetics, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the classification of this De Novo. The sponsor conducted a retrospective, multicenter study to evaluate the safety and performance of utilizing an excimer laser sheath during inferior vena cava (IVC) filter removal procedures through abstraction of medical records (multiple sites) and use of an existing published dataset (single site) from U.S. sites.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Multicenter Excimer Laser Sheath Assisted Retrieval of Embedded IVC Filters Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Study Period:** 3/2012 – 2/2021	**Population:** Patients presenting with IVC filters that were refractory to alternate removal techniques **Sample Size:** 265 patients (139 from 1 site and 126 from multiple sites) **Number of Sites:** 7 U.S. sites	**Type:** Performance goal **Population:** Derived from meta-analysis of existing literature	**Primary Safety Endpoint(s):** Major device-related complication rate **Primary Effectiveness Endpoint(s):** Procedural technical success rate

Example 8. De Novo – Classification of a Cardiovascular Machine Learning–Based Notification Software Using Medical Records [17, 18]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
DEN230003 8/3/2023	Viz HCM	Viz.ai, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the classification of this De Novo. The sponsor conducted a validation study using historical data from medical charts, imaging, and ECGs from 3 U.S. hospitals. Cardiologist review of medical charts and imaging was used to establish hypertrophic cardiomyopathy (HCM) status for each patient, and the device's ECG-based output was compared against this diagnosis.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Validation Study (RWE) **Study Design:** Case-Control Study Validation Study **Study Period:** 7/1/2017 – 6/30/2022	**Population:** HCM positive and negative ECG cases **Sample Size:** Total: 3,196 patients HCM-Positive ECG: 291 patients HCM-Negative ECG: 2,905 patients **Number of Sites:** 3 U.S. sites	**Type:** Clinician chart and imaging review	**Validation Study Endpoint(s):** Presence of HCM

Example 9. 510(k) – Clearance of a Machine Learning-Based Software to Predict Hemodynamic Instability Using Medical Records [19]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K200717 1/9/2021	CLEWICU System	CLEW Medical Ltd.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The sponsor conducted a retrospective validation study using patient-stay data from WakeMed Health System hospitals. A tagging system was developed and validated against human physician readers to generate clinical truth labels from the retrospective dataset. These labels were used to evaluate the performance of the CLEWICU predictive models in identifying patients at risk for future hemodynamic instability and those at low risk for deterioration.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Validation Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Study Period:** 11/5/2019 – 6/30/2020	**Population:** Patients at least 18 years old admitted to intensive care units **Number of Sites:** 2 U.S. sites	**Type:** Tagging system (validated against physician readers as ground truth) used to generate clinical truth labels	**Validation Study Endpoint(s):** CLEWHI index (likelihood of hemodynamic instability requiring vasopressor/inotrope support) and CLEWLR (indication that the patient is at “low risk” for deterioration)

Example 10. 510(k) – Clearance of an Anatomic Shoulder Prosthesis Using Medical Records [20]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K201391 2/16/2021	Easytech® Anatomical Shoulder System	FX Shoulder USA, Inc.	Medical records (EHR, EMR, or chart review) Public health surveillance data	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The sponsor conducted an OUS retrospective, single-arm, multicenter study, as part of the manufacturer's postmarket surveillance for its shoulder devices, to evaluate the safety and effectiveness of the device for total shoulder arthroplasty.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Outside-the-US Public health surveillance data Orthopedics

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Easytech Retrospective Clinical Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Postmarket surveillance **Follow-up/Duration:** 24+ months post implantation **Study Period:** 1/2015 – 12/2016	**Population:** Patients with primary diagnosis of osteoarthritis treated with the Easytech Anatomical Shoulder System **Sample Size:** 129 patients **Number of Sites:** 5 OUS sites (France)	**Type:** Performance goal; within-subject comparator	**Primary Effectiveness Endpoint(s):** Composite clinical success (defined as adjusted constant score of ≥54 and improved from baseline ≥10; no component migration or subsidence; maintenance of radiolucencies of the humeral or glenoid components; maintenance of implant integrity; no revision surgery; and no serious adverse device effects)

Example 11. 510(k) – Clearance of a Surgical System Using Medical Records [21]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K202166 3/2/2021	Senhance Surgical System	TransEnterix, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for modifications to the indications for use to expand the types of surgical procedures for which the Senhance Surgical System may be used. Chart review of patients who underwent Nissen fundoplication procedures with the Senhance System provided performance and safety results for the proposed indications. The clinical evidence also included 6 peer-reviewed publications describing clinical outcomes for 2 alternative surgical techniques, which provided comparison data for the chart review study.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Outside-the-US General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Chart Review Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm)	**Population:** Patients who underwent Nissen fundoplication procedures with the Senhance System **Sample Size:** 34 patients **Number of Sites:** OUS sites (Germany and Netherlands; number unspecified)	**Type:** Systematic literature review control (see Systematic Literature Review below)	**Primary Safety Endpoint(s):** Length of hospital stay, intraoperative complications, transfusion rate/ estimated blood loss (EBL), mortality, post-operative complications, and operative time **Primary Effectiveness Endpoint(s):** Conversion rate, readmission rate, and reoperation rate
Systematic Literature Review (Non-RWE) **Study Design:** Systematic Literature Review **Database(s):** PubMed and MEDLINE **Publication Date Period:** 2000 – 2020 **Methods of Note**: For additional details see the Decision Letter and Summary	**Population:** Adult patients in the European Union or U.S. who underwent laparoscopic or robotically assisted surgery **Number of Publications:** 6 publications	Not applicable for this study	**Primary Safety Endpoint(s):** Length of hospital stay, intraoperative complications, transfusion rate/EBL, mortality, post-operative complications, and operative time **Primary Effectiveness Endpoint(s):** Conversion rate, readmission rate, and reoperation rate

Example 12. 510(k) – Clearance of a Radiation Therapy Treatment Planning System Using Medical Records [22]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K202284 3/12/2021	Oncospace	Oncospace, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Clinician treatment plan record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The sponsor conducted a retrospective validation study of this software using a set of traditionally planned radiation treatment plans for prostate, thoracic, pancreas, and head and neck cancers to compare the number of iterations necessary with and without using Oncospace to demonstrate substantial equivalence to the predicate device.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Radiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Clinical Performance Validation Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study	**Population:** Oncospace-assisted radiation treatment plans for prostate, thoracic, pancreas, and head and neck cancers	**Type:** Clinician radiation treatment plans for patients with prostate, thoracic, pancreas, and head and neck cancers	**Validation Study Endpoint(s):** Number of iterations required to achieve a clinically viable and deliverable radiation treatment plan

Example 13. 510(k) – Clearance of a Rigid Gas Permeable Contact Lens Using Medical Records [23]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K203571 4/9/2021	Acuity 200™ (fluoroxyfocon A) Rigid Gas Permeable Contact Lens	Acuity Polymers, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical records data was a primary source of clinical evidence for the clearance of this 510(k) for modification to the indications for use to include management of irregular corneal conditions. The clinical evidence included data from the retrospective review of medical charts by 4 independent practitioners.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Ophthalmic

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Acuity 200 Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 13,760 days	**Population:** Patients with irregular corneal conditions managed using contact lenses manufactured from Acuity 200 (fluoroxyfocon A) material **Sample Size:** 41 patients (66 total eyes)	Not applicable for this study	**Primary Safety Endpoint(s):** Serious adverse reactions **Primary Effectiveness Endpoint(s):** Stable or improved irregular corneal conditions and vision

Example 14. 510(k) – Clearance of Dental Implant System Using Medical Records [24, 25]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K210356 2/4/2022	Noris Medical Ltd	Noris Medical Dental Implants System	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a modification to a dental implant system including expanded abutment angulations and gingival height options. The clinical evidence included 2 studies using medical records: (1) a retrospective single-arm cohort study of patients treated with a reference device from published literature, and (2) a retrospective study of patients treated with Noris Medical Multi Unit abutments to demonstrate substantial equivalence.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Outside-the-US Dental

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Nobel Biocare Multi Unit Retrospective Study – Lopes et al. 2021 (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 2 years post-implant **Study Period:** 7/2016 – 8/2020	**Population:** Patients 27–72 years old who underwent complete edentulous maxillary rehabilitations with the NobelZygoma 0° with a TiUnite surface **Sample Size:** 44 patients (77 implants) **Number of Sites:** 1 OUS site (Portugal)	**Type:** Within-subject comparator	**Primary Safety Endpoint(s):** Biological complications **Primary Effectiveness Endpoint(s):** Prosthetic success, implant success, and abutment success
Noris Medical Multi Unit Retrospective Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** Up to 48 months post-implant surgery **Study Period:** Implants placed 2013 – 2020	**Population:** Adult patients 36-86 years old treated with Noris Medical Multi Unit abutments **Sample Size:** 33 patients (with 88 implants)	**Type:** Within-subject comparator	**Primary Safety Endpoint(s):** Unspecified adverse events and inflammation **Primary Effectiveness Endpoint(s):** Survival of implant at least 12 months post-loading

Example 15. 510(k) – Clearance of a Adjunctive Hemodynamic Indicator with Decision Point Software Using Medical Records [26]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K212219 12/3/2021	AHI System	Fifth Eye Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical records data was a primary source of clinical evidence for the clearance of this 510(k) for an indication expansion for this device software function to predict a patient's likelihood of a future hemodynamic instability episode. The sponsor conducted an observational study using prospectively collected EHR data at 1 U.S. site to validate the device software function. The Analytic for Hemodynamic Instability Predictive Indicator (AHI-PI) predictive outputs were compared to a vital signs reference standard for episodes of hemodynamic instability. Performance was evaluated at the window level using probability estimates and lead-time metrics.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Observational Clinical Validation Study (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) Validation Study **Methods of Note**: Bootstrapping was used to account for multiple measurements per subject	**Population:** Patients at least 18 years old with continuous physiological monitoring with electrocardiography **Sample Size:** 65,969 windows of time analyzed **Number of Sites:** 1 U.S. site	**Type**: Reference standard based on hemodynamic vital signs	**Validation Study Endpoint(s):** Likelihood of a future hemodynamic instability episode

Example 16. 510(k) – Clearance of an Automatic Event Detection Software for Polysomnograph with Electroencephalograph Using Medical Records [27]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K221179 9/21/2022	SomnoMetry	Neumetry Medical Inc	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data associated with archived polysomnography files was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The sponsor conducted a retrospective cohort study to compare the device performance to a clinician's manual scoring of the same sleep recordings from routine clinical practice and to confirm there was no statistically significant difference in clinical performance compared to the predicate device.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Clinical Performance Testing (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Study Period:** Data collected over multiple years; specific dates not provided	**Population:** Patients 20–84 years old who had undergone sleep testing **Sample Size:** 201 patients **Number of Sites:** 2 U.S. sites (American Academy of Sleep Medicine accredited sleep testing facilities)	**Type:** Within-subject comparator; Ground truth based on clinician's manual scoring of data from the same test subjects	**Validation Study Endpoint(s):** Sleep staging scoring; diagnosing sleep apnea

Example 17. 510(k) – Clearance of a Transcranial Magnetic Stimulation System Using Electronic Health Records [28-30]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K222196 5/31/2024	BrainsWay Deep TMS™ System	BrainsWay Ltd.	Medical records (EHR, EMR, or chart review)	**Premarket:** Electronic health record (EHR) data was a supplemental source of clinical evidence for the clearance of this 510(k) to support the expansion of the adult population to include subjects ≥22 and ≤86 years old suffering from major depressive disorder (MDD) who failed to achieve satisfactory improvement from previous antidepressant medication treatment in the current episode. The device was originally cleared for subjects ≥22 to ≤68 years old. The clinical evidence included data from a published double-blind, randomized, sham-controlled trial and a sponsor's retrospective cohort study using EHR data to further support the safety and effectiveness of transcranial magnetic stimulation (TMS) treatment in patients >68 years old. The sponsor also conducted a literature review of studies using TMS to treat late-life depression. A subset of the literature reviewed incorporated RWD, including multiple studies that utilized medical record data.	Medical records (EHR, EMR, or chart review) Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Randomized Controlled Trial – Kaster et al. 2018 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 1 week, 2 weeks, 3 weeks, and 4 weeks **Study Period:** 6/2013 – 11/2016	**Population:** Patients (60–85 years old) with MDD diagnosis randomized to active repetitive TMS (rTMS) **Sample Size:** 25 patients **Number of Sites:** 1 OUS site (Canada)	**Type:** Randomized controls **Population:** Patients (60–80 years old) with MDD diagnosis randomized to sham rTMS **Sample Size:** 27 patients **Number of Sites:** 1 OUS site (Canada)	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** Remission rate defined as both 24-item Hamilton Depression Rating Scale (HDRS-24) ≤10 and ≥60% reduction from baseline on 2 consecutive weeks

Study Design	Population	Comparator	Key Endpoints
Adult MDD Patients Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Study Period:** 2012 – 2022	**Population:** Patients (69-86 years old) who received BrainsWay treatment for MDD and had a primary diagnosis of MDD **Sample Size:** 152 patients **Number of Sites:** 20 U.S. sites	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** Remission and response rates based on HDRS-21 scores only and/or Patient Health Questionnaire-9 score and HDRS-21 scores
Formal Literature Review of rTMS in late-live depression (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Publication Date Range:** 2001 – 2023 **Methods of Note**: For additional details see the Decision Letter and Summary	**Population:** Patients (40 years old and older) that received active rTMS treatment **Number of Publications:** 17 publications (n= 573) and 1 meta-analysis (n=338), including multiple studies using medical record data	**Type:** Concurrent controls **Population:** Patients (40 years old and older) in the inactive/control treatment group **Sample Size:** 17 publications (n= 438) and 1 meta-analysis (n=299)	**Primary Effectiveness Endpoint(s):** Remission and response rates
Retrospective Chart Review Study – Kryatova et al. 2024 (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** Every 10 TMS sessions **Study Period:** 2014 – 2021	**Population:** MDD patients (18–80 years old) who had 29–35 TMS treatments for depression treated with BrainsWay Deep TMS device **Sample Size:** 378 patients **Number of Sites:** 1 U.S. site	Not applicable for this study	**Primary Effectiveness Endpoint(s):** Remission and response rates assessed using percent reduction in Quick Inventory of Depressive Symptomatology Self-Report

Example 18. 510(k) – Clearance of an Endoscope and Accessories Using Medical Records [31]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K223080 11/22/2022	da Vinci® Xi and X Surgical Systems, Model IS4000 and Model IS4200	Intuitive Surgical, Inc.	Chargemaster and/or billing data Medical records (EHR, EMR, or chart review) Premier Health Database (PHD)	**Premarket:** Medical record and chargemaster data were a primary source of clinical evidence for the clearance of this 510(k) to support a labeling expansion to 4 specific duodenal switch bariatric surgical procedures. The sponsor conducted a retrospective study using data from the Premier Health Database (PHD) to compare patients who underwent robotic-assisted procedures or laparoscopic procedures complex/highest risk, duodenal switch bariatric surgical procedures ("umbrella" procedures) to demonstrate substantial equivalence to the cleared predicate devices.	RWE as a primary source of clinical evidence Chargemaster and/or billing data Comparator is, or is derived from, RWD Medical records (EHR, EMR, or chart review) General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
PHD Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 30 days **Study Period:** 2016 – 2020 **Methods of Note**: Propensity score matching	**Population:** Patients who underwent robotic-assisted procedures **Sample Size:** 377 patients	**Type:** Concurrent controls **Population:** Patients who underwent laparoscopic procedures **Sample Size:** 1,501 patients	**Primary Safety Endpoint(s):** Operative times, lengths of hospital stay, conversion rates, transfusion rates, intraoperative complication rates, 30-day post-operative complication rates, 30-day readmission rates, 30-day reoperation rates, and 30-day mortality rates

Example 19. 510(k) – Clearance of Stand-Alone Analytical Software Using Medical Records [32]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K233216 1/13/2024	CLEWICU System	Clew Medical Ltd.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for expansion of intended use environment from only the intensive care unit to all critical care areas of a hospital. A retrospective validation study was conducted using patient stay data from 2 separate health care systems. The performance of the CLEWICU predictive models in identifying patients at risk for future hemodynamic instability and those at low risk for deterioration was evaluated with a reduced input dataset to demonstrate that the system met the same statistical criteria established under the prior 510(k) (K200717) and could therefore be used in all critical care areas of the hospital.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Model Validation Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** Start of each patient stay through discharge	**Population:** Unique patient stays **Sample Size:** University of Massachusetts eICU dataset: 6,534 patient stays; MIMIC-III dataset: 5,069 patient stays **Number of Sites:** 2 U.S. sites	**Type:** Previously established reference standard for the originally cleared CLEWICU model (see K200717)	**Validation Study Endpoint(s):** CLEWHI index (likelihood of hemodynamic instability requiring vasopressor/inotrope support), CLEWLR (indication that the patient is at “low risk” for deterioration)

