U.S. FOOD & DRUG ADMINISTRATION

# Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions

Selected examples with file summaries, details on real-world data source, populations, and descriptions of use

Center for Devices and Radiological Health

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## Executive Summary

Real-world data (RWD) can be collected from a diverse array of sources, such as electronic health records, registries, administrative claims, pharmacy data and feedback from wearables and mobile technology. These data offer opportunities to generate evidence and better understand clinical outcomes. In support of the U.S. FDA's Center for Devices and Radiological Health (CDRH) 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 real-world evidence (RWE) to support regulatory decision-making. To further this goal, by developing a more complete understanding of RWE usage, CDRH has reviewed a sample of past decisions to identify examples leveraging RWE in premarket and postmarket decisions. We selected a set of 90 examples of submissions that illustrate the broad spectrum of RWE usage in support of regulatory decision-making from fiscal years 2012 through 2019.

The 90 examples come from the full continuum of clinical and device areas throughout all seven Offices of Health Technology in CDRH and across the medical device total product life cycle. These examples represent:

- 18 premarket notification (510(k)) submissions
- 14 De Novo classification requests
- two humanitarian device exemptions (HDE) applications
- 20 premarket approval (PMA) original applications
- 37 PMA panel track supplements.

This report is organized into six sections separated by device type (therapeutic devices, in vitro diagnostics) and RWD source (Registries, Administrative Claims Data, Medical Records, Other Sources).

The examples demonstrate a diversity in the usage of RWE, where:

- RWE served as the primary source of clinical evidence in submissions for new devices and expanded indications for currently marketed devices
- Prospective, randomized trials were nested within RWD sources
- Control arms and objective performance goals were generated for evaluating performance of the next generation of devices
- Registry infrastructure addressed important premarket and postmarket needs
- Diverse RWD sources were, at times, combined to generate RWE

This report also includes examples from areas where innovative device technologies are being developed.

- Three examples of digital health devices are included, demonstrating the validation of software as a medical device product using RWD.
- Two examples utilize patient-generated data and nine examples leverage device-generated data for both premarket and postmarket requirements.

Finally, four studies leveraged RWD sources to abstract radiographic imaging data to address endpoints, and one example is included for a peripheral vasculature imaging device that utilized a clinical trial embedded in a national registry, with enrollment, randomization, and data collection conducted through the registry platform to support a premarket decision.

CDRH strongly encourages the continued and expanded use of RWE to provide new insights into the performance and clinical outcomes associated with medical device use over the total product lifecycle. Manufacturers planning to seek marketing authorization for devices are encouraged to consider RWE

early on and communicate with FDA, as needed, to understand how to best utilize the RWE to support the marketing claims. Successful applications of RWE are most often achieved when principles of relevance and reliability are considered, as detailed in our guidance on **Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices.** We are actively engaged with the medical device stakeholder community to address challenges and advance the science of RWE generation, through the establishment of the National Evaluation System for health Technology, or NEST, which is integrating data from clinical registries, electronic health records, and medical billing claims to gather more comprehensive evidence of medical device safety and effectiveness while seeking to reduce the time and cost of RWE generation.

## Introduction

The FDA currently defines real-world data (RWD) as the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can be derived from a variety of different sources, including electronic health records (EHRs), claims and administrative data, data from product and disease registries, patient-generated data, and device-generated data. Real-world evidence (RWE) is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

RWD on patients' experiences with medical devices are regularly collected for non-regulatory purposes during routine care and treatment. FDA recognizes that this resulting wealth of RWD can be leveraged to deliver further understanding of the performance, clinical outcomes, and benefit-risk profiles related to medical device use and to reduce the resources required to generate the necessary clinical evidence to support medical device submissions and fulfill postmarket surveillance requirements. If RWD are reliable and relevant to the regulatory question at hand, they may be considered valid scientific evidence supporting both premarket and postmarket regulatory decisions made by the FDA. To foster the use of RWE in device submissions, FDA issued the guidance document *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* in 2017 to explain how FDA assesses RWD to determine if they are sufficient for generating RWE that can be utilized in support of the FDA's regulatory decision-making.

In continued support of its goal to increase both access to and use of RWE to support regulatory decision-making, CDRH has undertaken a retrospective review of past decisions to catalog and better understand examples of the use of RWE to support regulatory decisions. This review covered submissions with final decision dates from fiscal years 2012 through 2019, and initially encompassed De Novo Requests, original PMA applications and panel-track supplements, humanitarian device exemption applications, post-approval studies, and 522 postmarket surveillance studies. Beginning in 2018, 510(k) clearances were included in our retrospective review, while post-approval studies and 522 postmarket surveillance studies were omitted.

In our retrospective review, all submissions with final decisions in the date range, fiscal years 2012 through 2019, were selected for triage, although only those 510(k) submissions that included a clinical review were selected. The submissions were triaged to identify those in which the sponsor submitted RWD, with a more detailed review conducted of those submissions in which the RWD was considered important in supporting the final regulatory decision. The submissions identified from that review are included in this report. This effort resulted in a total of 90 examples of RWE used to support the final premarket or postmarket regulatory decision. These examples also demonstrate that the number of submissions and variety of device types supported by RWE have increased over time. The examples included in this report are not inclusive of all submissions or regulatory decisions that used RWE, but is

intended to provide a small sample that can showcase the various uses of RWE as valid scientific evidence.

These examples represent 18 premarket notification (510(k)) submissions, 14 De Novo classification requests, two humanitarian device exemption (HDE) applications, 20 PMA original applications, and 37 PMA panel track supplements, and include one continued access program. These examples come from the full continuum of clinical and device areas throughout all seven Offices of Health Technology (OHT) in CDRH and represent only a subset of regulatory submissions that utilize RWD. These examples represent a diversity in usage of RWD. In many examples, registry infrastructure addressed important premarket and postmarket needs. Among the examples in which RWE served as the primary source of clinical evidence for new devices or expanded indications for currently marketed devices, there are instances where prospective, randomized trials were nested within RWD sources. In still other examples control arms were comprised of RWD. In at least one instance, RWD was used to generate objective performance goals for evaluating the performance of the next generation of devices. And in some examples, diverse RWD sources were, at times, combined to generate RWE.

## Section I. Examples of Registries as a Source of Real-World Evidence

These examples use registries as the source of RWE. This section is divided into national and international registries and study sponsor registries.

### Subsection IA. Examples Leveraging National or International Registries for Real-World Data Collection

National registries can be leveraged as sources of clinical evidence, including in support of 510(k) submissions. An example is for a scalp cooling system (K173032) which used clinical evidence from the Dutch Scalp Cooling Registry, as well as for robotic surgical systems (K173585) which utilized data from the American Hernia Society Quality Collaborative Study. Additionally, for a large vessel occlusion catheter (K170411), data from the American Association for the Surgery of Trauma AORTA Registry were leveraged as the primary source of clinical evidence to support modification to the indication for use statement. Another example pertains to an ultrasonic pulsed echo imaging system (K173860) for an indication expansion to include use in the coronary arteries and vessels of the peripheral vasculature. The clinical data submitted to support this indication expansion was derived from a clinical study embedded in a national registry, the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Enrollment, randomization, and collection of standard-of-care patient data were all performed through the registry at 31 coronary intervention centers in the SCAAR network. Clinical evidence from this study supported a determination of substantial equivalence, exemplifying the use of a source of RWE as a platform for performing multiple phases of a clinical trial. In all these examples, information from several countries' national registries was leveraged to support modifications to the indications for use statements.