Example 20. 510(k) – Clearance of a Cloud-Based Software Application Using Medical Records [33]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K233253 6/21/2024	eCARTv5 Clinical Deterioration Suite ("eCART")	AgileMD, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The sponsor conducted retrospective and prospective validation studies using admissions and hospitalization data from 3 geographically distinct health systems. In both cohorts, eCART scores were categorized into pre-defined moderate- and high-risk groups (eCART ≥93 and ≥97), and these risk categories were evaluated against observed clinical deterioration and mortality.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** 24 hours following an eCART score **Study Period:** 2009 – 2023	**Population:** Adult ward patients **Sample Size:** 1,769,461 patient encounters from 934,454 unique patients **Number of Sites:** 3 sites (location unspecified)	**Type:** Observed clinical outcomes	**Validation Study Outcome(s):** Clinical deterioration within 24 hours and mortality within 24 hours following an eCART score
Prospective Study (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** 24 hours following an eCART score **Study Period:** 2023 – 2024	**Population:** Adult ward patients **Sample Size:** 205,946 patient encounters from 151,233 unique patients **Number of Sites:** 3 sites (location unspecified)	**Type:** Observed clinical outcomes	**Validation Study Endpoint(s):** Clinical deterioration within 24 hours and mortality within 24 hours following an eCART score

Example 21. 510(k) – Clearance of an Atrial Fibrillation Risk Prediction Machine Learning-Based Notification Software Using Medical Records [34]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K233549 6/21/2024	Tempus ECG-AF	Tempus AI, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The sponsor conducted a retrospective validation study using patient records and ECG tracings from 3 geographically distinct sites. The device's binary risk output was compared against atrial fibrillation/flutter status determined through duplicate manual chart review of medical records.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Clinical Performance Validation Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** 1 year	**Population:** Adults (65–89 years old) receiving an ECG as part of standard of care **Sample Size:** 4,017 patients **Number of Sites:** 3 sites (location un-specified)	**Type**: Clinical diagnosis of atrial fibrillation/flutter, as determined by duplicate manual chart review	**Validation Study Endpoint(s):** Atrial fibrillation/flutter in the next 12 months

Example 22. 510(k) – Clearance of a Surgical Device Using Medical and Billing Records and a Systematic Literature Review [35]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K240852 6/11/2025	da Vinci X Surgical System (IS4200); da Vinci Xi Surgical System (IS4000)	Intuitive Surgical, Inc.	Chargemaster and/or billing data Medical records (EHR, EMR, or chart review) Premier Health Database (PHD)	**Premarket:** Medical record and chargemaster data were a primary source of clinical evidence for the clearance of this 510(k) for a labeling expansion to include tracheobronchoplasty (TBP) for symptomatic, severe tracheobronchomalacia. Procedure codes and billing records from the Premier Healthcare Database (PHD) to assess patients who underwent TBP procedures at 6 U.S. hospitals from 2013 to 2023. The clinical evidence additionally included a systematic literature review, which included studies utilizing medical records, used to generate comparative data.	RWE as a primary source of clinical evidence Chargemaster and/or billing data Comparator is, or is derived from, RWD Medical records (EHR, EMR, or chart review) General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
PHD Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Study Period:** 2013 – Q1 2023 (2013 – 2015 excluded given no robotic TBP procedures occurred prior to 2016)	**Population:** Patients who underwent robotic TBP procedures **Sample Size:** 124 patients **Number of Sites:** 6 U.S. sites	**Type:** Comparator data generated from a systematic literature review (see Systematic Literature Review below)	**Primary Safety Endpoint(s):** Respiratory and pulmonary complications, bleeding-related events, surgical complications, cardiovascular/ systemic complications, 30-day readmission, 30-day reoperation, and mortality **Primary Effectiveness Endpoint(s):** Surgical time, hospital length of stay, intensive care unit (ICU) length of stay, conversion to open surgery, and discharge disposition

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Review (RWE) **Study Design:** Systematic Literature Review **Database(s):** Embase, Scopus, and PubMed **Publication Date Period:** 1/1/2000 – 12/31/2023 **Methods of Note**: For additional details see the Decision Letter and Summary	**Population:** Patients who underwent open TBP procedures **Number of Publications:** 3 publications, approximately 278 open TBP procedures **Number of Sites:** 2 U.S. sites	**Type:** Compared to PHD Study results	**Primary Safety Endpoint(s):** Respiratory and pulmonary complications, bleeding-related events, surgical complications, cardiovascular/ systemic complications, 30-day readmission, 30-day reoperation, mortality **Primary Effectiveness Endpoint(s):** Surgical time, hospital length of stay, ICU length of stay, discharge disposition

Example 23. 510(k) – Clearance of an Automatic Event Detection Software for Polysomnograph With Electroencephalograph Using Medical Records [36]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K241960 3/14/2025	DeepRESP	Nox Medical ehf	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The sponsor conducted a retrospective cohort study to compare the device performance to a clinician's manual scoring of the same sleep recordings from routine clinical practice and to confirm there was no statistically significant difference in clinical performance compared to the predicate device.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Clinical Performance Studies (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study	**Population:** Patients ≥ 22 years old who had undergone sleep testing **Sample Size:** 2,224 Type I sleep recordings (with electroencephalogram) and processed versions of 3,488 Type I and Type II sleep recordings to obtain a subset of signals representative of Type III sleep recordings (without EEG) **Number of Sites:** U.S. sites (number unspecified)	**Type:** Within-subject comparator; ground truth based on clinician's manual scoring of data from the same test subjects	**Validation Study Endpoint(s):** Sleep staging performance across 5 stages (Wake, N1, N2, N3, rapid eye movement (REM)); and sleep apnea severity performance across different apnea-hypopnea index thresholds (≥5, ≥15, ≥30)

Example 24. 510(k) – Clearance of a Temporary Cardiac Pacing Catheter Using Medical Records [37]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K242863 6/15/2025	Bioptimal Bipolar Pacing Catheter	Bioptimal International Pte. Ltd.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical records data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The sponsor conducted a retrospective study using medical records from patients from an OUS hospital.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Outside-the-US Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Clinical Data Analysis (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Study Period:** 3/2022 – 12/2024	**Population:** Patients (average age: 69 ± 12 years) treated for aortic valve procedures and for arrhythmias **Sample Size:** 85 patients **Number of Sites:** 1 OUS site (China)	**Type:** Performance goal	**Primary Safety Endpoint(s):** Complication-free rate **Primary Effectiveness Endpoint(s):** Pacing success rate

Example 25. 510(k) – Clearance of an Echocardiogram Processing Software Using Medical Records [38]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K250119 7/15/2025	Tempus ECG-Low EF	Tempus AI, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The clinical evidence included a retrospective validation study conducted using retrospective medical record data from ECG – transthoracic echocardiogram (TTE) pairs from 4 geographically distinct U.S. clinical sites, allowing the software's performance to be assessed in its intended use population under real-world clinical conditions. Patients were included if they had at least 1 qualifying 12-lead resting ECG within 30 days prior to a TTE. The device's output was compared against TTE-derived left ventricular ejection fraction measurements, which served as the reference standard.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Cohort Validation Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study	**Population:** Adult patients (age range: 40–90 years) with at least 1 qualifying 12-lead resting ECG-TTE pair, where the ECG occurred within 30 days prior to the TTE **Sample Size:** 14,924 patients with >15,000 ECGs **Number of Sites:** 4 U.S. sites	**Type:** Within-subject comparator; Left ventricular ejection fraction (LVEF) determined by TTE	**Validation Study Endpoint(s):** Low ejection fraction, defined as LVEF ≤40%

Example 26. 510(k) – Clearance of an Echocardiogram Image Processing Software Using Medical Records [39]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K250151 6/20/2025	Us2.ca	Eko.ai Pte. Ltd. d/b/a Us2.ai	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The clinical evidence included evaluation of device performance via a case-control study across various sites in the U.S. and Japan. Training and external validation datasets were sourced from separate data providers with no overlap and maintained full independence between development and evaluation. In the validation study, the device's output was compared against the known cardiac amyloidosis status of each patient.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Outside-the-US Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Case-Control Validation Study (RWE) **Study Design:** Case-Control Study Validation Study	**Population:** Patients from a case-control study receiving routine clinical echocardiograms, including both cardiac amyloidosis cases and non-amyloidosis controls **Sample Size:** 1,647 cardiac amyloidosis cases and non-amyloidosis controls **Number of Sites:** 6 U.S. and OUS sites (Japan)	**Type:** Known cardiac amyloidosis status	**Validation Study Endpoint(s):** Cardiac amyloidosis diagnosis

Example 27. 510(k) – Clearance of a Cardiovascular Machine Learning-Based Notification Software Using Medical Records [40]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K250649 9/19/2025	Bunkerhill ECG-EF	BunkerHill Health	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical records data was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The sponsor conducted a retrospective validation study using patient records from 2 health systems across 5 geographically distributed sites in the U.S. to validate the diagnostic accuracy of the algorithm within a clinically and demographically diverse population. The device's performance was evaluated by comparing the binary output from the device to echocardiogram-derived LVEF measurements obtained within 15 days of the ECG.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Validation Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study	**Population:** Patients at least 18 years old from 2 health systems across the U.S. with an echocardiogram obtained within 15 days of the ECG **Sample Size:** 15,994 medical records **Number of Sites:** 5 U.S. sites	**Type:** Within-subject comparator; ground truth established with echocardiogram using the Simpson's Biplane measurement method	**Validation Study Endpoint(s):** LVEF ≤40%

Example 28. 510(k) – Clearance of a Functional Magnetic Resonance Imaging Post-Processing Software Using Medical Record Data from Published Literature [41-46]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K251009 6/6/2025	Cirrus Resting State fMRI Software	Sora Neuroscience, Inc.	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data described in 2 peer-reviewed publications was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The sponsor conducted retrospective validation studies using previously collected patient magnetic resonance imaging (MRI) datasets from brain tumor and epilepsy patients. Three validation studies were included: (1) comparison of sensorimotor (SMN) and language (LAN) network maps generated by Cirrus to resting-state network maps described in peer-reviewed literature using RWD and non-RWD sources, including literature in which resting-state maps were compared to electrical cortical stimulation mapping; (2) within-subject comparison of Cirrus visual (VIS) network maps to same-patient task-activated functional MRI (fMRI) visual maps; and (3) cross-scanner validation assessing reproducibility of network maps across different MRI manufacturers.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Digital Health Medical records (EHR, EMR, or chart review) Pediatric Validation Radiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
SMN and LAN Map Validation Study (Non-RWE and RWE) **Study Design:** Cross-Sectional Study Validation Study	**Population:** Adult and pediatric brain tumor and epilepsy patients (3–71 years old)	**Type:** Peer-reviewed literature **Population:** Resting state network maps described in 5 peer-reviewed publications, including 2 studies that used RWD sources (medical records)	**Validation Study Endpoint(s):** Spatial correlation of SMN and LAN maps with corresponding SMN and LAN maps evaluated in the literature
Vision network Map Validation Study (Non-RWE) **Study Design:** Cross-Sectional Study Validation Study	**Population:** Adult and pediatric brain tumor and epilepsy patients (3–71 years old) **Sample Size:** 26 subjects	**Type:** Within-subject comparator; Same-patient task-activated vision maps	**Validation Study Endpoint(s):** Correspondence of Cirrus resting-state visual network maps with task-activated visual maps

Study Design	Population	Comparator	Key Endpoints
Validation for GE MRI Input Study (Non-RWE) **Study Design:** Cross-Sectional Study Validation Study **Methods of Note**: Comparison using permutation analysis	**Population:** Healthy normal subjects imaged with Siemens MR device **Sample Size:** 8 subjects **Number of Sites:** 5 sites (location unspecified)	**Type:** Within-subject comparator **Population:** Healthy normal subjects imaged with GE MR device **Sample Size:** 8 subjects **Number of Sites:** 3 sites (location unspecified)	**Validation Study Endpoint(s):** Within-subject and cross-subject similarity of network maps across scanner types

Section II. Examples Leveraging Registries as a Source of Real-World Data

Example 29. PMA – Approval of a PMA for an Indication Expansion for a Cochlear Implant System Using Sponsor Registry Data [47, 48]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P000025/S129 10/3/2024	MED-EL Cochlear Implant System	MED-EL Corp.	Medical records (EHR, EMR, or chart review) Registry MED-EL Hearing Solutions (MEHS) Registry Database	**Premarket:** Sponsor registry data was a primary source of clinical evidence for the approval of this PMA Supplement to support marketing claims regarding hearing preservation (HP) rates for the device. The primary clinical evidence additionally included a multicenter single-arm clinical trial for an indication expansion for individuals 18 years of age and older with bilateral, moderate to profound sensorineural hearing loss (SNHL) who obtain limited benefit from appropriately fit hearing aids in the ear(s) to be implanted. The sponsor conducted a multicenter, retrospective study using data from the MEHS registry to capture the residual hearing status after implantation among patients implanted with the MED-EL Cochlear Implant System, which was also supported by a systematic literature review, as the basis for the hearing preservation rates claims for the device. A subset of the literature reviewed incorporated RWD, including studies that utilized medical record data.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Outside-the-US Sponsor registry Ear, Nose, And Throat

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Pivotal Study (Non-RWE) **Study Design:** Single-arm Clinical Trial **Follow-up/Duration:** 1, 3, 6, and 12 months **Study Period:** 4/26/2018 – 3/27/2023	**Population:** Patients with bilateral moderate to profound SNHL who received a MED-EL Cochlear Implant System and who were ≥ 18 years old at the time of implantation **Sample Size:** 44 patients **Number of Sites:** 4 U.S. sites and 1 OUS site (Canada)	**Type:** Within-subject comparator	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** Improvement on Consonant Nucleus-Consonant Word Score, in quiet, and improvement on AzBio Sentence Score, in noise
MEHS Registry Study (RWE) **Study Design:** Pre-post Cohort Study **Follow-up/Duration:** Post-operative assessment between 6 and 36-months after implantation **Study Period:** 2021 – 2022	**Population:** Subjects enrolled in the MEHS registry who were implanted with a FLEX-type electrode and for whom pure-tone average (PTA) air-conduction thresholds were available both pre- and post-surgery. **Sample Size:** 2 methods for assessing low-frequency PTA3 (LFPTA3): 86 patients with frequency responses for 125, 250, 500 Hz (AAO scale), and 115 patients with frequency responses for 250, 500, 1000 Hz (Vienna Consensus) **Number of Sites:** 4 OUS sites (Germany)	**Type:** Within-subject comparator	**Primary Effectiveness Endpoint(s):** Residual hearing preservation
Systematic Literature Review to Support HP Claims (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** PubMed **Publication Date Period:** 11/7/2009 – 2/28/2022 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness	**Population:** Cochlear implant recipients with hearing preservation outcomes **Number of Publications:** 14 publications to define the presence of LFPTAs and compare functional hearing after implantation; 10 additional publications used to compare pre-to-post-operative changes in LFPTAs	Not applicable for this study	**Primary Effectiveness Endpoint(s):** Hearing preservation after implantation rates and complete or partial hearing preservation rates

Example 30. PMA – Approval of a PMA for an Indication Expansion for an Implantable Upper Airway Stimulation System Using Registry Data [49-51]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P130008/S090 6/8/2023	Inspire Upper Airway Stimulation (UAS) System	Inspire Medical Systems, Inc.	Registry Inspire Medical's ADHERE Registry	**Premarket:** Registry data was a primary source of clinical evidence for the approval of this PMA Supplement for an indication expansion to include patients with obstructive sleep apnea, 18 years old or older, with apnea-hypopnea index (AHI) ≤100 and support updating the body mass index (BMI) warning. The sponsor conducted a retrospective study using data from their ADHERE Registry which captures data on patients implanted with the Inspire Upper Airway Stimulation.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Sponsor registry Anesthesiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
ADHERE Registry Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 12 months post-implantation (the visit window for the first annual visit could be up to 2 years post-implant to allow patients to get full therapy optimization) **Study Period:** Patients enrolled in the ADHERE registry as of 7/22/2022	**Population:** Registry patients with baseline AHI of 65<AHI≤100 and registry patients with baseline BMI of 32<BMI≤40 **Sample Size:** Indication expansion: 57 patients BMI warning update: 279 patients	**Type:** Concurrent controls **Population:** Registry patients baseline AHI≤65; registry patients with baseline BMI≤32 **Sample Size:** Indication expansion: 1,483 patients BMI warning update: 1,218 patients	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** AHI and Epworth Sleepiness Scale

Example 31. PMA – Approval of a PMA for an Indication Expansion of a Transcarotid Stent System Using Professional Society Registry Data [52, 53]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	**RWE** Use Summary	Key Tags
P140026/S016 4/28/2022	ENROUTE® Transcarotid Stent System	Silk Road Medical, Inc.	Registry Carotid Artery Stenting (CAS) and Carotid Endarterectomy (CEA) Registries of the Society for Vascular Surgery Vascular Quality Initiative (SVS VQI)	**Premarket:** Registry data was a primary source of clinical evidence for the approval of this PMA Supplement to expand the indication of the Transcarotid Stent System to standard surgical risk patients undergoing transcarotid artery revascularization (TCAR). The clinical evidence included a retrospective, propensity-score matched cohort study using patient-level U.S. data from the VQI CAS and CEA registries.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Professional society registry Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
VQI TCAR *vs.* CEA Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 30 days and 1 year **Study Period:** 8/8/2016 – 9/2/2020 **Methods of Note**: 3:1 propensity score-matching. To assess potential bias due to missingness, a comparison between baseline characteristics for patients with complete and incomplete data was conducted.	**Population:** Adult patients (<80 years old) at standard surgical risk undergoing TCAR with the ENROUTE® Transcarotid Stent System of CEA. **Sample Size:** 5,066 TCAR patients; 996 TCAR patients with 1-year follow-up in matched primary endpoint analysis. **Number of Sites:** 565 U.S. sites	**Type:** Concurrent controls **Population:** Adult patients (<80 years old) at standard surgical risk undergoing CEA. **Sample Size:** 15,198 CEA patients; 2,988 CEA patients with 1-year follow-up in matched primary endpoint analysis. **Number of Sites:** 565 U.S. sites	**Composite Primary Safety and Effectiveness Endpoint(s):** Major adverse events (death/stroke/myocardial infarction) through 30 days and ipsilateral stroke from 31 days through 365 days

Example 32. PMA – Approval of a PMA for an Indication Expansion for a Drug-Coated Angioplasty Balloon Using Sponsor Registry Data [54-56]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P160049/S015 3/25/2022	Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon	Philips Image Guided Therapy Corporation	Registry Stellarex Vascular E-Registry (SAVER)	**Premarket:** Registry data was a supplemental source of clinical evidence for the approval of this PMA supplement for the indication expansion for treatment of in-stent restenosis (ISR). The primary evidence was the ILLUMENATE Global ISR prospective clinical study. RWD from the SAVER Registry provided real-world confirmation of safety and effectiveness in patients across Europe.	Outside-the-US Sponsor registry Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
ILLUMENATE Global ISR Study (Non-RWE) **Study Design:** Prospective Cohort Study (Single-Arm) **Follow-up/Duration:** 1, 6, 12, 24, and 36 months **Study Period:** 9/2016 – 3/2019 **Methods of Note**: Multiple imputation for missing data	**Population:** Patients 18–85 years old with symptomatic ISR (Rutherford Clinical Category (RCC) of 2, 3, or 4) **Sample Size:** Intention-to-Treat (ITT): 129 subjects Modified ITT: 122 subjects **Number of Sites:** 21 OUS sites (Australia, Europe, New Zealand)	**Type:** Performance goal	**Primary Safety Endpoint(s):** Freedom from safety composite events (device and procedure-related death through 30 days post-procedure, and target limb major amputation and clinically driven target lesion revascularization (CD-TLR) through 12 months post-procedure) **Primary Effectiveness Endpoint(s):** Primary patency at 12 months post-procedure, defined as the absence of target lesion restenosis, determined by duplex ultrasound, peak systolic velocity ratio (PSVR) ≤ 2.5, and freedom from CD-TLR

Study Design	Population	Comparator	Key Endpoints
SAVER ISR Study (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) **Follow-up/Duration:** As per site practice; recommended 12, 24, and 36 months **Study Period:** Enrollment through August 2021	**Population:** Patients ≥18 years old treated with the subject device for ISR in the superficial femoral or popliteal arteries. **Sample Size:** 325 patients treated with the device for ISR and eligible for the 12-month visit (out of 1,960 patients enrolled in SAVER across Europe). **Number of Sites:** 57 OUS sites (Europe)	**Type:** Performance goal	**Primary Safety Endpoint(s):** For RCC score 2–3 patients, freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and CD-TLR through 12 months post-procedure. For RCC 4–6 patients, freedom from major adverse limb event and perioperative death through 30 days post-procedure. **Primary Effectiveness Endpoint(s):** Freedom from CD-TLR at 12 months post-procedure, adjudicated by the clinical events committee

Example 33. PMA – Approval of New PMA of a Pediatric Pulmonary Stent Using Multicenter Registry Data [57, 58]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P220004 7/21/2023	PALMAZ MULLINS XD™ Pulmonary Stent	Cordis US Corp.	Registry Congenital Cardiovascular Interventional Study Consortium (CCISC) Registry	**Premarket:** Registry data was a primary source of clinical evidence for the approval of this PMA for a new device. The sponsor conducted a retrospective study using data from an identical device indicated for a different anatomical site from the CCISC Registry.	RWE as a primary source of clinical evidence Outside-the-US Pediatric Professional society registry Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Pulmonary Artery Stent Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 1 year post-operatively **Study Period:** Patients treated between 1/11/2006 – 9/22/2016. Data collected through 10/2/2019	**Population:** Pediatric and adult patients with pulmonary artery stenosis **Sample Size:** 108 patients **Number of Sites:** 11 U.S. and OUS sites (Canada)	Not applicable for this study	**Primary Safety Endpoint(s):** Occurrence of any “somewhat serious” or serious adverse event attributed to the stent or implantation procedure within 12 months of the procedure **Primary Effectiveness Endpoint(s):** Increase in the stented vessel minimum pulmonary artery diameter by ≥50% of the pre-stent diameter

Example 34. PMA – Approval of a New PMA for Breast Implants Using International Registry Data [59-61]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P230005 9/26/2024	Motiva SmoothSilk Round and Round Ergonomix Silicone Gel-Filled Breast Implants	Motiva USA, LLC	Registry Australian Breast Implant Registry (ABDR) and the Dutch Breast Implant Registry (DBIR)	**Premarket:** Registry data was a supplemental source of clinical evidence for the approval of this PMA for a new device. The clinical evidence included results from the Motiva USA Core Clinical Study, a prospective, multicenter clinical trial and supplemental RWE from 2 international registries – ABDR and DBIR – supporting device safety and effectiveness.	Comparator is, or is derived from, RWD Outside-the-US Registry General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Primary Clinical Study (Non-RWE) **Study Design:** Single-arm Clinical Trial **Follow-up/Duration:** 3 years **Study Period:** 4/17/2018 – 8/26/2019	**Population:** Females with primary breast augmentation or breast implant revision surgery **Sample Size:** 560 subjects (451 primary augmentation, 109 revision augmentation) with 1,119 Motiva implants **Number of Sites:** 20 U.S. and 3 OUS sites	Not applicable for this study	**Primary Safety Endpoint(s):** Total adverse event rate (“any complication”) through 3 years of follow-up **Primary Effectiveness Endpoint(s):** Patient satisfaction, physician satisfaction, changes in breast measurements (primary augmentation only), and the patient’s quality of life with their overall health, self-esteem, and body esteem
ABDR Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 6, 12, 24, 36, and 48 months post-implantation **Study Period:** 2/2016 – 12/2021	**Population:** Patients with primary and revision augmentation procedures with Motiva Implants **Sample Size:** 28,535 primary and revision augmentation procedures	Not applicable for this study	**Safety Endpoint(s):** Reoperation rates, all-cause revision incidence rates, complication-related revision rates, patient satisfaction at 2-year follow-up, and seroma/hematoma revision incidence rates **Effectiveness Endpoint(s):** Patient-reported outcomes: satisfaction with look of implants and satisfaction with feel of implants

Study Design	Population	Comparator	Key Endpoints
DBIR Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 36 months **Study Period:** 2021	**Population:** Patients with primary and revision augmentation procedures with Motiva Implants **Sample Size:** 17,850 total procedures (including Motiva and other implant types)	**Type:** Concurrent controls **Population:** Patients with other breast implants **Sample Size:** 17,850 total procedures (including Motiva and other implant types)	**Safety Endpoint(s):** Reoperation rates, reasons for reoperations, breast implant-associated anaplastic large cell lymphoma incidence, and reoperation-related complication incidence rates **Effectiveness Endpoint(s):** Patient-reported reasons for reoperation: Dissatisfaction with volume and suspicion of breast implant-associated illness

Example 35. PMA – Approval of a PMA for an Indication Expansion for a Spinal Cord Stimulator Using Registry Data [62-67]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P840001/S469 1/21/2022	Restore, Itrel, Synergy, Intellis, and Vanta Spinal Cord Stimulation Systems; Pisces, Specify and Vectris Spinal Cord Stimulation Leads	Medtronic Neuromodulation	Administrative claims data Medical records (EHR, EMR, or chart review) Public health surveillance data Registry Medtronic Product Surveillance Registry (PSR) Nationwide Inpatient Sample Truven MarketScan Commercial Claims and Encounters (CCAE) Database Medicare Supplemental Database	**Premarket:** Registry data was a supplemental source of clinical safety evidence for the approval of this PMA Supplement to support inclusion of diabetic peripheral neuropathy (DPN) of the lower extremities in the indications for use. The evidence to support device safety in DPN patients included adverse event data from a sponsor registry and 2 systematic literature reviews. A subset of the literature reviewed in the systematic literature reviews incorporated RWD, including multiple studies that utilized data from medical records, administrative claims, and public health surveillance. Effectiveness was supported by a meta-analysis of 2 randomized controlled trials from peer-reviewed publications.	Administrative claims data Comparator is, or is derived from, RWD Medical records (EHR, EMR, or chart review) Outside-the-US Public health surveillance data Sponsor registry Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Medtronic Product Surveillance Registry (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Postmarket Surveillance **Follow-up/Duration:** Median of 15 months device exposure **Study Period:** 4/15/2010 – 10/31/2020	**Population:** Patients treated with spinal cord stimulator (SCS) for painful diabetic neuropathy (PDN) as a primary or secondary indication **Sample Size:** 67 patients **Number of Sites:** U.S. and OUS sites (number unspecified)	**Type:** Survival Analysis **Population:** Non-PDN population enrolled in registry **Sample Size:** 2,733 patients	**Primary Safety Endpoint(s):** Adverse events and device events

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Review on Clinical Practice Guidelines on Perioperative Care of Diabetic Patients (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** Embase and MEDLINE **Publication Date Range:** 2016 – 2021 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Diabetic Patients **Number of Publications:** 11 publications	Not applicable for this study	Not applicable for this study
Systematic Literature Review on Safety and Effectiveness of SCS to Treat PDN (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** Embase and MEDLINE **Publication Date Range:** 1984 – 2021 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Diabetic Patients **Number of Publications:** Safety: 19 publications; Effectiveness: 12 publications; Meta-analysis: 2 publications	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events (infection; wound healing; cardiovascular events, dural puncture and cerebrospinal fluid leak; glycemic control; mortality and morbidity; SCS system survival; lead migration; and lead failure) **Primary Effectiveness Endpoint(s):** Pain reduction, probability of treatment success, and quality of life improvements
Randomized Controlled Trial – Slangen et al. 2014 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 6 months **Study Period:** 2/1/2010 – 2/28/2013 **Methods of Note**: Identified in systematic literature review, pooled with de Vos et al. 2014 randomized controlled trial for meta-analysis	**Population:** Moderate to severe painful DPN patients not responding to conventional therapy for 12 months randomized to SCS in combination with best medical practice (BMT) **Sample Size:** 22 subjects **Number of Sites:** 2 OUS sites (Netherlands)	**Type:** Randomized controls **Population:** Moderate to severe painful DPN patients not responding to conventional therapy for 12 months randomized to BMT only **Sample Size:** 14 subjects **Number of Sites:** 2 OUS sites (Netherlands)	**Primary Effectiveness Endpoint(s):** ≥50% pain reduction during daytime or nighttime or a score of ≥ 6 on a 7-point Likert scale of the patient global impression of change scale for pain and sleep

Study Design	Population	Comparator	Key Endpoints
Randomized Controlled Trial – de Vos et al. 2014 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 6 months **Methods of Note**: Identified in systematic literature review, pooled with Slangen et al. 2014 randomized controlled trial for meta-analysis	**Population:** Patients with DPN in the lower extremities for more than 1 year and refractory to conventional treatments, visual analog scale (VAS) pain rating ≥50 mm, and ≥18 years of age, randomized to SCS in combination with BMT **Sample Size:** 40 subjects **Number of Sites:** 7 OUS sites (Netherlands, Denmark, Belgium, and Germany)	**Type:** Randomized controls **Population:** Patients with DPN in the lower extremities for more than 1 year and refractory to conventional treatments, VAS pain rating ≥50 mm, and ≥18 years of age, randomized to BMT only **Sample Size:** 20 subjects **Number of Sites:** 7 OUS sites (Netherlands, Denmark, Belgium, and Germany)	**Primary Effectiveness Endpoint(s):** Treatment success at 6 months, ≥50% pain reduction

Example 36. De Novo – De Novo Classification of an Electronic Pharyngeal Stimulation System Using Registry Data [68-75]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
DEN220025 9/16/2022	Phagenyx System	Phagenesis Limited	Registry	**Premarket:** Sponsor registry data was a supplemental source of clinical evidence for the classification of this De Novo. The primary clinical evidence included 4 randomized controlled trials and an additional single-arm prospective observational study, which provided evidence of safety and /or effectiveness of the new device. Sponsor registry data provided supplemental safety and effectiveness data in a broad range of patients with neurogenic dysphagia.	Outside-the-US Sponsor registry Ear, Nose, And Throat

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
PHAST TRAC Randomized Controlled Trial (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** Last follow-up at 60-120 days **Study Period:** 5/29/2015 – 7/5/2017	**Population:** Tracheotomized patients >18 years old with severe persistent dysphagia post stroke, randomized to treatment arm **Sample Size:** 35 patients receiving pharyngeal electrical stimulation (PES) **Number of Sites:** 9 OUS sites (Germany, Austria, Italy)	**Type:** Randomized controls **Population:** Tracheotomized patients >18 years old with severe persistent dysphagia post stroke, randomized to sham arm **Sample Size:** 34 patients receiving sham treatment **Number of Sites:** 9 OUS sites (Germany, Austria, Italy)	**Primary Safety Endpoint(s):** Treatment- or device-related serious adverse events or deaths, treatment- or device-related non-serious adverse events **Primary Effectiveness Endpoint(s):** Warnecke assessment of swallowing function and secretion management and Dysphagia Severity Rating Scale (DSRS)
PHADER Single-arm Postmarket Registry (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) **Follow-up/Duration:** Up to 120 days post-initial treatment **Study Period:** 3/2015 – 9/2018	**Population:** Patients >18 years old with oropharyngeal dysphagia and a DSRS score of 6 or higher **Sample Size:** 177 patients **Number of Sites:** 14 OUS sites (United Kingdom, Germany, Austria)	Not applicable for this study	**Primary Safety Endpoint(s):** Serious and non-serious treatment- or device-related adverse events **Primary Effectiveness Endpoint(s):** DSRS, functional oral intake scale (FOIS) and penetration-aspiration scale (PAS)

Study Design	Population	Comparator	Key Endpoints
STEPS Randomized Controlled Trial (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** Up to 12-weeks post-treatment **Study Period:** 4/2012 – 9/2014	**Population:** Patients ≥18 years old with a recent ischemic or hemorrhagic stroke and dysphagia, randomized to treatment arm **Sample Size:** 87 patients assigned active PES (primary endpoint available in 70) **Number of Sites:** 20 OUS sites (United Kingdom, Germany, France, Spain, Denmark)	**Type:** Randomized controls **Population:** Patients ≥18 years old with a recent ischemic or hemorrhagic stroke and dysphagia, randomized to sham arm **Sample Size:** 75 patients assigned to sham treatment (primary endpoint available in 56) **Number of Sites:** 20 OUS sites (United Kingdom, Germany, France, Spain, Denmark)	**Primary Safety Endpoint(s):** All-cause fatality and cause-specific fatality; serious adverse events and serious adverse device-related events; and chest infection or pneumonia **Primary Effectiveness Endpoint(s):** Change in PAS score from baseline to 2-weeks post-initial treatment and PAS at 12 weeks
Randomized Controlled Trial – Youssef and El-Banna 2015 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 2 weeks post last treatment	**Population:** Adult stroke patients (41–73 years old) with severe dysphagia following stroke, randomized to treatment arm **Sample Size:** 9 patients **Number of Sites:** 1 OUS site (United Arab Emirates)	**Type:** Randomized controls **Population:** Adult stroke patients (41–73 years old) with severe dysphagia following stroke, randomized to sham arm **Sample Size:** 9 patients **Number of Sites:** 1 OUS site (United Arab Emirates)	**Primary Safety Endpoint(s):** Serious adverse events **Primary Effectiveness Endpoint(s):** PAS, FOIS, pharyngeal secretions, pharyngeal stasis at baseline and post treatment, and patient satisfaction at 2 weeks.
Randomized Controlled Trial – Suntrup et al. 2015 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 72 hours post-treatment **Study Period:** 6/2013 – 12/2014	**Population:** Consecutive stroke patients successfully weaned from the respirator but with severe dysphagia precluding decannulation, randomized to treatment arm **Sample Size:** 20 patients **Number of Sites:** 1 OUS site (Germany)	**Type:** Randomized controls **Population:** Consecutive stroke patients successfully weaned from the respirator but with severe dysphagia precluding decannulation, randomized to sham arm **Sample Size:** 10 patients **Number of Sites:** 1 OUS site (Germany)	**Primary Safety Endpoint(s):** Device- or treatment-related adverse events **Primary Effectiveness Endpoint(s):** Ability to decannulate the patient based on Warnecke assessment
Prospective Single-Site Observational Study (Non-RWE) **Study Design:** Prospective Cohort Study (Single-Arm) **Follow-up/Duration:** Discharge or decannulation (mean length of stay 35 days ± 11 days) **Study Period:** 10/2014 – 8/2015	**Population:** Patients with severe persistent dysphagia post stroke fully weaned from ventilation with a tracheostomy tube still in place, and who were treated with the Phagenyx device **Sample Size:** 23 patients **Number of Sites:** 1 OUS site (Germany)	Not applicable for this study	**Primary Safety Endpoint(s):** Device- or treatment-related adverse events **Primary Effectiveness Endpoint(s):** Improvement in swallowing function and secretion management as measured by Warnecke assessment