CDRH also continues to use RWE from national registries to meet post-approval requirements, including for an indication expansion for a portable normothermic perfusion system for donor lungs (P160013/S002). The United Network for Organ Sharing (UNOS) Registry was leveraged to perform two post-approval studies for the device, and match-run data from the UNOS Registry were additionally used to support premarket approval. In another example, for an indication expansion of a DCB percutaneous transluminal angioplasty catheter (P140010/S015), SVS VQI Registry data were used as control data for a standard-of-care cohort to compare to sponsor registry data using a propensity-score adjusted analysis based on 20 pre-specified variables, and SVS VQI Registry data were additionally utilized for condition-of-approval postmarket surveillance of patients up to 3 years. To support a conversion of HDE to PMA for a pediatric ventricular assist device (P160035), national registry data from the Extracorporeal Life

Support Organization Registry were leveraged as a historical control that was propensity-score matched to the HDE IDE trial population, and also included RWE from post-HDE approval patients. Condition-of-approval postmarket surveillance was conducted through an all-comers surveillance registry with a follow-up of five years.

## Subsection IB. Examples Leveraging Sponsor Registries for Real-World Data Collection

Sponsor or manufacturer registries represent another commonly utilized source of RWE. Included in this report are 19 examples of sponsor registries utilized as a source of premarket and postmarket clinical evidence. For a modification of the indications for use for a neurological stereotaxic instrument (K171257), registry data on patients treated with the device in standard practice served as the primary source of clinical evidence supporting a decision of substantial equivalence. Sponsor registry data were leveraged as both the primary source of clinical evidence supporting the approval of a total ankle replacement system (P160036) and as a source for deriving performance goals for the condition-of-approval postmarket study. For a modification of the indications for use for a vascular hemostasis device (P960043/S097), the sponsor's registry tracked patients who were treated with the subject device as part of a continued access study after the conclusion of the previous randomized controlled trial of the device. Data from this registry were the sole source of clinical evidence supporting approval of the supplement seeking an indication expansion. Additionally, for two coronary drug-eluting stents (P160043/S012 and P110013/S088), two bundled modifications of indications for use were submitted. Data from the sponsor's international registry were used to create a sub-cohort for analysis of the subject devices and served as a secondary source of clinical evidence supporting approval.

## Section II. Examples Leveraging Administrative Claims Data for Real-World Data Collection

In Section II, there are two examples of submissions leveraging administrative claims data as RWE. For a pediatric contact lens (P180035), in order to fulfill the condition-of-approval, a post-approval study was required to evaluate the rate of microbial keratitis (MK) against a performance goal. Due to the low-prevalence of MK, this type of endpoint would be difficult to assess in a traditional clinical trial. Instead, FDA is working with the sponsor on a novel approach that will nest a cohort post-approval study into an integrated health care and coverage organization. Outcomes of interest will be extracted from electronic health records and claims data. For an indication expansion of a multifocal intraocular lens (P040020/S049), the post-approval study will utilize Medicare Beneficiary Encrypted Files as part of a retrospective study of all cataract surgeries in the Medicare population from 2011 to 2013, comprising approximately 180,000 surgeries, in order to estimate the background rate of post-surgical intraocular inflammation to compare to the subject device.

## Section III. Examples Leveraging Both National Registries and Administrative Claims Data for Real-World Data Collection

Included in this section are 12 examples that leverage a combination of national registries and administrative claims data. All but one of these examples leverage the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STC/ACC TVT) Registry with linkage to administrative claims data in CMS claims database to monitor long-term outcomes through five years after implantation of the subject devices. Two examples of transcatheter heart valves (P140031/S028 and P130009/S034) utilized STS/ACC TVT Registry data for both condition-of-approval postmarket surveillance and clinical evidence supporting approval of the indication expansions sought in both devices through PMA supplements. The transcatheter heart valve in P140031/S028 additionally relied on STS/ACC TVT Registry data as the sole source of clinical evidence in supporting expansion to include aortic and mitral valve-in-valve replacement. Finally, for an implantable cardioverter-defibrillator

(P110042/S077), the condition-of-approval (CoA) postmarket surveillance study utilized multiple RWE sources to monitor the long-term performance of the subject device. The study leveraged existing national registry data from the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) ICD Registry, remote-monitoring of device-generated data, public and private payer claims data from CMS and Truven MarketScan databases, and the National Death Index.

## Section IV. Examples Utilizing Medical Records as Real-World Evidence

CDRH continues to review and make regulatory decisions on all types of submissions that use medical records as the primary or secondary source of clinical evidence. Medical records may serve as the primary source of clinical evidence for new submissions, as for a new version of a percutaneous catheter (K180986) which was supported solely by a retrospective medical record review of patients treated OUS, and for a new robotically assisted surgical device (K171120) to be cleared based on a retrospective analysis of medical records.

Utilizing medical records as a primary source of clinical evidence is common in submissions seeking an indication expansion. Other submissions illustrate use of RWE to support modifications to the indications for use statements for legally marketed devices. In most cases these modifications include use to treat a new disease or use in a new patient population or anatomic location. These submissions often incorporate systematic reviews or meta-analyses of existing literature to develop comparators or provide context for the real-world performance of the subject device. One example is for an indication expansion of a drug-eluting peripheral catheter (P140010/S037) to include treatment of longer lesions, primarily supported by a retrospective analysis of medical records from the sponsor's database. Another example is for a modified indications for use statement for a hemodialysis catheter end cap (K180111), which FDA has cleared to include information related to the reduction of bloodstream infections. The sponsor performed a cluster-randomized clinical trial in 40 dialysis centers across the U.S. to compare the subject device and a comparator device using data abstracted from electronic health records (EHRs). Both devices were legally marketed, and dialysis centers were randomized to use one or the other device. Patients were treated according to the local standard of care, which includes routine blood culture specimen collection for blood infection surveillance and reporting to the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN). Blood culture specimens were analyzed by a central laboratory and the results were then entered into the patient's EHR and into NHSN Dialysis Event forms for routine surveillance reporting. Data were then abstracted from the EHR and from the NHSN forms for the purposes of the study.

## Section V. Examples Utilizing Other Sources of Real-World Evidence

Section V is comprised of examples of other sources of RWE. Included in this section are PMAs submitted in response to a classification order requiring premarket approval of automated external defibrillators (AEDs). In these three examples for AEDs (P160012, P160032, and P160033), the subject devices had been marketed in the U.S. for over 10 years, and the submissions drew on postmarket device-generated data on out-of-hospital use in order to support their approvals. In P160012, when EMS were called to an out-of-hospital cardiac arrest, study data collectors traveled to the scene, interviewed witnesses, recorded data on the circumstances of the cardiac arrest, and collected data recorded by the AEDs.

Real-world evidence is also starting to be used to support regulatory decision-making for digital health technologies. One example is for a software platform that computes a Rothman Index score from data extracted from patients' electronic medical records (K172959). These RWD were used for development and validation of the device, as well as for comparing performance of the Rothman Index to the predicate patient status index when both were calculated from hospitals' electronic medical record systems. Another example is a De Novo classification request for a radiological computer-assisted triage and

notification software (DEN170073) that analyzes CT angiogram images and notifies a specialist when a large vessel occlusion has been identified for further image review. To support this submission, the sponsor performed standalone performance testing which evaluated the performance of the software against ground truth. The sponsor also performed a secondary analysis which compared the notification time of the device against a standard-of-care notification time extracted from corresponding standard-of-care radiologist reports. For a De Novo classification request for a mobile software application for contraception (DEN170052), the sponsor supported their submission by analyzing outside the U.S. (OUS) data from more than 15,000 women who had used the mobile application. RWE from this analysis was a primary source of clinical evidence for the submission.