Example 37. 510(k) – Clearance of an Extracorporeal Blood Oxygenation and Carbon Dioxide Removal System Using Registry Data [76]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K191407 2/21/2020	Novalung System	Fresenius Medical Care Renal Therapies Group, LLC	Registry Regensburg Extracorporeal Membrane Oxygenation (ECMO) Registry Extracorporeal Life Support Organization (ELSO) Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The clinical evidence included a retrospective analysis of clinical data from the Regensburg ECMO Registry to support substantial equivalence. Mortality and survival rates for this analysis were compared to clinical data for comparator devices obtained from the ELSO Registry.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Outside-the-US Professional society registry Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Regensburg ECMO Registry Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 30 days (maximum treatment: 65 days; cumulative treatment duration: 1,382 days)	**Population:** ECMO patients treated with the Novalung System **Sample Size:** 148 ECMO patients **Number of Sites:** 1 OUS site (Germany)	**Type:** External controls **Population:** Patients from the ELSO Registry	**Endpoint(s):** Mortality, survival, adverse events, and device events

Example 38. 510(k) – Clearance of a Cryosurgical Ablation Tool Using Registry Data [77]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K201183 12/7/2020	truFreeze® System, Vortex™ Radial Spray Catheter	CSA Medical, Inc.	Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) for a modification to the existing truFreeze® System adding a radial spray catheter configuration. To provide a safety profile of patients treated with circumferential spray of liquid nitrogen, clinical evidence was provided from an ongoing prospective, multicenter registry of patients treated with the predicate device who received circumferential ablation. The clinical evidence additionally included data from 3 peer-reviewed publications, which demonstrated the ability of the predicate device (i.e., linear spray) to achieve circumferential freezing of diseased tissue in the esophagus.	RWE as a primary source of clinical evidence Sponsor registry General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Multicenter Prospective Registry (RWE) **Study Design:** Prospective Cohort Study (Single-Arm)	**Population:** Patients in an ongoing prospective registry who were diagnosed with Barrett's esophagus (BE) and received circumferential ablation **Sample Size:** 49 patients with circumferential ablations (out of 112 BE patients in the registry) **Number of Sites:** Multicenter (number and location unspecified)	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events, stricture, and serious adverse events
Peer-reviewed Literature (Non-RWE) **Study Design:** Literature Review **Publication Date Period:** Since 2012	**Population:** Patients with BE who were treated with the predicate device (i.e., linear spray) to achieve circumferential freezing of diseased tissue in the esophagus **Sample Size/Number of Publications:** 73 patients from 3 publications	Not applicable for this study	**Primary Safety Endpoint(s):** Safety of ablating BE lesions **Primary Effectiveness Endpoint(s):** Efficacy of ablating BE lesions

Example 39. 510(k) – Clearance of an Extracorporeal Membrane Oxygenation Pump and Controller Using Registry Data [78]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K202751 3/26/2021	TandemHeart Pump and Escort Controller	CardiacAssist, Inc.	Registry Extracorporeal Life Support Organization (ELSO) Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) to add ECMO to the indications for use. The sponsor conducted a study using propensity score analysis using ELSO Registry data to demonstrate the ability of the TandemHeart Pump to provide assisted extracorporeal oxygenation of adult patients' blood.	RWE as a primary source of clinical evidence Professional society registry Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
ELSO Registry Study 1 – Weighted Propensity Score Analysis (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** Through hospital discharge **Study Period:** 1/1/2016 – 10/2020 **Methods of Note**: Overlap weights propensity score model	**Population:** Adults (at least 18 years old) using the TandemHeart pump **Sample Size:** 165 ECMO runs	**Type:** Concurrent controls **Population:** Adults (at least 18 years old) using non-TandemHeart pumps **Sample Size:** 3,525 ECMO runs	**Endpoint(s):** Pump failure, hemolysis, thrombosis or clots in circuit component, patient death within 24 hours of ECMO explant, and patient vital status at discharge
ELSO Registry Study 2 – TandemHeart Pump and Comparator Pumps Analysis (RWE) **Study Design:** Retrospective Cohort Study **Study Period:** 1/1/2016 – 1/22/2019	**Population:** Adult patients (at least 18 years old) with total TandemHeart pump ECMO hours <2160 (90 days) **Sample Size:** 79 TandemHeart runs **Number of Sites:** U.S. sites (number unspecified)	**Type:** Concurrent Controls **Population:** Adult patients (at least 18 years old) with total other centrifugal pump ECMO hours <2160 (90 days) **Sample Size:** 9,801 other centrifugal pump runs **Number of Sites:** U.S. sites (number unspecified)	**Endpoint(s):** Extracorporeal life support complications including pump failure, hemolysis, thrombosis/clots in circuit component, hemorrhagic complications, neurologic complications, renal complications, cardiovascular complications, pulmonary complications, and patient limb complications

Example 40. 510(k) – Clearance of a Percutaneous Catheter Using Registry Data [79, 80]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K211120 3/31/2022	ERIC™ Retrieval Device	MicroVention, Inc.	Registry Endovascular Treatment in Ischemic Stroke Follow-up Evaluation (ETIS) Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. Data from a prospective, multicenter, observational OUS study were used to demonstrate that the device performed similarly to the predicate devices in terms of successful reperfusion rate at the end of procedure, safety profile, and good clinical outcomes at 90 days post-procedure.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Outside-the-US Registry Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
ETIS Observational Cohort Study (RWE) **Study Design:** Prospective Cohort Study **Follow-up/Duration:** 90 days **Study Period:** 2011 – 2018	**Population:** Patients (≥ 18 years old) selected for endovascular neurothrombectomy and treated with ERIC Retrieval Device **Sample Size:** 206 patients **Number of Sites:** 7 OUS sites (France)	**Type:** Concurrent controls **Population:** Patients (≥ 18 years old) selected for endovascular neurothrombectomy and treated with Modified Trevo ProVue Retriever, Trevo XP ProVue Retriever, and Solitaire™ FR Revascularization devices captured in the ETIS registry **Sample Size:** 1,058 patients **Number of Sites:** 7 OUS sites (France)	**Effectiveness Endpoint(s):** Success rate of modified thrombolysis in cerebral infarction score (2b or greater) in the target vessel and good clinical outcome (90-day mRS 0-2) **Safety Endpoint(s):** Occurrence of symptomatic intracerebral hemorrhage within 24 hours post-procedure

Example 41. 510(k) – Clearance of a Metallic Bone Fixation Fastener Using Registry Data [81]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K221128 10/5/2022	Arthrex ACL TightRope®, PCL TightRope®, and TightRope® II	Arthrex Inc.	Registry Surgical Outcomes System Registry	**Premarket:** Registry data was a source of clinical evidence for the clearance of this 510(k) for an indication expansion to patients less than 22 years old. The clinical evidence included literature review on the subject devices used in pediatric patients and RWD/RWE provided from the Surgical Outcomes System registry.	Comparator is, or is derived from, RWD Pediatric Professional society registry Orthopedics

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Registry Study (RWE) **Study Design:** Cohort Study	**Population:** Patients less than 22 years old	**Population:** Patients equal and greater than 22 years old	Not available

Example 42. 510(k) – Clearance of a Peripheral Atherectomy Device Using Professional Society Registry Data [82, 83]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K231538 9/27/2023	FreedomFlow™ Orbital Circumferential Atherectomy System	Cardio Flow, Inc.	Registry Vascular Quality Initiative (VQI) Peripheral Vascular Intervention (PVI) Registry	**Premarket:** Registry data was a supplemental source of clinical evidence for the clearance of this 510(k) for a new device. The clinical evidence included a prospective, multicenter, single-arm clinical study to evaluate safety and effectiveness. The sponsor also conducted a hybrid study with a matched comparison of the FAST II FreedomFlow debulking effectiveness, with data from the VQI PVI Registry for other atherectomy devices, as a supplemental effectiveness analysis of the FAST II effectiveness performance.	Comparator is, or is derived from, RWD Professional society registry Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
FAST II Study (Non-RWE) **Study Design:** Single-arm clinical trial **Follow-up/Duration:** 30 days	**Population:** Patients with symptomatic peripheral arterial disease of the lower extremities	**Type:** Performance goal	**Primary Safety Endpoint(s):** Freedom from major adverse events at 30 days **Primary Effectiveness Endpoint(s):** Technical success (defined as ability to achieve residual diameter stenosis less than 50% without adjunctive therapy)
FAST II and VQI PVI Registry Study (RWE) **Study Design:** Hybrid Study **Methods of Note**: Propensity score methods	**Population:** FAST II Study subjects	**Type:** External controls **Population:** VQI PVI Registry rotational and orbital atherectomy patients	**Primary Effectiveness Endpoint(s):** Post-atherectomy stenosis (defined as the mean residual diameter stenosis after treatment with atherectomy without adjunctive therapy)

Example 43. 510(k) – Clearance of a Non Fusion Growing Rod System Using Registry Data [84]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K233593 2/6/2024	MAGEC Spinal Bracing and Distraction System	NuVasive Specialized Orthopedics, Inc.	Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) for an indication expansion to include skeletally immature patients of any age with early-onset scoliosis. The sponsor conducted a retrospective study using data from a registry to compare patients less than 10 years old treated with the subject device with patients 10 years old or older treated with the subject device to demonstrate substantial equivalence.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Registry Orthopedics

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Registry Study (RWE) **Study Design:** Retrospective Cohort Study	**Population:** Pediatric patients with early-onset scoliosis implanted with MAGEC before 10 years old **Sample Size:** 1,080 patients	**Type:** Concurrent Controls **Population:** Patients with early-onset scoliosis implanted with MAGEC at 10 years old or older **Sample Size:** 172 patients	**Primary Safety Endpoint(s):** Device-related adverse events **Primary Effectiveness Endpoint(s):** Major curve Cobb angle change, thoracic height change, and spinal height change

Example 44. 510(k) – Clearance of a Surgical System Using Registry Data [85]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K233866 7/19/2024	Senhance® Surgical System	Asensus Surgical, Inc	Registry TRUST Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) for an indication expansion to include laparoscopic urological surgery. The sponsor conducted a retrospective study using data from the TRUST registry and a systematic literature review. The sponsor compared the registry data with the results from peer-reviewed publications describing clinical outcomes for laparoscopic urological procedures using 3 alternative surgical techniques.	RWE as a primary source of clinical evidence Outside-the-US Sponsor registry General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
TRUST Registry Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 12 months	**Population:** Patients treated with laparoscopic urological procedures between December 2017 and August 2023 using the Senhance System **Sample Size:** 416 patients **Number of Sites:** 4 OUS sites	**Type:** Results from the systematic literature review by surgery type (robotic, laparoscopy, and open) (see Systematic Literature Review below)	**Endpoint(s):** Length of stay, surgical complications, conversion rate, estimated blood loss, readmission rates at 30 days, reoperation rates at 30 days, mortality, postoperative complications, and operative time.
Systematic Literature Review (Non-RWE) **Study Design:** Meta-Analysis **Database(s):** Embase and PubMed **Publication Dates Period:** Not reported; studies were included if data was collected between 2018 and August 17, 2023 **Methods of Note**: For additional details see the Decision Letter and Summary	**Number of Publications:** 62 publications	Not applicable for this study	**Endpoint(s):** Length of stay, surgical complications, conversion rate, estimated blood loss, readmission rates at 30 days, reoperation rates at 30 days, mortality, postoperative complications, and operative time

Example 45. 510(k) – Clearance of an Extracorporeal Life Support Circuit and Accessories Using National Registry Data [86]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K240880 9/12/2024	VitalFlow™ Set with Balance™ Biosurface	Medtronic Inc.	Registry Extracorporeal Life Support Organization (ELSO) Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The sponsor submitted a summary of reports of the clinical experience with the VitalFlow Set from the ELSO Registry prepared by the ELSO to demonstrate the performance of the subject device.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Registry Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
ELSO Registry Study (RWE) **Study Design:** Retrospective Cohort Study	**Population:** Adult VitalFlow Set patients in the ELSO Registry **Sample Size:** 195 ECMO runs	**Type:** Concurrent controls **Population:** Adults on all other ECMO systems **Sample Size:** 61,176 patients	**Endpoint(s):** Complications from ECMO, ECMO duration and device performance in ECMO procedures

Example 46. 510(k) – Clearance of an Orthopedic Implant Using Registry Data [87-89]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K243578 3/6/2025	BEAR® (Bridge-Enhanced ACL Restoration) Implant	Miach Orthopaedics, Inc	Registry BRIDGE Registry	**Premarket:** Registry data was a co-primary source of clinical evidence for the clearance of this 510(k), which expanded the indications for use of the device to patients < 14 years old and added partial rupture of anterior cruciate ligament (ACL) to the indications for use. The sponsor conducted a retrospective cohort study using data from the BRIDGE Registry to compare effectiveness outcomes of the device in patients under 14 years old to patients ≥ 14 years old. The clinical evidence included a non-RWE study (BEAR III Study) which was a prospective, multicenter single arm cohort study as co-primary clinical evidence to evaluate safety and effectiveness outcomes by pooling data from both studies.	RWE as a primary source of clinical evidence Pediatric Sponsor registry Orthopedics

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
BRIDGE Registry Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 2 years post-implant **Study Period:** Study started on 2/28/2023 **Methods of Note**: Pooled data for patients less than 14 years old from the BRIDGE Registry and BEAR III clinical trial	**Population:** Patients <14 years old who have received the BEAR implant **Sample Size:** 15 patients **Number of Sites:** 30 U.S. sites	**Type:** Compared to patients ≥ 14 years old in BEAR III Study	**Primary Safety Endpoint(s):** Rate of adverse events, serious adverse events, and device-related adverse events and serious adverse events **Primary Effectiveness Endpoint(s):** International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Score at 2 years and Lachman knee laxity at 1 year

Study Design	Population	Comparator	Key Endpoints
BEAR III Study (Non-RWE) **Study Design:** Prospective Cohort Study **Follow-up/Duration:** 2 years post-implant **Study Period:** Study started on 4/17/2018	**Population:** Patients 12–14 years old or with partial ACL tears **Sample Size:** 12–14 years old: 3 patients Partial ACL tears: 27 patients **Number of Sites:** 7 U.S. sites	**Type:** Concurrent controls **Population:** Patients ≥ 14 years old or with complete ACL tears **Sample Size:** ≥ 14 years old: 148 patients Complete ACL tear: 124 patients	**Primary Safety Endpoint(s):** Rate of adverse events, serious adverse events, unanticipated adverse device effects, and device-related adverse events and serious adverse events **Primary Effectiveness Endpoint(s):** IKDC Subjective Knee Evaluation score and IKDC Objective Physical Exam score at 2 years post-implant

Example 47. 510(k) – Clearance of a Digital Therapy Device For Amblyopia Using Sponsor Registry Data [90, 91]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K243819 4/9/2025	Luminopia	Luminopia, Inc.	Registry	**Premarket:** Registry data was a primary source of clinical evidence for the clearance of this 510(k) for an indication expansion to include 8 to <13-year-old pediatric patients. The sponsor conducted a prospectively designed, retrospective analysis of data from a patient registry to evaluate improvement in amblyopic eye best-corrected visual acuity (BCVA) in pediatric patients aged 4 to <13 years old following treatment with Luminopia, with follow-up extended up to 72 weeks after beginning treatment. Prior safety and effectiveness were established through a randomized controlled trial supporting De Novo classification (DEN210005) for pediatric patients aged 4 -7 years old.	RWE as a primary source of clinical evidence Pediatric Registry Ophthalmic

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Real-World Registry Study (RWE) **Study Design:** Pre-post Cohort Study **Follow-up/Duration:** 12, 24, 36, 48, 60, and 72 weeks	**Population:** Patients 4 to <13 with a diagnosis of amblyopia associated with anisometropia and/or strabismus, with Luminopia use of at least 12 weeks. **Sample Size:** 290 pediatric patients	**Type:** Within-subject comparator	**Primary Safety Endpoint(s):** Reported adverse events: eye redness, headache, dizziness, teary eye, and nightmare event **Primary Effectiveness Endpoint(s):** Improvement in amblyopic eye BCVA and mean from baseline to last visit and over time (12-72 weeks)

Section III. Examples Leveraging Both Medical Records and Registries as Sources of Real-World Data

Example 48. PMA – Approval of a PMA for an Indication Expansion for an Implantable Infusion Pump Using a Systematic Literature Review [92, 93]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P080012/S068 1/12/2022	Prometra® Programmable Infusion Pump System	Flowonix Medical, Inc.	Medical records (EHR, EMR, or chart review) Registry	**Premarket:** Data from a systematic literature review was a primary source of clinical evidence for the approval of this PMA Supplement for an indication expansion to allow use of the pump system for baclofen drug therapy in pediatric adolescents (12–21 years old). A subset of the literature reviewed in the systematic literature review incorporated RWD, including studies that utilized medical record and sponsor registry data. These studies provided real world clinical performance of currently available implantable intrathecal drug delivery systems (IDDS) used to deliver baclofen therapy in pediatric populations. The clinical evidence additionally included an analysis of Prometra® Programmable Infusion Pump System performance in adults.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Pediatric Sponsor registry General Hospital

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Review (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** MEDLINE/PubMed and Embase **Publication Date Period:** 1/1/2000 – 1/1/2021 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Use of IDDS for the treatment of chronic intractable pain and severe spasticity in adult and pediatric populations **Number of Publications:** 35 publications referenced in the SSED	Not applicable for this study	**Primary Safety Endpoint(s):** Complication and adverse event rates **Primary Effectiveness Endpoint(s):** Effectiveness of intrathecal infusion of baclofen
Prometra® Programmable Infusion Pump Adult Performance Study (Non-RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 12 months **Study Period:** 2013 – mid-2020	**Population:** Adults receiving the Prometra® Programmable Infusion Pump **Sample Size:** 9,288 procedures	Not available	**Primary Safety Endpoint(s):** Incidence of revisions

Example 49. PMA – Approval of a New PMA for an Ultrasound Imaging Device Using Medical Records [94-96]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P200040 10/6/2021	SoftVue™ Automated Whole Breast Ultrasound System with Sequr™ Breast Interface Assembly	Delphinus Medical Technologies	Medical records (EHR, EMR, or chart review) Registry Prospective Case Clinical (PCC) Registry	**Premarket:** Registry and medical record data were primary sources of clinical evidence for the approval of this PMA for a new device. The sponsor conducted Multi-Reader Multi-Case Retrospective Reader Studies (RRS) from multiple clinical centers to evaluate the safety and effectiveness of the SoftVue system as an adjunct to mammography for breast cancer screening in women with dense breast parenchyma. The prospectively maintained PCC registry was used for case selection. The RRS validation studies were retrospective and used previously collected imaging data from the registry along with corresponding clinical data from patient medical records. These data were used to establish the ground truth for each case evaluated.	RWE as a primary source of clinical evidence Medical records (EHR, EMR, or chart review) Sponsor registry Validation Radiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Reader Study 2 (RRS2) (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** 1 year follow-up completed within 455 days **Study Period:** 9/2018 – 3/2020	**Population:** Female patients ≥18 years old, asymptomatic with heterogeneous or extremely dense breast parenchyma who had SoftVue automated breast ultrasound (SV) and digital screening mammography (FFDM) combined (cases selected using PCC registry) **Sample Size:** 200 cases (50 with cancer and 150 without cancer) **Number of Sites:** 7 U.S. sites	**Type:** Within subject comparison with screening mammography alone	**Validation Study Endpoint(s):** Detection and correct laterality localization of biopsy-confirmed malignant breast lesions

Study Design	Population	Comparator	Key Endpoints
Retrospective Reader Study 3 (RRS3) (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** 1 year follow-up completed within 455 days **Study Period:** 9/2018 – 3/2020	**Population:** Female patients ≥18 years old, asymptomatic with heterogeneous or extremely dense breast parenchyma who had SV and FFDM combined (cases selected using PCC registry) **Sample Size:** 140 cases (36 with cancer and 104 without cancer) **Number of Sites:** 6 U.S. sites	**Type:** Within subject comparison with screening mammography alone	**Validation Study Endpoint(s):** Detection and correct laterality localization of biopsy-confirmed malignant breast lesions

Example 50. 510(k) – Clearance of a Transcranial Magnetic Stimulator Using Medical Records and Registry Data [97-100]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K220127 7/15/2022	NeuroStar TMS Therapy System, NeuroStar Advanced Therapy System, NeuroStar, and NeuroStar Advanced Therapy for Mental Health	Neuronetics, Inc	Medical records (EHR, EMR, or chart review) Registry TrakStar Registry	**Premarket:** Registry and medical record data were supplementary sources of clinical evidence for the clearance of this 510(k) to support a modification in the indication for use for decreasing anxiety symptoms in adult patients suffering from major depressive disorder (MDD) who may exhibit comorbid anxiety symptoms. The primary clinical evidence to support the safety and effectiveness of the device included 2 randomized controlled trials, and additional supplementary evidence included 2 retrospective chart review studies — 1 from a peer-reviewed publication and 1 using the TrakStar Registry as the data source.	Medical records (EHR, EMR, or chart review) Sponsor registry Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Randomized Controlled Trial – O'Reardon et al. 2007 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 6 weeks	**Population:** Adult patients with moderate to severe MDD who failed to receive benefit from 1 to 4 prior antidepressant medications randomized to treatment arm **Sample Size:** 155 patients	**Type:** Randomized controls **Population:** Adult patients with moderate to severe MDD who failed to receive benefit from 1 to 4 prior antidepressant medications randomized to sham arm **Sample Size:** 146 patients	**Primary Effectiveness Endpoint(s):** Hamilton-D anxiety/somatization factor (HAMD AS/F) scale
Randomized Controlled Trial – George et al. 2010 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 6 weeks	**Population:** Adult patients with moderate to severe MDD who failed to receive benefit from 1 to 4 prior antidepressant medications randomized to treatment arm **Sample Size:** 92 patients	**Type:** Randomized controls **Population:** Adult patients with moderate to severe MDD who failed to receive benefit from 1 to 4 prior antidepressant medications randomized to sham arm **Sample Size:** 98 patients	**Primary Effectiveness Endpoint(s):** HAMD AS/F

Study Design	Population	Comparator	Key Endpoints
Retrospective Chart Review – Tuinstra et al. 2022 (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 6 weeks **Study Period:** 7/1/2014 – 12/31/2018	**Population:** Adult patients (18-77 years old) with a primary diagnosis of treatment resistant depressions treated with repetitive transcranial magnetic stimulation using the NeuroStar Advanced Therapy System **Sample Size:** 77 patients, 57 with clinically significant anxiety symptoms **Number of Sites:** 1 U.S. site	**Type:** Within-subject comparator	**Primary Effectiveness Endpoint(s):** Reduction in anxiety symptoms (as measured by HAMD-21 and Generalized Anxiety Disorder-7 (GAD-7))
TrakStar Registry Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 6 weeks **Study Period:** 2008 – 2023	**Population:** Adult patients (22–70 years old) with a primary diagnosis of MDD and baseline score on the GAD-7 ≥10 who received the standard NeuroStar treatment protocol for MDD **Sample Size:** 664 patients **Number of Sites:** 75 U.S. sites	**Type:** Within-subject comparator	**Primary Effectiveness Endpoint(s):** Improvement in the GAD-7 score and depression scores on the Physician Health Questionnaire-9

Example 51. 510(k) – Clearance of a Mobile Health App Using Hospital Trauma Registry Data and Medical Records [101]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K233249 4/5/2024	APPRAISE-HRI	The Surgeon General, Department of the Army (TSG-DA)	Medical records (EHR, EMR, or chart review) Registry	**Premarket:** Medical record and registry data were a primary source of clinical evidence for validation testing to support the clearance of this 510(k) for a new device. The sponsor conducted a retrospective validation study using vital-sign data collected during patient transport and emergency department care, along with trauma registry data used to establish hemorrhage status (hemorrhage vs. control patients). The device's hemorrhage risk output was compared against the hemorrhage status identified in the trauma registry for both the hemorrhage and control patients.	RWE as a primary source of clinical evidence Digital Health Medical records (EHR, EMR, or chart review) Registry Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Clinical Validation Study (RWE) **Study Design:** Case-Control Study Validation Study **Follow-up/Duration:** Data collected both during transport of patients from point of injury to the receiving hospital (8 sites) and at a hospital's Emergency Department (1 site)	**Population:** Hemorrhage trauma patients ages ≥18 and ≤90 years old **Sample Size:** 543 hemorrhage patients **Number of Sites:** 9 sites (location unspecified)	**Type:** Concurrent controls **Population:** Trauma control patients ages ≥18 and ≤90 years old **Sample Size:** 5,352 control patients **Number of Sites:** 9 sites (location unspecified)	**Validation Study Endpoint(s):** Likelihood Ratios for hemorrhage risk index (HRI) Levels I, II, and III for the first HRI output of each patient

Example 52. 510(k) – Clearance of a Surgical Device Using Data from Systematic Literature Reviews
[102, 103]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K242318 11/26/2024	da Vinci SP Surgical System, Model SP1098	Intuitive Surgical, Inc.	Medical records (EHR, EMR, or chart review) Registry	**Premarket:** Data from studies identified in systematic literature reviews was used as comparative source of clinical evidence for the clearance of this 510(k) for a labeling modification, including adding "colorectal surgical procedures" to the indications, and to add new representative, specific procedures in the Professional Instructions for Use. The sponsor conducted 2 systematic literature reviews on relevant literature published between 2010 and March 2024 to compare results with the pivotal clinical trial, the primary source of clinical evidence, on a U.S. and South Korean patient population. A subset of the literature reviewed in the systematic literature reviews incorporated RWD, including studies that utilized medical records and registry data.	Comparator is, or is derived from, RWD Medical records (EHR, EMR, or chart review) Outside-the-US Registry General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Da Vinci SP Colorectal Surgical Procedures Study (Non-RWE) **Study Design:** Single-arm Clinical Trial	**Population:** Patients that underwent colorectal procedures surgical **Sample Size:** 60 subjects **Number of Sites:** 8 U.S. sites and 2 OUS sites (South Korea)	**Type:** Comparator results generated from systematic literature review (see Systematic Literature Review below)	**Primary Safety Endpoint(s):** Serious adverse events rate, device-related serious adverse events rate, intraoperative adverse event rate, and major adverse events **Primary Effectiveness Endpoint(s):** Operative time, estimated blood loss, blood transfusion rate, conversion rate, length of hospital stay, rate of positive surgical margins, readmission rate, reoperation rate, and mortality rate

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Reviews (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Publication Date Period:** 2010 – 3/2024 **Methods of Note**: For additional details see the Decision Letter and Summary	**Population:** Multiport robotic systems for low anterior resection/total mesorectal excision (LAR/TME) and right colectomy procedures **Number of Publications:** LAR/TME: 55 publications Right Colectomy: 18 publications **Number of Sites:** U.S. and OUS sites (number unspecified)	Not applicable for this study	**Endpoint(s):** Operative time, length of stay, estimated blood loss, intra-operative adverse events, major adverse event complication rate, anastomotic complication rate, transfusion rate, conversion rate, mortality rate, readmission rate, and reoperation rate

Example 53. 510(k) – Clearance of a Surgical Device Using a Systematic Literature Review [104]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K243714 4/24/2025	da Vinci SP Surgical System (SP1098)	Intuitive Surgical, Inc.	Medical records (EHR, EMR, or chart review) Registry	**Premarket:** A systematic literature review was a primary source of clinical evidence for the clearance of this 510(k) for a labeling change to include transanal local excision (TALE). The sponsor conducted the systematic literature review on literature published between January 2018 and October 2024 that compared device-assisted TALE to the same procedure performed using other existing instruments. A subset of the literature reviewed in the systematic literature review incorporated RWD, including studies that utilized medical record and registry data.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Medical records (EHR, EMR, or chart review) Registry General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Review (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** PubMed, Scopus, and Embase **Publication Date Period:** 1/1/2018 – 10/22/2024 **Methods of Note**: For additional details see the Decision Letter and Summary	**Population:** Publications for robotic-assisted TALE using the da Vinci SP system **Number of Publication:** 10 publications identified for data review; 4 out of the 10 publications with a high level of evidence (81 patients)	**Type:** Comparator results generated from systematic literature review **Population:** Publications for handheld devices performing transanal endoscopic microsurgery, transanal minimally invasive surgery, and transanal endoscopic operation published between 1/1/2018 and 12/16/2023 **Sample Size:** 42 publications (~21,121 patients)	**Primary Safety Endpoint(s):** Intraoperative complication rates, 30-day post-operative complication rate, major complication rate, average length of hospital stay, re-admission/ re-operation rate, and overall mortality rate **Primary Effectiveness Endpoint(s):** Average operative time, average estimated blood loss, transfusion rate, conversion to open surgery, and negative surgical margin

Section IV. Examples Leveraging Administrative Claims Data as a Source of Real-World Data

Example 54. PMA – Approval of a PMA for an Indication Expansion for a Spinal Cord Stimulation System Using Administrative Claims Data [64-67, 105-107]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P010032/S189 1/24/2023	Prodigy, Proclaim, and Proclaim XR Spinal Cord Stimulation (SCS) Systems	Abbott Medical	Administrative claims data Medical records (EHR, EMR, or chart review) Public health surveillance data Centers for Medicare and Medicaid Services (CMS) Research Identifiable File Medicare Fee-for-service claims data Medicare Supplemental Database Nationwide Inpatient Sample Truven MarketScan Commercial Claims and Encounters (CCAE) Database	**Premarket:** Administrative claims data was a supplemental source of clinical safety evidence for the approval of this PMA Supplement to support inclusion of DPN of the extremities for the tonic stimulation mode in the indications for use. The sponsor conducted 2 systematic literature reviews and a retrospective cohort study using CMS Medicare administrative claims data. A subset of the literature reviewed in the systematic literature reviews incorporated RWD, including multiple studies that utilized data from medical records, administrative claims, and public health surveillance. The retrospective cohort study linked patients identified in the Abbott Patient Device Tracking database with CMS claims data to assess safety outcomes. The primary clinical evidence came from 2 randomized controlled trials identified through the systematic literature review.	Administrative claims data Comparator is, or is derived from, RWD Linkage Medical records (EHR, EMR, or chart review) Public health surveillance data Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Systematic Literature Review (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** Embase and PubMed **Publication Date Period:** 1984 – 2022 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Diabetic population **Number of Publications:** Safety: 22 publications (n= 2,965) and 6 meta-analyses Effectiveness: 14 publications (n= 248) and 5 meta-analyses	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** Pain reduction
CMS Claims Data Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 12 months post-implantation **Study Period:** 1/1/2014 – 9/30/2020 **Methods of Note:** Linkage performed between the Abbott Patient Device Tracking database and CMS claims data	**Population:** Medicare patients implanted with an Abbott SCS system **Sample Size:** 507 patients	**Type:** Concurrent controls **Population:** Medicare non-DPN patients implanted with an Abbott SCS **Sample Size:** 35,497 patients	**Primary Safety Endpoint(s):** Device- or procedure-related safety events up to 12 months following implantation
Systematic Literature Review on Clinical Practice Guidelines on Perioperative Care of Diabetic Patients (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** Embase and PubMed **Publication Date Period:** 2017 – 2022 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Diabetic Patients **Number of Publications:** 31 publications	Not applicable for this study	Not applicable for this study

Study Design	Population	Comparator	Key Endpoints
Randomized Controlled Trial – Slangen et al. 2014 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 6 months **Study Period:** 2/1/2010 – 2/28/2013 **Methods of Note**: Identified in systematic literature review, pooled with de Vos et al. 2014 randomized controlled trial for meta-analysis	**Population:** Moderate to severe painful DPN patients not responding to conventional therapy for 12 months randomized to SCS in combination with best medical practice (BMT) **Sample Size:** 22 subjects **Number of Sites:** 2 OUS sites (Netherlands)	**Type:** Randomized controls **Population:** Moderate to severe painful DPN patients not responding to conventional therapy for 12 months randomized to BMT only **Sample Size:** 14 subjects **Number of Sites:** 2 OUS sites (Netherlands)	**Primary Effectiveness Endpoint(s):** ≥50% pain reduction during daytime or nighttime; or a score of ≥ 6 on a 7- point Likert scale of the patient global impression of change scale for pain and sleep
Randomized Controlled Trial – de Vos et al. 2014 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 6 months **Study Period:** 11/2008 – 10/2012 **Methods of Note**: Identified in systematic literature review, pooled with Slangen et al. 2014 randomized controlled trial for meta-analysis	**Population:** Patients with DPN in the lower extremities for more than 1 year and refractory to conventional treatments, visual analog scale (VAS) pain rating ≥50 mm, and ≥18 years old, randomized to SCS in combination with BMT **Sample Size:** 40 subjects **Number of Sites:** 7 OUS sites (Netherlands, Denmark, Belgium, and Germany)	**Type:** Randomized controls **Population:** Patients with DPN in the lower extremities for more than 1 year and refractory to conventional treatments, VAS pain rating ≥50 mm, and ≥18 years old, randomized to BMT only **Sample Size:** 20 subjects **Number of Sites:** 7 OUS sites (Netherlands, Denmark, Belgium, and Germany)	**Primary Effectiveness Endpoint(s):** Treatment success at 6 months and ≥50% pain reduction

Example 55. 510(k) – Labeling Modification for a Surgical System Using Administrative Claims Data [108]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K240723 5/24/2024	da Vinci Xi Surgical System (IS4000) and da Vinci X Surgical System (IS4200)	Intuitive Surgical	Administrative claims data Optum Clinformatics Data Mart de-identified administrative healthcare claims data	**Premarket:** Administrative claims data was a primary source of clinical evidence for the clearance of this 510(k) to support a labeling modification to the Precaution for Representative Uses statement for radical prostatectomy (RP) performed using the subject device. The sponsor conducted a retrospective cohort study using secondary administrative healthcare claims data of U.S. patients with treatment-naive prostate cancer.	RWE as a primary source of clinical evidence Administrative claims data Comparator is, or is derived from, RWD General & Plastic Surgery

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Robotic-Assisted Radical Prostatectomy Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** Primary endpoint at 5 years and secondary endpoints annually at 6–10 years **Study Period:** 7/2007 – 12/2020 **Methods of Note**: Propensity score method with stratification	**Population:** Male patients at least 35 years old with treatment-naive prostate cancer undergoing a robotic-assisted surgical device (RASD) procedure **Sample Size:** 18,949 patients	**Type:** Concurrent controls **Population:** Male patients at least 35 years old with treatment-naive prostate cancer undergoing a non-RASD RP procedure **Sample Size:** 5,401 patients	**Primary Endpoint(s):** Difference in probability of overall survival at 5 years after RP procedure

Section V. Examples Leveraging Both Registries and Administrative Claims Data as Sources of Real-World Data