## Additional Consideration: Use of Real-World Evidence from Pediatric Populations

This section examines the benefits of the use of RWE for pediatric patients, a population that has historically been difficult to study in traditional clinical trials. From the sections organized by data source above, examples have been selected in which RWE from pediatric patients was used to support modifying device labeling to explicitly include use in pediatric populations. While these submissions may also include extrapolation from adult data, the real-world pediatric use information was vital to support the regulatory decision by assessing the totality of available data. In the submissions for AEDs (P160032 and P160012) mentioned previously in Section VI, the sponsors utilized RWE from postmarket observational studies of their device modifications for pediatric patients to support approval. Another example, regarding a high velocity nasal insufflation device (DEN170001), illustrates how RWD from a pediatric population can be used to provide supplementary clinical evidence to augment a prospective randomized trial performed for the adult population. In addition to the adult trial, the sponsor utilized published literature studies for the neonate population, including a retrospective cohort study of pulmonary outcome data extracted from medical records in the Vermont Oxford Network database. Moreover, FDA approved a vertebral body tethering system (HDE H190005) using clinical data collected from pediatric subjects implanted with a similar device approved for use in adult patients. The pediatric subjects were retrospectively identified from medical records, and then prospectively enrolled in a clinical study to collect the long-term follow-up data that were used to support the HDE decision. A second pediatric scoliosis device approved via HDE, H170001, used RWD from commercial use of the device OUS. Long-term safety and probable benefit of this device will be assessed in post-approval study that utilizes a U.S. registry.

Another example is for a pediatric contact lens (P180035) mentioned in Section III. The sponsor performed a randomized controlled trial to support the effectiveness endpoint and was also required to demonstrate that the rate of Microbial Keratitis (MK) is no higher than 0.4% per patient-year, since the risk has not been well characterized previously for children due to the lower level of contact lens use. To address this concern, the sponsor conducted a retrospective study investigating RWD from soft contact lens use among children by analyzing the medical records of 782 pediatric patients wearing commercially available soft contact lens from seven U.S. community clinics. Also, as mentioned previously, a post-approval study was required to collect long-term safety and effectiveness data, including the rate of MK assessed against a performance goal. The study will be conducted within integrated eyecare practices or healthcare and coverage organization systems, with outcome data collected via health records and administrative claims.

## Section VI. Examples of Real-World Evidence Use for In Vitro Diagnostics

In addition to therapeutic devices, CDRH also reviews and makes regulatory decisions on submissions for IVDs. IVDs represent a technological area that warrants specific attention, as there are clinical, logistical, and technological characteristics that are unique to IVDs as compared to therapeutic devices. This report includes eight examples of use of RWE in regulatory decisions for IVDs, including six premarket

decisions, one postmarket decision, and one example involving both premarket and postmarket use of RWE that spans the "total product life cycle" (TPLC). These examples include RWE from the sources described above, including medical records, published literature, and sponsor database data. One particularly innovative example included in this report is a newborn screening IVD utilizing dried blood specimens (DEN150035). The pivotal trial for the device was embedded in the Missouri State Public Health Laboratory's routine screening program and evaluated the device performance on all samples submitted to this state laboratory. The Missouri Department of Health and Senior Services' active surveillance program was also utilized to track reports of false negatives. This study served as the sole source of clinical evidence supporting the regulatory decision to grant the De Novo classification request. Another example is a De Novo classification request for a next generation sequencing-based tumor profiling test (DEN170058). Clinical data for this submission came from an electronic medical record database of advanced cancer patients with associated pathological and clinical data generated as part of routine workflow at Memorial Sloan Kettering Cancer Center. A retrospective analysis of the electronic medical records provided evidence to support a pan-cancer claim, to validate a test cut-off, and to provide data on somatic mutation prevalence. The original PMA submission for an IVD to assess risk of spontaneous preterm delivery by testing cervicovaginal secretions (P160052) is a total-product lifecycle example with patients' medical records serving as the primary source of clinical evidence for both the premarket approval and post-approval study. The sponsor submitted an observational clinical study of patients tested with the subject device for premarket clinical evidence and as a condition-of-approval, and the sponsor will collect postmarket clinical evidence by conducting a confirmatory study in a larger population of patients tested with the subject device. These examples demonstrate how RWD sources can be leveraged to support clinical research and generate evidence for marketing submissions for IVDs, and further examples can be found in **Appendix Section I.**

## Key Tag Definitions

The tag definitions below are used for all examples:

1. **Administrative claims data** – Example includes (or will use) data from administrative claims.
2. **Device-generated data** – Example includes (or will use) real-world data from the device during commercial use.
3. **Digital Health example** – Example is for a digital health device.
4. **Medical records (EHR, EMR, or chart review)** – Example includes (or will use) data from medical records (includes electronic health records, electronical medical records, and medical chart reviews).
5. **Next-generation sequencing** – Example is a next-generation sequencing device.
6. **Outside-the-US** – Example includes RWE from outside the U.S.
7. **Patient-generated or patient-entered data** – Example includes patient-generated or patient-entered RWD, such as through a mobile application.
8. **Pediatric RWE** – Example includes RWE from a pediatric population.

9. **Performance goal or comparator derived from RWE** – Example includes a performance goal or comparator derived from real-world evidence.
10. **Registry data** – Example includes (or will use) registry data.
11. **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.
12. **Total-Product Lifecycle Example** – Example includes RWE for both premarket decision-making and to support a post-approval study.

# Appendix Section I. Examples of Registries as a Source of Real-World Evidence

## Subsection A. Examples Leveraging National Registries for Real-World Data Collection

## Guide to Examples Leveraging National Registries for Real-World Data Collection

| | File (510k Summary at fda.gov) | Sponsor | Device | Real-World Data (RWD) Source(s) | RWE Use | Key Tags |
|---|---|---|---|---|---|---|
| **1** | K170411 | Prytime Medical Devices, Inc. | ER-REBOA Catheter | American Association for the Surgery of Trauma (AAST) Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) Registry | **Premarket:** RWE was a primary source of clinical evidence supporting modifications to the labeling and to modify the indications for use statement to add a specific indication, "patients requiring emergency control of hemorrhage," to the general indications for use. | Registry data;<br>RWE as a primary source of clinical evidence; |
| **2** | K173032 | Paxman Coolers Limited | Paxman Scalp Cooler | Dutch Scalp Cooling Registry (OUS) | **Premarket:** RWE was a primary source of clinical evidence for this 510(k) to expand the indication of the subject device to include all cancer patients with solid tumors, with data from patients in the Dutch Scalp Cooling Registry supporting a decision of substantial equivalence. | Outside-the-US;<br>Registry data;<br>RWE as a primary source of clinical evidence; |
| **3** | K173585 | Intuitive Surgical, Inc. | da Vinci Xi Surgical System (Model IS4000), da Vinci X Surgical System (Model IS4200) | Americas Hernia Society Quality Collaborative (AHSQC) Registry | **Premarket:** RWE was the primary source of clinical data supporting modifications to the indications for use statement to include adding "Ventral Hernia Repair" under the cleared "general laparoscopic surgical procedures." | Registry data;<br>RWE as a primary source of clinical evidence; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **4** | K173860 | Volcano Corporation | s5/s5i/CORE/ CORE Mobile Precision Guided Therapy System | OUS randomized trial embedded in national registries (Swedish Coronary Angiography and Angioplasty Registry) | **Premarket:** For this 510(k) submitted to modify the subject device's indication, the sponsor submitted clinical evidence from three studies, including a randomized controlled trial embedded in an OUS national registry. | Outside-the-US;<br>Registry data;<br>RWE as a primary source of clinical evidence; |
| **5** | H170001 | ApiFix, Ltd. | Minimally Invasive Deformity Correction (MID-C) System | Outside-the-US commercial use<br><br>Postmarket registry | **Premarket:** OUS commercial use provided the majority of clinical use cases for this submission. The RWE was used in combination with other clinical data from OUS studies.<br><br>**Postmarket:** The sponsor has agreed to perform a post-approval study (PAS) that will use registry-based data collection. | Outside-the-US;<br>Pediatric RWE;<br>Registry data;<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |
| **6** | P160035 | Berlin Heart Inc. | EXCOR Pediatric Ventricular Assist Device | Real-world data from non-study patients, ELSO Registry, postmarket registry | **Premarket:** In this conversion of an HDE to a PMA, national registry data from the Extracorporeal Life Support Organization (ELSO) Registry was leveraged as a historical control that was propensity-score matched to the HDE trial population. RWE also served as a source of supplemental clinical evidence in the form of post-HDE patient data.<br><br>**Postmarket:** As a condition-of-approval, postmarket surveillance will be conducted through an all-comers registry for five years. | Pediatric RWE;<br>Registry data;<br>Total-Product Lifecycle Example; |