Example 56. PMA – Approval of a PMA for an Indication Expansion and Post-Approval Study of a Percutaneous Aortic Valve Using Registry and Administrative Claims Data [109-111]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P130021/S174 8/27/2025	Medtronic Evolut PRO+ system Medtronic Evolut FX system Medtronic Evolut FX+ system	Medtronic, Inc.	Administrative claims data Registry Society of Thoracic Surgeons (STS)/ American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry CMS claims and encounter data	**Premarket:** Registry data was a primary source of clinical evidence for the approval of this PMA Supplement for indication expansion to include patients with a failing transcatheter bioprosthetic aortic valve (redo transcatheter aortic valve replacement (TAVR)) who are deemed to be at high or greater risk for surgical therapy. The sponsor performed an analysis of real-world off-label use data captured in the STS/ ACC TVT Registry using standardized data collection forms to establish reasonable assurance of safety and effectiveness of the Medtronic Evolut PRO+, FX, and FX+ systems in patients receiving redo TAVR treatment. The sponsor linked the registry data to CMS claims and encounter data to obtain additional mortality events and follow-up time. The study was a retrospective cohort study with the objective to evaluate safety and effectiveness outcomes in patients who received commercially available Evolut valves for redo TAVR. **Postmarket:** The Registry-based Real-World Use Surveillance study was mandated to assess real-world performance of Evolut systems used for redo TAVR procedures involving all consecutive patients treated within the first 2 years following device approval or a total of 500 consecutively treated patients (whichever is greater) entered into the STS/ACC TVT Registry. Follow-up through 10 years post-procedure will be achieved by linking registry data with the CMS claims database.	RWE as a primary source of clinical evidence Administrative claims data Linkage PRO derived from RWD Professional society registry Total-Product Lifecycle Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
STS/ACC TVT Registry Real-World Analysis (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 30 days and 1 year **Study Period:** Treatment cutoff date: 9/30/2023 **Methods of Note**: Linkage performed between STS/ACC TVT Registry data and CMS claims and encounter data via 1-to-1 match to augment all-cause mortality outcomes	**Population:** Patients (mean age 78.9 ± 9.1 years old) who received a commercially available Evolut valve for redo TAVR on or before the treatment cutoff date. **Sample Size:** Attempted implant population: 744 patients Valve implant population: 740 patients Linked to CMS claims data: 588 patients	Not applicable for this study	**Safety Endpoint(s):** All-cause mortality; stroke and transient ischemic attack; major vascular complications; life-threatening/major bleeding; and other adverse events assessed at 30 days and 1 year post-procedure **Effectiveness Endpoint(s):** Aortic valve reintervention, valve performance based on echocardiographic data (mean aortic gradient, aortic regurgitation), New York Heart Association (NYHA) functional classification, and Kansas City Cardiomyopathy Questionnaire (KCCQ) score assessed at 30 days and 1 year post-procedure

Post-Approval Study Requirement Using an RWD Source

Study Design	Population	Comparator	Key Endpoints
Registry-Based Real-World Use Surveillance **Study Design:** Prospective Cohort Study (Single-Arm) Postmarket Surveillance **Follow-up/Duration:** 10 years post-procedure **Methods of Note:** Data through 1 year will come from the STS/ACC TVT Registry. Data from the STS/ACC TVT Registry will be linked with CMS database for surveillance through 10 years.	**Population:** Patients with a failing transcatheter bioprosthetic aortic valve who are deemed to be at high or greater risk for surgical therapy and are treated with an Evolut PRO+/FX/FX+ valve. **Sample Size:** All consecutive patients treated within first 2 years following device approval or 500 consecutively treated patients (whichever is greater) that are entered into the STS/ACC TVT Registry	Not applicable for this study	**Safety and Effectiveness Endpoint(s):** All-cause mortality, all stroke, repeat procedure for valve-related dysfunction (surgical or interventional therapy) through 10 years

Example 57. PMA – Approval of a PMA for an Indication Expansion and Post-Approval Study of a Transcatheter Heart Valve System Using Registry and Administrative Claims Data [112–114]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P140031/S112 9/9/2020	Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve (THV) System	Edwards Lifesciences LLC	Administrative claims data Registry STS/ACC TVT Registry CMS claims database	**Premarket:** Registry data was a primary source of clinical evidence for the approval of this PMA Supplement for an indication expansion to include patients with a failing transcatheter bioprosthetic aortic valve (i.e., THV-in-THV) who are at high or greater risk for surgical aortic valve replacement (SAVR). The sponsor conducted a single-arm retrospective cohort study of patients from the STS/ACC TVT Registry to evaluate safety and effectiveness for this submission. **Postmarket:** As a condition of approval, the sponsor agreed to conduct comprehensive postmarket surveillance through the STS/ACC TVT Registry linked to the CMS claims database for long-term monitoring extending to 10 years post-implantation.	RWE as a primary source of clinical evidence Administrative claims data Linkage PRO derived from RWD Professional society registry Total-Product Lifecycle Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
STS/ACC TVT Registry Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 30 days and 1 year **Study Period:** Patients treated between 8/4/2015 – 6/9/2018	**Population:** Patients (mean age 78.9 ± 10.5 years old) receiving a commercially available Edwards SAPIEN 3 or Edwards SAPIEN 3 Ultra THV in an aortic THV-in-THV procedure **Sample Size:** 263 patients **Number of Sites:** 138 sites	Not applicable for this study	**Safety Endpoint(s):** All-cause mortality; all stroke and transient ischemic attack; valve re-interventions; and other key adverse events including conduction/native pacer disturbance requiring pacer and valve-related readmission assessed at 30 days and 1 year post-procedure **Effectiveness Endpoint(s):** Echocardiographic valve performance (mean aortic gradient, aortic regurgitation), NYHA functional class, length of stay, KCCQ assessed at 30 days and 1 year post-procedure

Post-Approval Study Requirement Using an RWD Source

Study Design	Population	Comparator	Key Endpoints
Edwards SAPIEN 3 and SAPIEN 3 Ultra Aortic Real-World Use Surveillance (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) Postmarket Surveillance **Follow-up/Duration:** 30 days, 12 months, 2–10 years **Methods of Note:** Data at 30 days and 1 year will come from the STS/ACC TVT Registry. Data from the STS/ACC TVT Registry will be linked with CMS database for surveillance through 10 years.	**Population:** Patients with a failing transcatheter bioprosthetic aortic valve treated with Edwards SAPIEN 3 and SAPIEN 3 Ultra THV System **Sample Size:** All consecutive patients treated within the first 3 years after PMA approval that are entered into the STS/ACC TVT Registry	Not applicable for this study	**Safety and Effectiveness Endpoint(s):** (1) device success (intra-procedure)**;** (2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, repeat procedure for valve-related dysfunction at 30 days and 1 year; (3) neurological (non-stroke), vascular complications, KCCQ outcomes at 30 days and 1 year; (4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) through 10 years post-implantation

Example 58. PMA – Approval of a PMA for an Indication Expansion and Post-Approval Study of a Transcatheter Heart Valve and Accessories Using Registry and Administrative Claims Data [115-117]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P140031/S162 5/23/2024	Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve (THV) Systems	Edwards Lifesciences LLC	Administrative claims data Registry STS/ACC TVT Registry CMS database	**Premarket:** Registry and prospective clinical trial data were primary sources of clinical evidence for the approval of this PMA Supplement for an indication expansion to include patients with a failing surgical bioprosthetic mitral valve who are at intermediate risk for open surgical therapy (i.e., THV-in surgical valve). The sponsor conducted a pooled analysis of data from the STS/ACC TVT Registry and a single-arm clinical trial (PARTNER 3 Mitral Valve-in-Valve (P3 MVIV) study) assessing improvement in valve hemodynamics and against performance goals for the co-primary safety endpoints. **Postmarket:** As a condition of approval, the sponsor agreed to conduct comprehensive postmarket surveillance through the STS/ACC TVT Registry linked to the CMS claims database for long-term monitoring extending to 10 years post-implantation. The sponsor also agreed to follow subjects in the P3 MVIV study through 10 years post-implantation.	RWE as a primary source of clinical evidence Administrative claims data Linkage PRO derived from RWD Professional society registry Total-Product Lifecycle Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Pool Analysis of STS/ACC TVT Registry and P3 MVIV Study Data (Non-RWE and RWE) **STS/ACC TVT Registry Data (RWE)** **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 30 days and 1 year **Study Period:** Treatment cutoff date: 11/27/2021 **P3 MVIV Study (Non-RWE)** **Study Design:** Single-arm Clinical Trial **Follow-up/Duration:** 30 days and 1 year **Study Period:** Treated 6/2018 – 8/2021 **Methods of Note**: Tipping point analysis to estimate effect of missing data. Data from the STS/ACC TVT registry were pooled with prospective clinical trial data from the P3 MVIV study.	**Population:** Adult patients (mean age 71.7 ± 10.10 years) with a failing mitral bioprosthetic valve, who were at intermediate risk for open surgical therapy and treated with an Edwards SAPIEN 3 or Edwards SAPIEN 3 Ultra THV **Sample Size:** 502 patients (452 patients from STS/ACC TVT Registry + 50 patients from P3 MVIV cohort) **Number of Sites:** STS/ACC TVT Registry: unspecified P3 MVIV Study: 12 sites (location unspecified)	**Type:** Performance goal	**Co-primary Safety and Effectiveness Endpoints:** (1) Composite of all-cause death or stroke at 30 days, and (2) all-cause death at 1 year

Post-Approval Study Requirement Using an RWD Source

Study Design	Population	Comparator	Key Endpoints
Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Mitral Valve-in-Valve Intermediate Risk Indication Real-World Use Surveillance (RWE) **Study Design:** Prospective Cohort (Single-Arm) Postmarket Surveillance **Follow-up/Duration:** 10 years **Methods of Note:** Data at 30 days and 1 year will come from the STS/ACC TVT Registry. Registry data will be linked with the CMS database for surveillance through 10 years.	**Population:** Patients with a failing surgical bioprosthetic mitral valve, who are at intermediate risk for open surgical therapy and treated with a commercially available Edwards SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN 3 Ultra RESILIA transcatheter heart valve **Sample Size:** All consecutive patients treated within the first 3 years after PMA approval that are entered into the STS/ACC TVT registry, or a total of 1,000 patients, whichever is greater. Enrollment will continue for underrepresented groups as follows: 150 Hispanic, 150 Black/African American, 100 Asian, 50 American Indian/Alaskan Native, and 25 Native Hawaiian/Pacific Islander	Not applicable for this study	**Safety and Effectiveness Endpoints:** Device implanted successfully; all-cause mortality, all stroke, life-threatening/ major bleeding, new requirement for dialysis, myocardial infarction, mitral valve reintervention, transient ischemic attack, and vascular complications at 30 days and 1 year; 6-minute walk distance, KCCQ , and change in NYHA functional class at 30 days and 1 year; mitral valve hemodynamics at 30 days and 1 year; and all-cause mortality, all stroke, and mitral valve reintervention through 10 years post-implantation

Example 59. PMA – Approval of a New PMA for an Implanted Device for the Treatment of Refractory or Recurrent Ascites Using Administrative Claims and Registry Data [118, 119]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P230044 12/20/2024	alfapump® System	Sequana Medical NV	Administrative claims data Registry The North American Consortium for the Study of End Stage Liver Disease III (NACSELD III Registry) Centers for Medicare and Medicare Inpatient & Outpatient Hospital Standard Analytical Files (SAFs)	**Premarket:** Administrative claims and registry data were supplemental sources of clinical evidence for the approval of this PMA for this breakthrough device. The POSEIDON trial, a single-arm trial, was the primary source of clinical evidence. To demonstrate the safety of the alfapump® System, the sponsor conducted 2 studies using external controls from 2 RWD sources, NACSELD III registry and Medicare, to compare with POSEIDON trial data.	Administrative claims data Comparator is, or is derived from, RWD Outside-the-US Registry Gastroenterology/ Urology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
POSEIDON Pivotal Trial (Non-RWE) **Study Design:** Single-arm Clinical Trial **Follow-up/Duration:** Pre-implant 3-month observation period through up to 24 months ± 45 days postoperatively **Study Period:** 10/11/2019 – 11/1/2023	**Population:** Adult (42–83 years old) subjects with refractory or recurrent ascites due to liver cirrhosis implanted with the alfapump® **Sample Size:** 40 implanted pivotal cohort patients (29 implanted roll-in patients additionally assessed for safety) **Number of Sites:** 15 U.S. and OUS sites (Canada)	**Type:** Within-subject comparator	**Primary Safety Endpoint(s):** Combined rate of open surgical reintervention (requiring general anesthesia or laparotomy) due to pump system-related adverse event or to restore pump functionality, pump explant (without replacement) due to pump system-related adverse event, or pump system-related adverse event, or pump system-related death from time of pump implant through 6 months post-implant **Primary Effectiveness Endpoint(s):** Per-patient ratio of post-implant to pre-implant average monthly number of therapeutic paracentesis and proportion of patients with at least 50% reduction in therapeutic paracenteses

Study Design	Population	Comparator	Key Endpoints
NACSELD III Registry Control Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 6 months **Methods of Note**: 1:1 matched analysis comparing POSEIDON trial patients with NACSELD III registry patients.	**Population:** POSEIDON trial subjects **Sample Size:** 37 matched patients **Number of Sites:** 15 U.S. and OUS sites (Canada)	**Type:** External controls **Population:** Patients from the NACSELD III registry **Sample Size:** 37 matched registry patients **Number of Sites:** U.S. and OUS sites (number unspecified; Canada)	**Primary Safety Endpoint(s):** Any serious adverse event resulting in death or requiring hospitalization over 6 months
Medicare SAF Control Study (RWE) **Study Design:** Retrospective Cohort Study **Follow-up/Duration:** 6, 12, and 24 months **Study Period:** 2017 – 2020 (this study period was chosen to avoid using data during the COVID pandemic)	**Population:** POSEIDON trial subjects ≥65 years old **Sample Size:** 19 patients **Number of Sites:** 15 U.S. and OUS sites (Canada)	**Type:** External controls **Population:** Medicare beneficiaries (65 years old and older) with refractory ascites **Sample Size:** 701 patients **Number of Sites:** U.S. sites (number unspecified)	**Primary Safety Endpoint(s):** Cumulative percent mortality, cumulative percent of patients with inpatient hospitalizations, and hospitalizations per patient

Section VI. Examples Leveraging Public Health Surveillance Data as a Source of Real-World Data

Example 60. PMA – Approval of a New PMA for an Adjustable Balloon System Using Postmarket Surveillance Data [120-122]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P190012 10/15/2021	Spatz3 Adjustable Balloon System	Spatz FGIA, Inc	Public health surveillance data	**Premarket:** Clinical product surveillance data was a supplemental source of clinical evidence for the approval of this PMA for a new device. The clinical evidence included a randomized controlled trial conducted at U.S. investigational sites and data on adverse event complaints reported through OUS clinical product surveillance.	Outside-the-US Public health surveillance data Gastroenterology/ Urology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Spatz3 U.S. Pivotal Study (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 56 weeks total (32 weeks treatment period plus 6-month follow-up) **Study Period:** 8/30/2013 – 3/15/2021 **Methods of Note**: Multiple imputation procedure for missing data and last observation carried forward (LOCF) procedure	**Population:** Adults 22–64 years old with a BMI ≥30 kg/m2 and <40 kg/m2 who failed to achieve and maintain weight-loss with a weight control program. **Sample Size:** 187 subjects **Number of Sites:** 7 U.S. sites	**Type:** Randomized controls **Population:** Adults aged 22–65 years old **Sample Size:** 101 subjects **Number of Sites:** 7 U.S. sites	**Primary Safety Endpoint(s):** Incidence, frequency, and severity of adverse events related to treatment with the device. **Co-primary Effectiveness Endpoint(s):** (1) Percent change in total body weight (%TBL) at 32 weeks and (2) Clinical response (at least 5% TBL at 32 weeks)

Study Design	Population	Comparator	Key Endpoints
OUS Clinical Product Complaint Data (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Postmarket Surveillance **Study Period:** 8/30/2012 – 3/15/2021	**Sample Size:** 88,614 implants	Not applicable for this study	**Primary Safety Endpoint(s):** Serious adverse events, device failures leading to inability to implant, device failures leading to inability to adjust, and device failures during treatment phase

Example 61. 510(k) – Clearance of a Dental Implant System Using Medical Records and Postmarket Surveillance Data [123-125]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K211109 12/21/2021	N1™ TiUltra™ TCC Implant System	Nobel Biocare Services AG	Medical records (EHR, EMR, or chart review) Public health surveillance data	**Premarket:** Medical record data was a primary source of clinical evidence for the clearance of this 510(k) for a new device. The sponsor conducted a multicenter, single-arm, retrospective cohort study in Europe to evaluate clinical parameters for at least 12 months post-loading to support the success and safety of the device and its associated implant site preparation drilling technique. The clinical evidence also included a comparison of postmarket surveillance complaint rates in countries accepting CE-marks between the new device in its first year of CE-marketing and the predicate device during its first year of marketing.	RWE as a primary source of clinical evidence Comparator is, or is derived from RWD Medical records (EHR, EMR, or chart review) Outside-the-US Public health surveillance data Dental

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
T-193 EVOLUTION Study (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) **Follow-up/Duration:** 12-months post-implant	**Population:** Patients who received the Nobel Biocare N1 Concept System implant **Sample Size:** 95 patients with 165 implants **Number of Sites:** OUS sites (Europe; number unspecified)	**Type:** Performance goal generated using RWE from published studies of the predicate device (MacLean et al. 2016; Aldahlawi et al. 2018)	**Primary Effectiveness Endpoint(s):** Marginal bone level change at 12-months post-loading
Postmarket Surveillance Study (RWE) **Study Design:** Retrospective Cohort (Single-Arm) Postmarket Surveillance **Study Period:** 5/2020 – 7/2021	**Population:** Patients treated using Nobel Biocare N1™ TiUltra™ TCC implants, as well as the associated restorative components from CE-mark accepting countries	**Type:** Historical controls **Population:** Patients treated with the primary predicate device (NobelActive) during first year of marketing (2008 – 2009)	**Primary Safety Endpoint(s):** Postmarket surveillance complaint rates

Example 62. 510(k) – Clearance of an Intravascular Administration Set Using Public Health Surveillance Data [126, 127]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K250616 6/5/2025	Clave™ Neutral-Displacement Needlefree Connectors	ICU Medical, Inc.	Public health surveillance data Healthcare-associated infection (HAI) national database (via CMS Healthcare Associated Infections website) Clave NC technologies (NCT) customer database	**Premarket:** Public health surveillance data (healthcare-associated infection (HAI) national dataset) was a primary source of clinical evidence for the clearance of this 510(k) for an indication expansion for this intravascular administration set with needlefree connector (NC). Clearance was based on a published retrospective study comparing hospitals from the healthcare associated infection national database that utilized CLAVE NCT with hospitals where patients received any other type of NC. The HAI national dataset was linked to the CLAVE NCT customer database to identify hospitals using NCTs.	RWE as a primary source of clinical evidence Comparator is, or is derived from, RWD Linkage Public health surveillance data General Hospital

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Study of Public Health Surveillance Data – Ryder and Battle 2024 (RWE) **Study Design:** Retrospective Cohort Study **Study Period:** 1/1/2019 – 12/31/2019 **Methods of Note**: Linkage of a public health database to manufacturer's customer database.	**Population:** Patients in acute care hospitals using CLAVE NCT **Sample Size:** Total of 17,452,575 central line-days (CLAVE NCT and non-CLAVE) **Number of Sites:** 1,288 U.S. sites	**Type:** Concurrent controls **Population:** Patients in acute care hospitals using non-CLAVE connectors **Number of Sites:** 1,699 U.S. sites	**Primary Safety Endpoint(s):** Central line-associated bloodstream infection and bloodstream infection-associated mortality

Section VII. Examples Leveraging Device-Generated Data as a Source of Real-World Data

Example 63. PMA – Approval of a New PMA for Defibrillation Electrodes Using Device-Generated Data [128-135]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P160028 5/11/2020	HeartStart FR3 Defibrillator Models 861388 (Text) and 861389 (ECG Display), Primary Battery (Models 989803150161, 989803150171), Rechargeable Battery (Model 989803150241), Charger for the Rechargeable Battery (Model 861394), SmartPads III (Models 98980314)	Philips Medical Systems, Inc.	Device-generated data	**Premarket:** Device-generated data from a published study was a primary source of clinical evidence for approval of this PMA for a new device in a pediatric population. The published study reported on a prospective study that analyzed pediatric patients who had been treated with an automated external defibrillator (AED) with pediatric pads. To support the safety and effectiveness of the device in adult population, the clinical evidence additionally included 5 randomized control trials, which have been published in peer-reviewed journals.	RWE as a primary source of clinical evidence Device-generated data Medical records (EHR, EMR, or chart review) Outside-the-US Pediatric Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Gemini I Feasibility Study (Non-RWE) **Study Design:** Randomized Controlled Trial	**Population:** Adult patients (39–79 years old) undergoing a planned procedure for implantable cardioverter defibrillator (ICD) implantation, receiving rescue shocks with biphasic truncated exponential waveforms (115J and 130J) **Sample Size:** 30 patients **Number of Sites:** 1 U.S. site	**Type:** Randomized controls **Population:** Adult patients undergoing a planned procedure for ICD implantation, receiving rescue shocks with a 200J monophasic damped sine waveform	**Primary Effectiveness Endpoint(s):** Percent defibrillation efficacy (ventricular fibrillation (VF) termination within 3 seconds)
Gemini II Pivotal Study (Non-RWE) **Study Design:** Randomized Controlled Trial **Study Period:** 11/23/1994 – 10/31/1995	**Population:** Adult patients (17–87 years old) undergoing testing for insertion of an implantable defibrillator or follow-up electrophysiological evaluation post-implantation, given biphasic (115J or 130J) rescue shocks **Sample Size:** 294 patients (513 shocks delivered) **Number of Sites:** 14 U.S. and OUS (Canada) sites	**Type:** Randomized controls **Population:** Adult patients undergoing testing for insertion of an implantable defibrillator or follow-up electrophysiological evaluation post-implantation, given monophasic (200J or 360J) rescue shocks	**Primary Effectiveness Endpoint(s):** Percent defibrillation efficacy (based on patient defibrillation on the first shock by restoring a supraventricular, paced, or baseline rhythm within 16 RR intervals after shock)
Gemini II Safety Sub-Study (Non-RWE) **Study Design:** Randomized Controlled Trial	**Population:** Adult patients (39–76 years old) undergoing ICD implantation, receiving biphasic rescue shocks **Sample Size:** 30 patients **Number of Sites:** 1 U.S. site	**Type:** Randomized controls **Population:** Adult patients undergoing ICD implantation, receiving monophasic rescue shocks	**Primary Safety Endpoint(s):** Post-Shock ST-segment elevation in beat 10 s after shock delivery
ORCA Clinical Trial – Schneider et al. 2000 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** Until patient hospital discharge **Study Period:** 12/1996 – 12/1998	**Population:** Adult patients (30–87 years old) with known or suspected out-of-hospital cardiac arrest, who received the SMART biphasic waveform (Philips Forerunner 150J) **Sample Size:** 54 patients **Number of Sites:** 4 OUS sites (Germany, Belgium and Finland)	**Type:** Randomized controls **Population:** Adult patients (37–94 years old) with known or suspected out-of-hospital cardiac arrest, who received either the monophasic damped sine or monophasic truncated exponential waveforms (escalating from 200J, 200J, then 360J) **Sample Size:** 61 patients **Number of Sites:** 4 OUS sites (Germany, Belgium and Finland)	**Primary Effectiveness Endpoint(s):** Percentage of patients with VF as the initial monitored rhythm who were defibrillated in the first series of ≤ 3 shocks

Study Design	Population	Comparator	Key Endpoints
Postmarket Surveillance Study of Pediatric AED Use – Atkins et al. 2005 (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) Postmarket Surveillance **Follow-up/Duration:** Until hospital discharge **Study Period:** 5/2001 – 11/2004	**Population:** Reported use of Philips FR2 AED with Pediatric Attenuated Electrodes and the HeartStart OnSite AED with the infant/child SMART pads cartridge in pediatric patients (0–23 years old) **Sample Size:** 23 patients **Number of Sites:** U.S. and OUS sites (number unspecified)	Not applicable for this study	**Primary Effectiveness Endpoint(s):** Detection of shockable rhythm, successful VF termination, and survival to hospital discharge
SMART CPR Clinical Trial – Freese et al. 2013 (Non-RWE) **Study Design:** Randomized Controlled Trial **Study Period:** 5/2006 – 6/2009	**Population:** Patients (18–97 years old) in cardiac arrest who received waveform-analysis of VF which guided therapy (SMART cardiopulmonary resuscitation (CPR)) **Sample Size:** 487 patients **Number of Sites:** 2 U.S. and OUS (England) sites	**Type:** Randomized controls **Population:** Patients (18–97 years old) in cardiac arrest who received standard shock-first CPR protocol **Sample Size:** 500 patients **Number of Sites:** 2 U.S. and OUS (England) sites	**Primary Effectiveness Endpoint(s):** Survival to hospital discharge

Example 64. PMA – Approval of a New PMA for Defibrillation Electrodes Using Device-Generated Data [136-140]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P190007 8/7/2020	Kendall™ Multi-Function Defibrillation Electrodes, Medi-Trace™ Cadence Multi-Function Defibrillation Electrodes, Physio-Control/ Stryker QUIK COMBO Pacing/ Defibrillation/ ECG Electrode	Cardinal Health	Device-generated data Medical records (EHR, EMR, or chart review) Public health surveillance data	**Premarket:** Device-generated data from a published study was a primary source of clinical evidence for the approval of this PMA for a new device. The primary clinical evidence also included published clinical data from 2 peer-reviewed publications of randomized controlled trials evaluating adult and pediatric uses of the device. Supplementary clinical evidence included adult and pediatric postmarket complaint data from October 2013 to September 2018.	RWE as a primary source of clinical evidence Device-generated data Medical records (EHR, EMR, or chart review) Outside-the-US Pediatric Public health surveillance data Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Randomized Control Trial – Higgins et al. 2000 (Non-RWE) **Study Design:** Randomized Controlled Trial	**Population:** Patients ≥18 years old undergoing electrophysiologic testing for ventricular arrhythmias or for evaluation of an ICD, randomized to receive a first shock of 200-J monophasic waveform administered to terminate ventricular arrhythmias or for evaluation of an ICD, randomized to receive a first shock of 200-J monophasic waveform administered to terminate VF **Sample Size:** 68 patients **Number of Sites:** Multicenter (number and location unspecified)	**Type:** Randomized controls **Population:** Patients ≥18 years old undergoing electrophysiologic testing for ventricular arrhythmias or for evaluation of an ICD, randomized to receive a first shock of 200-J or 130-J biphasic waveform administered to terminate VF **Sample Size:** 200-J biphasic waveform: 39 130-J biphasic waveform: 47 **Number of Sites:** Multicenter (number and location unspecified)	**Primary Effectiveness Endpoint(s):** Success of the first shock in terminating VF

Study Design	Population	Comparator	Key Endpoints
Randomized Controlled Trial – Van Alem et al. 2003 (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 5 seconds and 1 minute following first shock **Study Period:** 1/2000 – 6/2002	**Population:** Patients with VF who received shock from LIFEPAK 500 Biphasic Truncated Exponential AED **Sample Size:** 51 patients **Number of Sites:** OUS sites (Netherlands; number unspecified)	**Type:** Randomized controls **Population:** Patients with VF who received shock from LIFEPAK 500 monophasic damped sinusoidal AED **Sample Size:** 69 patients **Number of Sites:** OUS sites (Netherlands; number unspecified)	**Primary Effectiveness Endpoint(s):** Termination of VF and return of organized rhythm for at least 2 QRS complexes of similar morphology
Clinical Study – Hess et al. 2011 (RWE) **Study Design:** Prospective Cohort Study (Single-Arm) **Follow-up/Duration:** Through hospital discharge **Study Period:** 9/2008 – 3/2010	**Population:** Out-of-hospital cardiac arrest patients ≥18 years old with VF as the initial rhythm who were defibrillated by paramedics using a rectilinear biphasic waveform. VF was defined as the initial rhythm if a shock was delivered by a first responder AED prior to arrival of paramedics or when VF documented using AED ECG data) **Sample Size:** 94 patients **Number of Sites:** 9 U.S. sites	Not applicable for this study	**Primary Effectiveness Endpoint(s):** Termination of VF within 5 seconds post-shock, return of spontaneous circulation, and survival to hospital discharge
Postmarket Complaint Study (RWE) **Study Design:** Retrospective Cohort (Single-Arm) Postmarket Surveillance **Study Period:** 10/2013 – 9/2018	**Population:** Adult and pediatric patients exposed to the composite and tin Kendall™ Multifunction Defibrillation Electrodes and MEDI-TRACE™ Cadence Defibrillation Electrodes **Sample Size:** Adult composite electrodes: 156 complaints Pediatric composite electrodes: 2 complaints Tin electrodes: 37 complaints	Not applicable for this study	**Primary Safety Endpoint(s):** Overall complaint rate and reportable complaint rate

Example 65. 510(k) – Clearance of an Adjunctive Predictive Cardiovascular Indicator Software Using Data from an Outside-the-US National Health Database [141, 142]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K230842 10/25/2023	SignalHF	Implicity Inc.	Administrative claims data Device-generated data Système National Des Données de Santé (SNDS)	**Premarket:** OUS administrative claims data was a primary source of clinical evidence for the clearance of this 510(k) for a new device software function. The sponsor conducted a retrospective study to test the algorithm performance using data from the French SNDS national health database and Implicity proprietary databases. The device-generated heart failure risk score was assessed by comparing predicted alerts to hospitalizations with heart failure as the primary diagnosis. Performance was assessed based on sensitivity for detecting these events and alert timing relative to the hospitalizations.	RWE as a primary source of clinical evidence Administrative claims data Device-generated data Digital Health Outside-the-US Validation Cardiovascular

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
FORESEE-HF Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** 2017 – 2021 **Study Period:** 2017 – 2021	**Population:** Patients in France implanted with an ICD, cardiac resynchronization therapy (CRT)-defibrillator (CRT-D), or CRT-pacemaker (CRT-P) with at least 1 remote monitoring data transmission during the follow-up period **Sample Size:** Validation cohort: 3,678 patients Clinical cohort: 6,740 patients **Number of Sites:** Multicenter (number and location unspecified)	**Type:** Observed heart failure (HF) hospitalization events recorded in the French national health database	**Validation Study Endpoint(s):** Hospitalizations with HF as primary diagnosis; Unexplained alert rate per patient-year; True positive alerts raised at least 15 days before HF hospitalization event

Example 66. 510(k) – Clearance of a Neurostimulation Device Using Device- and Patient-Generated Data from Published Literature [143-147]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K250405 5/14/2025	Nerivio and Nerivio Infinity	Theranica Bio-Electronics Ltd	Device-generated data Patient-generated data	**Premarket:** Device- and patient-generated data reported in a peer-reviewed publication was a primary source of clinical evidence for the clearance of this 510(k) for removal of precaution statements from the device labeling. Device- and patient-generated data from the use of the subject/predicate device were utilized to demonstrate safety with longer-term (1-year or greater) use of the device. The clinical evidence also included a peer-reviewed publication of a retrospective survey of pregnant women using the device, which provided evidence of safety of device use during pregnancy.	RWE as a primary source of clinical evidence Device-generated data Digital Health Patient-generated or patient-entered data Neurology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Retrospective Cohort Study – Synowiec et al. 2024 (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) **Follow-up/Duration:** 12 months **Study Period:** 10/1/2019 – 8/31/2022	**Population:** Patients (mean age: 45.8 years old) who completed treatments with the device for at least 12 consecutive calendar months. **Sample Size:** 409 patients **Number of Sites:** U.S. sites (number unspecified)	**Type:** Within-subject comparator	**Primary Safety Endpoint(s):** Device-related adverse events **Primary Effectiveness Endpoint(s):** Pain relief, functional relief, pain freedom, functional freedom, photophobia freedom, nausea/committing freedom, phonophobia freedom, and freedom from at least 1 associated symptom

Study Design	Population	Comparator	Key Endpoints
Retrospective Survey Study – Peretz et al. 2023 (Non-RWE) **Study Design:** Cross-Sectional Study **Follow-up/Duration:** Up to 3 months postpartum **Study Period:** Study conducted between 8/1/2022 – 12/7/2022 among women who became pregnant between 11/1/2019 – 8/1/2021	**Population:** Pregnant women (age range: 18–45 years old) who experienced migraines during pregnancy and treated their migraine with the subject device **Sample Size:** 59 patients	**Type:** Concurrent controls **Population:** Pregnant women (age range: 18–45 years old) who experienced migraines during pregnancy and did not treat their migraines with the subject device **Sample Size:** 81 patients	**Primary Safety Endpoint(s):** Gestational age at delivery, baby's birth weight, miscarriage rate, preterm birth rate, birth defect rate, stillbirth rate, rate of meeting baby's developmental milestones 3 months postnatal, emergency room visits

Section VIII. Examples Leveraging Other Combinations of Real-World Data Sources

Example 67. PMA – Approval of a New PMA for a Diaphragm Pacing System Using Data from Published Literature [148-161]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
P200018 3/31/2023	NeuRx® Diaphragm Pacing System (NeuRx DPS®)	Synapse Biomedical, Inc.	Administrative claims data Medical records (EHR, EMR, or chart review) Public health surveillance data Registry National Spinal Cord Injury Statistical Center (NSCISC) National Department of Veteran Affairs datasets Nationwide Inpatient Sample database National Nosocomial Infections Surveillance system (Japan)	**Premarket:** Data from published literature, including publications of studies using RWD sources, was a supplemental source of clinical evidence for this conversion of an HDE to a PMA. The clinical evidence included a prospective, single-arm, multicenter clinical trial. The sponsor conducted a meta-analysis of results from the clinical trial and from 4 published studies of HDE patients. The publications incorporated RWD as they utilized data from medical records, trauma registry, and a professional billing database. The RWE also provided comparative safety data for adverse event rates in real-world populations with spinal cord injuries receiving standard care from published literature compared to the diaphragm pacing system (DPS) primary cohort. A subset of the literature reviewed incorporated RWD, including multiple studies that utilized data from registries, medical record data, and national public health surveillance systems.	Administrative claims data Comparator is, or is derived from, RWD Medical records (EHR, EMR, or chart review) Outside-the-US Public health surveillance data Registry Anesthesiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Pivotal Trial (Non-RWE) **Study Design:** Single-arm Clinical Trial **Follow-up/Duration:** 3, 6, and 12 months for patients who had not achieved steady state **Study Period:** 3/6/2000 – 6/17/2008	**Population:** Patients with stable, high spinal cord injuries with stimulable diaphragms, but who lack control of their diaphragms, 18 years and older **Sample Size:** 53 patients (primary cohort) **Number of Sites:** 5 U.S. and OUS sites	**Type:** Performance goal; within-subject comparator Safety data compared descriptively to data from the literature (see Peer-reviewed Literature below)	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** Use of the NeuRx DPS® to breathe without the assistance of mechanical ventilation for at least 4 continuous hours a day
Meta-Analysis of Pivotal Trial and Data from Peer-Reviewed Publications (Non-RWE and RWE) **Study Design:** Meta-Analysis **Follow-up/Duration:** Up to 25 years **Study Period:** 2000 – 2017 **Methods of Note**: For additional details see the Summary of Safety and Effectiveness Data	**Population:** Secondary cohort (pooled of primary cohort with HDE patients from Onders et al. 2018) **Sample Size:** Secondary cohort: 106 patients (primary cohort + 53 HDE patients [Onders et al. 2018 total n=92, 39 from Pivotal Trial]) Meta-analysis: 196 patients (secondary cohort + 90 HDE patients from 3 published studies (n=40 [Kerwin et al. 2018], n=31 [Lammertse et al. 2016], and n=29 [Posluszny et al. 2014]) **Number of Sites:** 22 U.S. and OUS sites	**Type:** Performance goal	**Primary Safety Endpoint(s):** Adverse events and survival rates **Primary Effectiveness Endpoint(s):** Use of the NeuRx DPS® to breathe without the assistance of mechanical ventilation for at least 4 continuous hours a day
NSCISC Annual Report 2018 (RWE) **Study Design:** Prospective Cohort Study **Study Period:** 2018	**Population:** Patients with spinal cord injury **Sample Size:** > 14,000 patients **Number of Sites:** 14 U.S. sites	Not available	**Primary Safety Endpoint(s):** Adverse events (Pneumonia and pulmonary infections)
Peer-reviewed Literature (Non-RWE and RWE) **Study Design:** Literature Review	**Population:** SCI patients receiving standard of care **Number of Publications:** 7 publications, including 5 studies using RWD sources	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events