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|---|---|---|---|---|---|---|
| **7** | P100047 | Medtronic, Inc. | HeartWare | INTERMACS Registry | **Premarket:** For this PMA, RWE from the INTERMACS Registry was utilized as a contemporaneous control for the sponsor's clinical trial data.<br><br>**Postmarket:** The INTERMACS Registry will be leveraged to compare outcomes through two years between patients receiving the subject device and other LVADs. | Registry data;<br>Total-Product Lifecycle Example; |
| **8** | P150036 | Edwards Lifesciences, LLC | INTUITY Elite Valve | STS Adult Cardiac Surgery Database | **Premarket:** For this PMA, data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) on mean aortic cross-clamp and cardiopulmonary bypass surgical times was leveraged as a comparison metric against data from the sponsor's clinical trial. | Registry data; |
| **9** | P180001 | William Cook Europe ApS | Zenith Dissection Endovascular System | Society for Vascular Surgery Vascular Quality Initiative (VQI) Registry | **Postmarket:** As a condition-of-approval for this PMA original application, the postmarket surveillance study will utilize the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry. | Registry data; |
| **10** | P160013/S002 | TransMedics, Inc | Organ Care System (OCS) Lung System | United Network for Organ Sharing (UNOS) Registry<br><br>Sponsor Registry (Postmarket only) | **Premarket:** To support this PMA supplement for modifying the indications for use, the sponsor provided supplemental, match-run data from the United Network for Organ Sharing (UNOS) database.<br><br>**Postmarket:** The sponsor will conduct two post-approval studies as a condition of approval, one that follows current clinical trial patients for five years utilizing the UNOS database, and one that collects postmarket data in all-comers registry with some data collected from the UNOS registry. | Registry data;<br>Total-Product Lifecycle Example; |

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|---|---|---|---|---|---|---|
| **11** | P070026/S004 | DePuy Orthopaedics | DePuy Ceramax Ceramic Total Hip System | UK National Joint Registry, Australian NJRR | **Postmarket:** As a condition-of-approval, OUS data from the UK National Joint Registry and Australia Orthopaedic Association National Joint Replacement Registry will be collected and analyzed for device survivorship, revision, and death rates. | Outside-the-US;<br>Registry data; |
| **12** | P970003/S207 | Cyberonics, Inc. (LivaNova) | VNS Therapy System | OUS Postmarket surveillance registry | **Premarket:** For this indication expansion, the primary source of clinical evidence was RWE from a postmarket study in Japan conducted through the Japan VNS Registry, a national registry launched by three Japanese professional societies for this study. The sponsor also submitted adverse event data from their postmarket surveillance database. | Outside-the-US;<br>Registry data;<br>RWE as a primary source of clinical evidence; |
| **13** | P070015/S128<br>P110019/S075 | Abbott Vascular | XIENCE Family of Everolimus Eluting Coronary Stents | ACC CathPCI Registry | **Premarket:** A primary source of clinical evidence submitted for these PMA supplements for an indication expansion of drug-eluting coronary stents was data from the American College of Cardiology (ACC) CathPCI Registry that was included in the sponsor's Bayesian Hierarchical analysis. | Registry data;<br>RWE as a primary source of clinical evidence; |
| **14** | P140010/S015 | Medtronic Vascular | IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter | SVS Vascular Quality Initiative (VQI) Registry | **Premarket:** For this indication expansion, data from the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry were utilized as a control for standard-of-care percutaneous, transluminal angioplasty for a superiority analysis of the sponsor's clinical trial data.<br><br>**Postmarket:** For postmarket surveillance, the sponsor is required to follow sequential patients from the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry for 36 months post-procedure. | Registry data;<br>Total-Product Lifecycle Example; |

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|---|---|---|---|---|---|---|
| **15** | P070014/S037 | Bard Peripheral Vascular, Inc. | LifeStent Vascular Stent System | Society for Vascular Surgery Vascular Quality Initiative (VQI) Registry | **Postmarket:** As a condition-of-approval, postmarket surveillance of sequential patients for two years will be conducted through the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI). | Registry data; |
| **16** | P040043/S051 | W.L. Gore & Associates, Inc. (Gore) | GORE TAG Thoracic Endoprosthesis | Society for Vascular Surgery Vascular Quality Initiative (VQI) Registry | **Postmarket:** For this PMA supplement, postmarket surveillance through the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry for up to five years was required as a condition of approval. | Registry data; |
| **17** | P100040/S012 | Medtronic Vascular | Valiant Thoracic Stent Graft with Captivia Delivery System | Society for Vascular Surgery Vascular Quality Initiative (VQI) Registry | **Postmarket:** As a condition-of-approval, the sponsor for this PMA supplement will conduct short-term and long-term performance data through the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI). | Registry data; |
| **18** | P010031/S232 | Medtronic, Inc. Cardiac Rhythm Disease Management | CONCERTO/CONCERTO II; CONSULTA; MAXIMO II; AND PROTECTA/PROTECTA XT | ACC National Cardiovascular Data Registry ICD Registry<br><br>National Death Index Sponsor Registry | **Postmarket:** For this implantable cardioverter defibrillator, two post-approval studies were required. One follows patients implanted with the subject device enrolled in the American College of Cardiology NCDR ICD Registry, with long-term mortality data collected through the National Death Index. The second will utilize a sponsor registry to collect additional data on survival probability of freedom from adjudicated heart failure events or all-cause death. | Registry data; |

## Example 1. 510(k) - Modification to Indications for Use Statement for a Large Vessel Occlusion Catheter Using the American Association for the Surgery of Trauma AORTA Registry [1, 2]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K170411 | Prytime Medical Devices, Inc. | ER-REBOA Catheter | The ER-REBOA Catheter is intended for temporary occlusion of large vessels and blood pressure monitoring including patients requiring emergency control of hemorrhage. | American Association for the Surgery of Trauma (AAST) Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) registry<br><br>Case series | **Premarket:** Primary source of clinical evidence |

### Premarket Use – American Association for the Surgery of Trauma AORTA Registry and Case Series

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **AORTA Registry (RWE):** Patients treated with the ER-REBOA catheter for management of emergency hemorrhage.<br><br>**Case Series (RWE):** Additional patients managed with the ER-REBOA catheter in a military setting (published literature). | **Safety and Effectiveness:**<br>Aorta occlusion success<br>Use of medical imaging in device placement |

**Narrative:**

The sponsor submitted this 510(k) to make modifications to the labeling and to modify the indications for use statement to add a specific indication to the general indications for use. To support the labeling changes and the addition of "including patients requiring emergency control of hemorrhage," the sponsor provided clinical evidence from the American Association for the Surgery of Trauma (AAST) Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) registry and a case series. The AORTA registry was established by the AAST to collect observational data on patients treated with aortic occlusion in accordance to local standard of care. In this example, critically-injured patients needing emergency-hemorrhage control---who were treated with the device---were identified in the registry. Data on successful aortic occlusion with and without imaging placement were analyzed from the registry. These data along with additional case reports served as the primary source of clinical evidence for this 510(k).