Example 68. De Novo – Classification of an Endoscopic Suturing Device for Altering Gastric Anatomy for Weight Loss Using Registry and Postmarket Surveillance Data [162-164]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
DEN210045 7/12/2022	APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX Systems	Apollo Endosurgery, Inc.	Registry Public health surveillance data System for Uniform Surveillance (SUS)	**Premarket:** Data from 2 registries, a literature review, and postmarket surveillance were supplemental sources of clinical evidence for the classification of this De Novo. The primary clinical evidence was the MERIT pivotal randomized controlled trial. The supplemental RWD included information from a professional society registry and a private-practice registry, a structured literature review (which included studies using registry data), and postmarket surveillance data which represented real-world device use and supported the overall assessment of safety and effectiveness for the device's new classification.	Outside-the-US Professional society registry Public health surveillance data Registry Gastroenterology/ Urology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
MERIT Trial (Non-RWE) **Study Design:** Randomized Controlled Trial **Follow-up/Duration:** 52 (1 year) and 104 weeks (2 years) **Study Period:** 2018 – 2022 **Methods of Note**: Modified intention-to-treat and completers analyses; missing data imputation	**Population:** Patients ages 21–65 years old with BMI ≥30 and ≤40 kg/m^2 who had failed to achieve and maintain weight loss with a non-surgical program **Sample Size:** Intent-to-treat (ITT): 85 subjects Modified intent-to-treat (mITT): 77 subjects Safety analyses: 150 subjects (includes controls that crossed over) **Number of Sites:** 9 U.S. sites	**Type:** Randomized controls **Population:** Patients ages 21–65 years old with BMI ≥30 and ≤40 kg/m^2 who had failed to achieve and maintain weight loss with a non-surgical program (lifestyle modification only) **Sample Size:** ITT: 124 subjects mITT: 110 subjects Completers at 52 weeks: 89 subjects **Number of Sites:** 9 U.S. sites	**Primary Safety Endpoint(s):** Device- or procedure-related adverse events **Primary Effectiveness Endpoint(s):** Response to treatment at 52 weeks follow-up

Study Design	Population	Comparator	Key Endpoints
Apollo Endosurgery & American Gastroenterological Association Registry (RWE) **Study Design:** Cohort Study (Single-Arm)	**Population:** Patients who underwent an endoscopic sleeve gastroplasty (ESG) procedure or a transoral outlet reduction (TORe) procedure **Sample Size:** ESG: 80 patients TORe: 39 patients **Number of Sites:** 15 sites (location unspecified)	Not applicable for this study	Not available
Private-Practice Registry (RWE) **Study Design:** Cohort Study (Single-Arm) **Follow-up/Duration:** 6 and 12 months	**Population:** Patients who underwent ESG or TORe procedures in a private practice in the U.S. and Brazil **Sample Size:** ESG: 295 patients TORe: 201 patients **Number of Sites:** 1 U.S. and 1 OUS site (Brazil)	Not applicable for this study	Not available
Structured Literature Review (Non-RWE and RWE) **Study Design:** Systematic Literature Review **Database(s):** PubMed **Publication Date Period:** 1/1/2017 – present **Methods of Note**: For Additional Details see De Novo Decision Summary	**Population:** Patients undergoing ESG or TORe procedures **Number of Publications:** 51 publications retrieved, and 9 additional publications considered due to their relevance	Not applicable for this study	**Primary Safety Endpoint(s):** Adverse events **Primary Effectiveness Endpoint(s):** Weight loss
Postmarket surveillance for Identical OverStitch Systems (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Postmarket Surveillance	**Population:** MDRs for the APOLLO ESG, ESG SX, REVISE and REVISE SX Systems used for ESG or TORe **Sample Size:** 75 MDRs	Not applicable for this study	**Primary Safety Endpoint(s):** Internal organ perforation, abdominal pain, hemorrhage/intestinal hemorrhage, death, sepsis, lacerations of the esophagus, pneumothorax, peritonitis, nausea, respiratory tract infection, pulmonary embolism, liver abscess, fever, and indeterminate tissue damage

Section IX. Examples Leveraging Real-World Data Sources for In Vitro Diagnostics

Example 69. De Novo – Classification of an In Vitro Diagnostic Test Using International Biobank Data [165, 166]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
DEN200044 11/9/2022	Eonis SCID-SMA Kit	PerkinElmer, Inc.	Clinically annotated biobanks Danish Newborn Screening Biobank (NBS-Biobank)	**Premarket:** Clinical evidence for the classification of this De Novo was based on a retrospective screening study and accuracy study conducted using dried blood spot (DBS) specimens from a clinically annotated biobank as a primary source of clinical screening samples. The sponsor conducted a clinical study to evaluate the performance of the Eonis SCID-SMA Kit using the Danish Newborn Screening Biobank. Retrospective archived newborn DBS specimens from subjects confirmed positive for spinal muscular atrophy (SMA) were included in the study data to enrich the Danish Newborn Screening Biobank cohort. Comparator test results were used for the SMA-confirmed positive cases, while the clinical status of unaffected subjects from the biobank was determined through retrospective review by clinical experts.	Biobank data Outside-the-US Pediatric Validation Molecular Genetics

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Clinical Screening Study (RWE) **Study Design:** Retrospective Cohort Study Validation Study	**Population:** Newborn DBS specimens from the U.S. and Denmark **Sample Size:** 3,069 DBS specimens (3,018 normal newborn screening specimens from the Danish Newborn Screening Biobank and 51 confirmed SMA cases from retrospective archived newborn DBS specimens collected from the U.S. and Denmark).	**Type:** Comparator test results for SMA confirmed positive cases **Population:** Retrospective clinical expert review of follow up information on DNS-Biobank samples from patient medical records to confirm that the newborn was unaffected	**Validation Study Endpoint(s):** Detection of homozygous deletion of SMN1 exon 7 as a marker for SMA (Positive percent agreement, negative percent agreement, and overall percent agreement; and positive and negative predictive values)
Accuracy Study (Non-RWE) **Study Design:** Case-Control Study Validation Study	**Population:** Confirmed positive SMA samples (U.S. and Danish DBS specimens) and negative samples from the NBS-Biobank **Sample Size:** 106 specimens (51 confirmed positive SMA samples (U.S. and Danish DBS specimens) and 55 negative samples from the NBS-Biobank)	**Type:** Comparator Test - Molecular genetic testing for both SMA positive and negative specimens	**Validation Study Endpoint(s):** Detection of homozygous deletion of SMN1 exon 7 (Positive percent agreement, negative percent agreement, and overall percent agreement)

Example 70. 510(k) – Clearance of an In Vitro Diagnostic Test Using International Biobank Data [167]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K203035 11/9/2022	Eonis SCID-SMA Kit	PerkinElmer, Inc.	Clinically annotated biobanks Medical records (EHR, EMR, or chart review) Registry Danish Newborn Screening Biobank Danish Neonatal Screening Biobank California Department of Public Health Genetic Disease Screening Program Biobank	**Premarket:** Clinical evidence for the clearance of this 510(k) for a new device was based on a retrospective accuracy study conducted using anonymized residual dried blood spot (DBS) specimens. The sponsor conducted a clinical study to evaluate the performance of the Eonis SCID-SMA Kit using specimens from the Danish Newborn Screening Biobank, Danish Neonatal Screening Biobank, California Department of Public Health Genetic Disease Screening Program Biobank, Danish medical records, and a Danish hospital registry. Retrospective archived newborn DBS specimens from subjects confirmed positive for severe combined immunodeficiency disorder (SCID) and X-linked agammaglobulinemia (XLA) were included to enrich the Danish Newborn Screening Biobank cohort. Comparator test results were used for the SCID- and XLA-confirmed positive cases, while the clinical status of unaffected subjects was determined through retrospective review of Danish hospital registry and patient medical records. A cutoff determination study was conducted using specimens from the Danish Newborn Screening Biobank to produce population distribution data and select clinical cutoff values for the pivotal study.	Biobank data Outside-the-US Pediatric Registry Validation Molecular Genetics

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Clinical Biobank Study (RWE) **Study Design:** Case-Control Study Validation Study **Methods of Note**: Age-matched storage controls for confirmed positive specimens (SCID, XLA) were used to ensure specimen integrity under storage conditions.	**Population:** Specimens from newborns <7 days old, collected from the study site at least 5.5-17 years before the study start, information from medical records to confirm no clinical signs of SCID or XLA, and documentation of confirmed diagnosis, gene mutation or flow cytometry results for SCID or XLA. **Sample Size:** 3,432 DBS specimens in the cutoff phase and 3,383 specimens in the pivotal phase (with confirmed positive cases including: 17 SCID cases and 1 XLA case from the California Department of Public Health Genetic Disease Screening Program Biobank, and 3 XLA cases from the Danish Neonatal Screening Biobank). The rest of the specimens were from the Danish Newborn Screening Biobank. **Number of Sites:** 1 OUS testing site (Denmark)	**Type:** Comparator test results for confirmed positive cases **Population:** Clinical assessment of clinical outcomes from patient medical record data to confirm that the newborn was unaffected	**Validation Study Endpoint(s):** Semi-quantitative determination of TREC and KREC levels as markers for SCID and XLA, respectively (Positive percent agreement, negative percent agreement, and overall percent agreement; Positive and negative predictive values [for SCID])

Example 71. 510(k) – Clearance of an In Vitro Diagnostic Test Using Public Health Surveillance Data [168]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K240867 2/11/2025	cobas SARS-CoV-2 Qualitative for use on the cobas 5800/6800/8800 Systems	Roche Molecular Systems, Inc.	Public health surveillance data National Football League (NFL) COVID-19 Surveillance Program	**Premarket:** Public health surveillance data, in the form of occupational surveillance testing, was a supplemental source of clinical evidence for the clearance of this 510(k) to expand the intended use to include individuals without signs and symptoms of COVID-19. The primary clinical evidence included data from the 2021 Test Us at Home longitudinal study, a prospective clinical study in which clinical performance was estimated using a comparator algorithm based on 2 consecutive test results collected over 48 hours. The clinical performance of the cobas SARS-CoV-2 Qualitative with individuals without signs and symptoms of COVID-19 was additionally assessed using data collected from the 2020 NFL COVID-19 Occupational Surveillance Testing Program. Samples collected and tested between 8/2020 and 1/2021 were selected for analysis where the candidate test and the comparator test results were evaluable to establish the COVID-19 status for each sample.	Public health surveillance data Validation Microbiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
NFL Surveillance Program (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Study Period:** 8/2020 – 1/2021	**Population:** Anterior nasal swab samples prospectively collected on a near-daily basis from asymptomatic NFL players and staff **Sample Size:** 1,776 samples	**Type:** Comparator algorithm **Population:** Comparator test results and/or clinical adjudication performed within the NFL testing program	**Validation Study Endpoint(s):** SARS-CoV-2 detection

Study Design	Population	Comparator	Key Endpoints
Test Us at Home Study (Non-RWE) **Study Design:** Prospective Cohort Study (Single-Arm) Validation Study **Follow-up/Duration:** 15 days **Study Period:** 10/2021 – 4/2022	**Population:** Anterior nasal swab samples that were prospectively collected every 48 hours from each asymptomatic participant **Sample Size:** 38,192 samples	**Type:** Comparator algorithm **Population:** 2 consecutive test results (molecular test) over 48 hours used to determine comparator result	**Validation Study Endpoint(s):** SARS-CoV-2 detection

Example 72. 510(k) – Clearance of an In Vitro Diagnostic Test Using International Biobank Data [169, 170]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K241220 1/24/2025	Tina-quant Lipoprotein(a) Gen.2 Molarity	Roche Diagnostics Operations	Clinically annotated biobanks UK Biobank	**Premarket:** UK Biobank Study data was a primary source of clinical evidence for the labeling of this 510(k) for a new device. The UK Biobank Study assessed the association between Lp(a) levels and atherosclerotic cardiovascular disease (ASCVD) and provided clinical evidence to support labeling, using data from a large observational cohort of approximately 460,000 adults in the United Kingdom drawn from a clinically annotated biobank with linkage to hospital records and other longitudinal data.	RWE as a primary source of clinical evidence Biobank data Outside-the-US Clinical Chemistry

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
UK Biobank Study (RWE) **Study Design:** Prospective Cohort Study **Follow-up/Duration:** Median follow-up of 11.2 years **Study Period:** Patients enrolled 2006 – 2010	**Population:** Patients (40–69 years old) with Lp(a) concentrations measured at baseline **Sample Size:** 460,506 patients **Number of Sites:** OUS sites (United Kingdom; number unspecified)	Not applicable for this study	**Primary Effectiveness Endpoint(s):** Incident ASCVD, defined as a composite of coronary artery disease and ischemic stroke

Example 73. 510(k) – Clearance of an In Vitro Diagnostic Test Using Medical Records [171]

Submission Number Authorization Date	Device	Sponsor	RWD Source(s)	RWE Use Summary	Key Tags
K250768 6/10/2025	Elecsys Anti-SARS-CoV-2	Roche Diagnostics	Medical records (EHR, EMR, or chart review)	**Premarket:** Medical record data was a supplementary source of clinical evidence for the clearance of this 510(k) for a new device. The primary clinical evidence included a traditional clinical study that assessed the negative percent agreement (NPA) and the positive percent agreement (PPA) of the immunoassay using 9,007 pre-pandemic specimens and 288 specimens (of which 254 tested positive) collected ≥15 days post-symptoms onset, respectively. The clinical evidence additionally included medical record and laboratory data that further confirmed the PPA of the immunoassay.	Medical records (EHR, EMR, or chart review) Validation Microbiology

Premarket Clinical Evidence

Study Design	Population	Comparator	Key Endpoints
Medical Record Study (RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Study Period:** 3/2020 – 3/2021	**Population:** Samples from non-immunocompromised, non-vaccinated subjects with a positive SARS-CoV-2 RT-PCR that were also tested with the Elecsys Anti-SARS-CoV-2 assay (which was being used on the U.S. market under an Emergency Use Authorization (EUA): EUA 200514) **Sample Size:** 285 samples **Number of Sites:** 1 U.S. site	**Type:** Confirmatory test results **Population:** SARS-CoV-2 RT-PCR results for the same samples **Sample Size:** 285 samples **Number of Sites:** 1 U.S. site	**Validation Study Endpoint(s):** PPA of anti-SARS-CoV-2 assay against positive RT-PCR results in non-immunocompromised patient samples collected ≥15 days post-symptoms onset

Study Design	Population	Comparator	Key Endpoints
Traditional Clinical Study (Non-RWE) **Study Design:** Retrospective Cohort Study (Single-Arm) Validation Study **Study Period:** NPA specimens: Prior to 12/2019 PPA specimens: 4/2020 – 12/2020	**Population:** NPA analyses: Presumed anti-SARS-CoV-2 negative samples collected prior to the COVID-19 pandemic PPA analyses: Samples collected from individuals with history of SARS-CoV-2 infection confirmed by prior SARS CoV-2 positive test result using FDA-authorized RT-PCR test **Sample Size:** NPA: 9,007 specimens PPA: 254 specimens **Number of Sites:** U.S. and OUS sites (Germany; number unspecified)	**Type:** Confirmatory test results **Population:** NPA analyses: None (all specimens presumed negative) PPA analyses: Three Anti-SARS-CoV-2 serology assays (the predicate and 2 EUA Anti-SARS-CoV-2 serology assays) **Sample Size:** PPA: 254 specimens	**Validation Study Endpoint(s):** NPA of anti-SARS-CoV-2 assay in samples collected pre-pandemic; PPA of anti-SARS-CoV-2 assay in samples collected ≥15 days post-symptoms onset

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