## Example 2. 510(k) - Modification to Indications for Use Statement for a Scalp Cooling System using Real-world Evidence from an OUS Registry [3, 4, 5, 6]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K173032 | Paxman Coolers Limited | Paxman Scalp Cooler | The Paxman Scalp Cooler is indicated to reduce the likelihood of chemotherapy-induced alopecia (CIA) in cancer patients with solid tumors. | **Premarket:** Registry | **Premarket:** Primary source of clinical evidence |

### Premarket Use – OUS Registry Study

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Dutch Scalp Cooling Registry (RWE):** 1411 cancer patients with multiple cancer types and various chemotherapy regimens<br><br>**Paxman Coolers Limited SCALP Study (Non-RWE):** 182 women with breast cancer requiring chemotherapy<br><br>**Peer-reviewed Literature with Studies Conducted Using RWD Sources:** 15 published studies including 6 retrospective studies (data from some studies is included in the Dutch Scalp Cooling Registry study above)<br>See 510(k) Letter and Summary for additional details. | **Efficacy:**<br>Hair preservation after the fourth cycle of chemotherapy (measured as <50% not requiring use of wig or head covering)<br>European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 score<br>Hospital Anxiety and Depression Scale score<br>Body Image Scale summary scale<br>Alopecia occurrence<br><br>**Safety:**<br>Scalp metastases<br>Device-related adverse events |

**Narrative:**

For this 510(k), RWE from a registry study in the Netherlands, the Dutch Scalp Cooling Registry, was used as the primary source of clinical evidence. For this study, patients were enrolled from multiple sites in the Netherlands, with nurses recording patient data including chemotherapy history, hair characteristics, and whether they wore a head cover. These data along with a literature review and a small randomized clinical trial conducted in the US were used to support a substantial equivalence determination.

## Example 3. 510(k) - Modification to Indications for Use Statement for Da Vinci Surgical Systems Using the Americas Hernia Society Quality Collaborative (AHSQC) Registry [7]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K173585 | Intuitive Surgical, Inc. | da Vinci Xi Surgical System (Model IS4000), da Vinci X Surgical System (Model IS4200) | da Vinci Xi Surgical System<br>The Intuitive Surgical Endoscopic Instrument Control System (da Vinci Xi Surgical System, Model: IS4000) is intended to assist in the accurate control of Intuitive Surgical Endoscopic Instruments including rigid endoscopes, blunt and sharp endoscopic dissectors, scissors, scalpels, forceps/pick-ups, needle holders, endoscopic retractors, electrocautery and accessories for endoscopic manipulation of tissue, including grasping, cutting, blunt and sharp dissection, approximation, ligation, electrocautery, suturing, and delivery and placement of microwave and cryogenic ablation probes and accessories, during urologic surgical procedures, general laparoscopic surgical procedures, gynecologic laparoscopic surgical procedures, general thoracoscopic surgical procedures and thoracoscopically-assisted cardiotomy procedures. The system can also be employed with adjunctive mediastinotomy to perform coronary anastomosis during cardiac revascularization. The system is indicated for adult and pediatric use. It is intended to be used by trained physicians in an operating room environment in accordance with the representative, specific procedures set forth in the Professional Instructions for Use.<br><br>da Vinci X Surgical System<br>See 510(k) Summary for Full Indications for Use. | Americas Hernia Society Quality Collaborative (AHSQC) Registry | **Premarket:** Primary source of clinical evidence |

### Premarket Use –AHSQC Registry

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **AHSQC Registry (Non-Complex Ventral Hernia Repair Procedures):** Propensity-matched comparison between robotic-assisted, open-surgery, and laparoscopic surgery cohorts<br><br>**AHSQC Registry (Complex Ventral Hernia Repair Procedures):** Propensity-matched comparison between robotic-assisted and | Information from the AHSQC for non-complex and complex robotic-assisted, laparoscopic, and open VHR procedures was used to generate comparisons for the following key measures:<br>• Length of Stay,<br>• Intraoperative Complications,<br>• Transfusions,<br>• Postoperative Complications through 30 days, | Propensity score matching |

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| open-surgery cohorts. Unmatched comparison between robotic-assisted and laparoscopic surgery cohorts. | • Readmission Rates through 30 days,<br>• Re-encounter Rates (in clinic and in Emergency Room) through 30 days,<br>• Reoperation Rates through 30 days,<br>• Recurrence Rates through 30 days, Mortality through 30 days,<br>• Operative Time<br>See 510(k) Summary for additional details and complete list | |

**Narrative:**

This submission sought clearance for a labeling modification to include “Ventral Hernia Repair” (VHR) procedures under the cleared “general laparoscopic surgical procedures” Indication for Use of the da Vinci Xi Surgical System, Model IS4000 and the da Vinci X Surgical System, Model IS4200. In support of this change, the sponsor provided information collected from the AHSQC registry containing propensity matched comparisons of key measures for robotic-assisted, laparoscopic and open procedures

## Example 4. 510(k) - Modification to Indications for Use Statement for Ultrasonic Pulsed Echo Imaging System Supported by Data from an OUS Randomized Trial Embedded in a National Outside the U.S. Registry [8]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K173860 | Volcano Corporation | s5/s5i/CORE/ CORE Mobile Precision Guided Therapy System | The Volcanos5TM/s5i/CORE/CORETM Mobile Precision Guided Therapy System is used for the qualitative and quantitative evaluation of vascular morphology in the coronary arteries and vessels of the peripheral vasculature. It is also indicated as an adjunct to conventional angiographic procedures to provide an image of vessel lumen and wall structures.<br><br>Please see Decision Letter and Summary for Full Indications for Use Statement | Registry Embedded Clinical Trial | **Premarket:** Registry Embedded Clinical Trial submitted in support of the 510(k) submission |

## Premarket Use – Outside-the-US Randomized Trial Embedded in National Registries (e.g. Swedish Coronary Angiography and Angioplasty Registry, SWEDEHEART, Danish National Patient Registry and the Western Denmark Heart Registry)

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome):** 2017 patients with coronary artery disease included in the Swedish Coronary Angiography and Angioplasty Registry from all 30 coronary intervention centers in Sweden and a single site in Iceland | **Primary:** Composite rate of all-cause mortality, non-fatal myocardial infarction, or unplanned revascularization within 12 months after the index procedure<br><br>Please see Summary of Safety and Effectiveness Data for additional details and complete list. | OUS randomized clinical trial was embedded in national registry, with enrollment, randomization, and data collection conducted through the registry platform. |

**Narrative:**

This submission sought clearance to modify the indications for use statement to reflect use of the dichotomous 0.89 intravascular pressure index as a cut-point in guiding revascularization procedures. For the 510(k) submission, the sponsor provided clinical evidence from three clinical studies, including a multicenter observation study, (ADVISE II), a randomized control trial (DEFINE-FLAIR), and a second randomized control trial (iFR-SWEDEHEART) in which outside-the-US national registries were used for patient enrollment, data collection, and follow-up.

The iFR SWEDEHEART trial used registry-based enrollment and randomization, in which patients eligible for the trial (and who had consented) were randomized into one of two arms (Instantaneous Wave-free Ratio versus Fractional Flow Reserve). For this trial, data were entered into Swedish Coronary Angiography and Angioplasty Registry (SCAAR), using an additional module to collect data specific for the trial. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) is a national registry that collects standard-

of-care patient data from 31 coronary intervention centers (all centers (30) in Sweden, 1 in Iceland) for the purposes of quality improvement and benchmarking. For this trial, follow-up data were obtained from national registries (e.g. SWEDEHEART) and healthcare records.

Clinical evidence from these studies were used to support the clearance of this 510(k) submission. This submission is an example illustrating the use of real-world data sources (national registries) as a data collection and clinical trial platform supporting a randomized clinical trial.

For additional details, please see the Decision Letter and Summary and Götberg et al.

## Example 5. HDE - Approval for Spinal Posterior Ratcheting Rod System Using OUS Commercial Data and Sponsor Registry to Satisfy Post-Approval Requirements [10, 11, 12]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| H170001 | ApiFix, Ltd. | Minimally Invasive Deformity Correction (MID-C) System | The MID-C System is indicated for use in patients with adolescent idiopathic scoliosis (AIS) for treatment of single curves classified as Lenke 1 (thoracic major curve) or Lenke 5 (thoracolumbar/lumbar major curve), having a Cobb angle of 45 to 60 degrees which reduces to less than or equal to 30 degrees on lateral side-bending radiographs, and thoracic kyphosis less than 55 degrees as measured from T5 to T12. | OUS commercial use data in the European Union, Singapore, and Israel. | **Premarket:** Primary source of clinical evidence<br><br>**Postmarket:** Post-approval study |

### **Premarket Use –** OUS Commercial Use Data

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **OUS Prospective, Multi-Center, Non-Randomized, Open Label Clinical Study (Non-RWE):** 20 patients with AIS in Hungary, Romania, and Israel<br><br>**OUS Postmarket Clinical s=Studies (Non-RWE):** 26 patients from OUS post-market clinical studies, 9 patients from special access cases in Canada<br><br>**Target Population (RWE):** 25 patients implanted with the HDE Device Version of the MID-C System, as of September 15, 2018, that meet the US Indications for Use.<br><br>**Expanded Target Population (RWE):** 49 patients implanted with the HDE Device Version of the MID-C System, as of September 15, 2018, that meet either the US Indications for Use (N=25) or an Expanded US Indications for Use (N=24) for patients with 40 to 44-degree curves.<br><br>See Summary of Safety and Probably Benefit for additional details regarding inclusion criteria. | **Safety:**<br>Reoperations<br>Adverse events<br><br>**Probable Benefit:**<br>Primary Cobb angle less than or equal to 35 degrees and no curve progression at 24-months compared to baseline following treatment with the device. |

**Narrative:**

This Humanitarian Device Exemption (HDE) was approved for a non-fusion spinal device intended to prevent spinal curve progression in adolescent patients with idiopathic scoliosis. The decision was based on information gathered from use of the device outside-the-US (OUS) from sources that included an open label clinical study as well data from commercial use of the device.

## Postmarket Use – Post-Approval Study Using Sponsor Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| Minimum of 200 patients from 10 US centers with AIS, as assessed by Risser grade, Sanders score, or a combination of the two | **Primary Safety:** Significant adverse events, device or procedure-related adverse events.<br><br>**Primary Probable Benefit:** Maintenance of major Cobb angle less than or equal to 40 degrees at 60 months post-surgery | 5 years |

**Narrative:**

As a condition-of-approval, the sponsor has agreed to perform a post-approval study that **will use an external registry for data collection.**

## Example 6. PMA - Approval and Postmarket Surveillance of a Pediatric Ventricular Assist Device Utilizing National Registry Data [13, 14]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160035 Conversion of HDE to PMA | Berlin Heart Inc. | EXCOR Pediatric Ventricular Assist Device | EXCOR Pediatric Ventricular Assist Device (referred to as EXCOR Pediatric) is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR Pediatric. | Extracorporeal Life Support Organization (ELSO) Registry (Historical ECMO control for HDE IDE Trial)<br><br>Real-world data from all non-study patients post-HDE approval (FDA requested) | **Premarket:** Primary (Control) and Supplemental (FDA-requested data from all non-study patients post-HDE approval)<br><br>**Postmarket:** CoA to conduct postmarket surveillance in a registry |

## Premarket Use – Real-World Data from All Non-Study, Post-HDE Approval Patients and ELSO Registry Data

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **Non-Study Patients Post-HDE (RWE):** Data from all non-study patients, post-HDE approval (245 patients through December 31, 2015). Pooled with data from IDE, compassionate-use and PAS patients.<br><br>**IDE Trial Population (Non-RWE)**: 48 patients treated with the device and divided into two cohorts by body-surface area (BSA), 24 patients each (H100004).<br><br>**ELSO Registry (RWE):** Historical extracorporeal membrane oxygenation (ECMO) control with 48 patients propensity-score matched to each IDE BSA cohort (H100004). | **Pooled Data Set**: Freedom-from-death, competing outcomes, significant adverse events, neurological events, stroke incidence, and mortality.<br><br>**Safety:** The control RWE ELSO cohort was not used for analysis of safety. Serious adverse event rates from the IDE trial were compared to performance goals derived from literature and clinical experience.<br><br>**Effectiveness:** Hazard rates between EXCOR and ELSO ECMO cohorts; survival to successful outcome; survival time; duration of support; competing outcomes | Propensity-score analysis in IDE trial for original HDE approval.<br><br>Propensity-score analysis done based on age, weight, diagnosis, ventilator status, inotrope use, and prior cardiac arrest. |

**Narrative:**

The EXCOR device was previously approved under an HDE (H100004) and provides cardiac support for pediatric patients awaiting cardiac transplantation. This submission was to convert the HDE to a PMA. For the HDE approval, the sponsor conducted an IDE clinical trial to demonstrate device safety and probable benefit. Specifically, the sponsor compared safety endpoints from a population treated with the device and a performance goal. In the IDE trial, the sponsor also compared endpoints between the EXCOR trial population and an historical ECMO control from the ELSO registry, which collects real-world data on extracorporeal life support procedures. For the HDE approval, FDA reviewed data that compared hazard ratios between pediatric patients treated with EXCOR and those treated with ECMO. FDA reviewed analyses of survival to successful outcome or failure as well as competing outcomes vs days-post-implant between the device and ELSO cohorts. These data were incorporated into the PMA submission by reference. For the HDE-to-PMA conversion, FDA also reviewed data from the sponsor's HDE post-approval study. Finally for the HDE-to-PMA conversion, FDA reviewed pooled freedom-from-death, competing outcomes, significant adverse events, neurological events, stroke incidence, and mortality data from the IDE cohort (n=94), HDE post-approval study patients (n=39), compassionate use patients from IDE sites (n=54), compassionate-use patients from non-IDE sites (n=133), as well as real-world data from non-PAS-study implanted patients (n=245).

## Postmarket Use – Surveillance Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| Minimum of 62 pediatric patients, (all-comers population, pediatric age range only, <22 years of age) | **Primary Endpoints:**<br>Observed stroke rate overall; data on anticoagulation protocol<br><br>**Secondary Endpoints:**<br>Thrombotic event rates, adverse event rates, patient outcomes (e.g. survival to transplant, survival to recovery) | Five years of surveillance. |

**Narrative:**

Surveillance of pediatric patients will be conducted in an all-comers registry. The purpose of surveillance is to continue to monitor the safety and effectiveness of this device and to quantify the stroke rate overall and as newer concomitant medication therapies (anticoagulant/antithrombotic regimens) are adopted by the medical community. Adverse events will also be recorded and reported.

## Example 7. PMA - Approval and Postmarket Surveillance for a Left Ventricular Assist Device Using National Registry Data [15, 16, 17, 18]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P100047 | HeartWare, Inc. (now Medtronic) | HeartWare Ventricular Assist System | The HeartWare Ventricular Assist System (Heart Ware VAS) is indicated for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end stage left ventricular heart failure. The Heart Ware VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter. | INTERMACS Registry | **Premarket:** Primary (Control)<br><br>**Postmarket:** CoA study to leverage INTERMACS Registry |

## Premarket Use – Control cohort from INTERMACS Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| **ADVANCE TRIAL (Treatment cohort) (Non-RWE):** 140 patients in the intent-to-treat population<br><br>**ADVANCE TRIAL: INTERMACS control (RWE):** 499 patients enrolled into the registry between August 18, 2008 and February 18, 2010 (who met the study criteria) | **Primary:** Proportion of study patients alive on the originally implanted device, transplanted, or explanted for recovery at 180 days to the same proportion obtained from the INTERMACS cohort (non-inferiority analysis) | **Treatment cohort**: Every day for first week, once-a-week for weeks 2-4, at week 6 and 8, monthly for first year, every other month for year 2 (until transplant or device removal).<br><br>30 day and 6-month follow-up after device explant or transplant, then check-ups bi-annually through 5 years.<br><br>Annual follow-up for years 2 -5 for patients using the device.<br><br>**INTERMACS:** Standard-of-care follow-up (1 week, 1 month, 3 months post-implant, at 6 months, and then every 6 months (if device is in place). For explant patients that are not transplanted, patients followed for 1 year. |

**Narrative:**

The primary source for clinical evidence and basis for approval came from the ADVANCE Trial comparing HeartWare VAS patients against a contemporaneous control from the INTERMACS Registry.

## Postmarket Use – INTERMACS Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up / Duration |
|---|---|---|
| 600 HeartWare VAS recipients<br>600 non-HeartWare left ventricular assist device (LVAD) recipients | **Primary endpoints**:<br>Success at 180 days (e.g. alive, recovery, transplant)<br><br>**Secondary:**<br>Overall survival on device, re-hospitalization, adverse events, quality-of-life, functional status, post-stroke quality of life, functional and neurocognitive assessments. | Two-years (post-implant) |

**Narrative:**

This post approval study utilizes the INTERMACS registry to compare outcomes and adverse events in HeartWare recipients to a control cohort of patients receiving a LVAD other than HeartWare. Enrollees are followed per standard of care through two-years post-implant.

## Example 8. PMA - Approval of a Heart Valve Replacement Using National Registry Data [12, 19]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P150036 | Edwards Lifesciences, LLC | INTUITY Elite Valve System | The EDWARDS INTUITY Elite valve is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves. | The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database | **Premarket:** Primary (Comparison metric in evaluation of surgical times (aortic cross clamp time and cardiopulmonary bypass time)) |

## Premarket Use – Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD)

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **TRANSFORM Study (Non-RWE)**: 889 patients (839 patients received the device for aortic valve replacement (AVR))<br><br>**STS Adult Cardiac Surgery Database (RWE)**: AVR patients (7/2011 – 12/2012) | **Effectiveness:** Average aortic cross-clamp and cardiopulmonary bypass surgical times | TRANSFORM: Discharge, 3-months, 1 year, annually to minimum of 5 years<br><br>STS Adult Cardiac Surgery Database: (Procedural data) | STS surgical time data stratified by procedure type (isolated AVR, isolated AVR using minimally-invasive surgery, AVR and coronary artery bypass grafting (CABG) with 1,2,3 or 4+ grafts) |

**Narrative:**

Clinical evidence from the TRANSFORM clinical trial was the primary basis for PMA approval. The safety endpoints were complication and survival rates compared against objective performance criteria (ISO 5840:2009) and literature-derived valves. The effectiveness endpoints were echo-derived hemodynamic performance data; NYHA classification; and average aortic cross-clamp and cardiopulmonary bypass surgical times.

In this example, the sponsor also evaluated the latter two effectiveness endpoints (aortic cross-clamp and cardiopulmonary bypass surgical times) by comparing average aortic cross-clamp and cardiopulmonary bypass surgical times from TRANSFORM patients against mean aortic cross-clamp and cardiopulmonary bypass surgical times recorded in the STS Adult Cardiac Surgery Database (data entered between 7/11 – 12/12).

## Example 9. PMA - Approval of a New PMA for an Endovascular System with a Post-approval Study using the Society for Vascular Surgery Vascular Quality Initiative (VQI) Registry [20, 21]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P180001 | William Cook Europe ApS | Zenith Dissection Endovascular System | The Zenith Dissection Endovascular System (Zenith TX2 Dissection Endovascular Graft with Pro-Form and Zenith Dissection Endovascular Stent) is indicated for the endovascular treatment of patients with Type B aortic dissection. The Zenith TX2 Dissection Endovascular Graft with Pro-Form is intended to seal entry tears and to exclude aneurysms associated with chronic dissections. The Zenith Dissection Endovascular Stent is intended to be used as a distal component to provide support to delaminated segments of non-aneurysmal aorta with dissection distal to a Zenith TX2 Dissection Endovascular Graft with Pro-Form. The system is indicated for use in patients having vascular anatomy suitable for endovascular repair, including:<br>• Adequate iliac/femoral access compatible with the required introduction systems,<br>• For the Zenith TX2 Dissection Endovascular Graft with Pro-Form:<br>  ○ Non-dissected/aneurysmal aortic segments (fixation sites) distal to the left common carotid artery and proximal to the entry tear with a length of at least 20 mm,<br>  ○ Non-dissected/aneurysmal aortic segments (fixation sites) distal to the left common carotid artery and proximal to the entry tear with a diameter (measured outer-wall to outer-wall) of no greater than 38 mm and no less than 20 mm, and<br>• For the Zenith Dissection Endovascular Stent:<br>  ○ Diameter at non-aneurysmal intended implant site (measured outer-wall to outer-wall) of no greater than 38 mm (true lumen) and no less than 20 mm (total aortic diameter). | Society for Vascular Surgery Vascular Quality Initiative (VQI) Registry | **Postmarket:** Post-approval study using VQI |

## Postmarket Use – VQI Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up |
|---|---|---|
| **VQI Registry:**<br>Patients with acute Type B dissection treated with the Zenith TX2 Dissection Endovascular Graft with Pro-Form and the Zenith Dissection Endovascular Stent. | **Primary endpoints**:<br>Freedom from dissection-related mortality (all devices combined endpoint).<br>Device technical success and device procedural success at 30 days (device-specific endpoints).<br><br>**Secondary endpoints:**<br>Device technical (during the procedure) and procedural success for each project device. | Five years |

| Population | Key Elements or Endpoints from RWE Source | Follow-up |
|---|---|---|
| Patients with chronic Type B dissections, treated using the Zenith Dissection Endovascular System. | Additional endovascular and surgical dissection-related interventions.<br>Dissection treatment success and the individual elements of the composite endpoint dissection treatment success. | |

**Narrative:**

As a condition-of-approval for this PMA original application, the sponsor will conduct a post-approval study that will use the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry. Data will be collected through five-years.

# Example 10. PMA - Modification to Indications for Use Statement and Postmarket Surveillance for a Portable Normothermic Organ Perfusion, Ventilation and Monitoring Medical Device Using National Registry Data [22, 23, 24, 25]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160013/S002 | TransMedics, Inc | Organ Care System (OCS) Lung System | The TransMedics Organ Care System (OCS) Lung is a portable, normothermic organ perfusion, ventilation and monitoring medical device indicated for preservation of standard criteria donor lung pairs and for preservation of donor lung pairs initially deemed unacceptable for procurement and transplantation based on limitations of cold static preservation. The device allows for ex vivo assessment of donor lungs prior to transplantation. | United Network for Organ Sharing (UNOS)<br><br>Sponsor Registry | **Premarket**: Match-run data<br><br>**Postmarket**: CoA for two post-approval studies that will leverage RWE |

## Premarket Use – Additional Match-Run Data from UNOS Registry

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **EXPAND Clinical Trial (Non-RWE):** Single-arm, multi-center, international, prospective clinical trial (n=79,55 in US, 24 OUS).<br><br>**UNOS Organ Procurement and Transplantation Network Database (RWE):** Match-run data was obtained from UNOS on US lungs enrolled in the EXPAND (66 out of 67 US lungs). | Number of times EXPAND enrolled lungs were refused by transplant centers prior to EXPAND exclusion |

**Narrative:**

The sponsor submitted this PMA supplement to modify the indications for use statement to include "preservation of donor lung pairs initially deemed unacceptable for procurement and transplantation based on limitations of cold static preservation." The primary basis and source of clinical evidence for this PMA supplement was the EXPAND trial. The sponsor also provided additional, match-run data from the UNOS database, which contained data on the number of times US lungs were rejected prior to enrollment in EXPAND.

## Postmarket Use – Post-Approval Study Using RWE

| Population | Key Elements or Endpoints from RWE Source | Follow-up |
|---|---|---|
| **PAS001:** Continued follow-up of patients enrolled in the Lung EXPAND clinical trial. Annual follow-up data on US patients will be collected using the United Network for Organ Sharing (UNOS) database. Data from OUS patients will be collected from participating sites.<br><br>**PAS002:** Patients transplanted with initially-deemed unacceptable OCS-preserved lungs per the indications for use. Data will be collected in an all-comers, sponsor registry that leverages the UNOS database for data collection. | **PAS001 Endpoints:**<br>Bronchiolitis Obliterans Syndrome (BOS)-free survival (freedom from BOS and mortality) through 5 years<br>Please see PAS Database: EXPAND Continuation PAS for full details.<br><br>**PAS002 Primary Endpoints:**<br>12-month patient and graft survival post double-lung transplant<br>Please see PAS Database: OCS-Lun-PAS for full details. | Five years |

**Narrative:**

As a condition-of-approval for the PMA supplement, the sponsor is required to conduct two post-approval studies. The first post-approval study will follow all patients currently enrolled in the Lung EXPAND clinical trial for five years. For currently-enrolled US patients, follow-up data will be collected annually using the United Network for Organ Sharing (UNOS) database. UNOS administers the Organ Procurement and Transplantation Network in the United States and maintains a national database with data on organ matching and transplantation. The second post-approval study will collect additional postmarket data using an all-comers registry, the TOP registry. The TOP registry collects data on all US patients transplanted with OCS-preserved lungs. Data for this PAS study will also come from the UNOS registry in addition to data specifically collected to meet post-approval requirements

## Example 11. PMA - Postmarket Surveillance of a Total Hip Replacement Using Two OUS National Registries [26, 27]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P070026/S004 | DePuy Orthopaedics | DePuy Ceramax Ceramic Total Hip System | The Ceramax® Ceramic Total Hip System is indicated for noncemented use in skeletally mature individuals undergoing primary total hip replacement surgery for rehabilitation of hips damaged as a result of noninflammatory degenerative joint disease (NIDJD) or any of its composite diagnoses of osteoarthritis, avascular necrosis, and post-traumatic arthritis. | UK and Australian National Joint Registry Data | **Postmarket:** CoA to leverage UK and Australian National Joint Registry Data for postmarket evaluation |

### Postmarket Use – UK National Joint Registry (UK NJR) and Australia Orthopaedic Association National Joint Replacement Registry

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| 36mm Ceramic-on-ceramic (CoC) patients in UK and Australia joint registries;<br><br>Minimum of 500 patients. | **Primary:** Device survivorship, revision and death rates |

**Narrative:**

This PAS collects, retrospectively and prospectively, short, medium, and long-term information regarding the performance and safety of the 36mm Ceramax Ceramic-on-Ceramic Total Hip System from series of subjects (minimum of 500 subjects) in the UK National Joint Registry (UK NJR) and Australia Orthopaedic Association National Joint Replacement Registry (NJRR). The primary endpoints are device survivorship, revision and death rates.

## Example 12. PMA - Approval of an Indication Expansion for an Implanted Autonomic Nerve Stimulator for Epilepsy Based on OUS National Registry Data in a Bayesian Hierarchical Analysis [28, 29, 30]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P970003/S207<br>Supplement to expand indication | Cyberonics, Inc. | VNS Therapy System | The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications. | OUS postmarket registry data (all consecutive patients treated with VNS per Japan MHLW approved indication) | **Premarket:** Primary<br><br>Bayesian analysis of real-world data from a mandated Japan postmarket study enrolling all subjects treated with VNS (per MHLW approved indication) serving as current data and data from previous clinical trials serving as the prior |

## Premarket Use – OUS PMDA Mandated postmarket surveillance capturing data from all consecutive patients treated with VNS (per MHLW approved indication) using a registry

| Population | Key Elements or Endpoints from RWE Sources | Methods of Note |
|---|---|---|
| **Japan PAS (RWE):** MHLW/PMDA mandated study captures data from all consecutive Japanese patients treated with VNS (per Japan MHLW approved indication).<br><br>**E03 (Non-RWE)**: Randomized controlled trial comparing two treatment arms (high and low stimulation) in patients with refractory partial onset seizures<br>**E04 (Non-RWE)**: Open -label study of adjunctive VNS Therapy in patients with refractory seizures<br>**E05 (Non-RWE)**: Randomized controlled trial comparing two treatment arms (low and high stimulation) in patients with refractory partial onset seizures. E05 patients followed in subsequent **XE5 study**.<br>**E06 (Non-RWE)**: Randomized study comparing VNS to drug therapy in a pediatric population (17 years or less)<br><br>**Postmarket Surveillance Database (RWE):** Sponsor postmarket surveillance database containing passively reported adverse event reports and device tracking data | **Primary Safety:** Incidence rate of device-related treatment emergent adverse events through 12 months of treatment.<br><br>**Primary Effectiveness:** Proportion of patients (Japan PAS, 4-11 years of age) with at least a 50% reduction in the frequency of seizures following 12 months of treatment. | Bayesian Hierarchical Analysis |

**Narrative:**

The primary study reviewed by FDA was the Japan postmarket study, which collects data on all patients treated with VNS (per the MHLW approved indication) following market approval), including 30 patients aged 4-11. The postmarket study was mandated by the Japan PMDA to collect data on all VNS cases for three years following market approval [28]. Three Japanese professional societies helped launch the Japan VNS Registry to respond to the PMDA request [29, 30]. To demonstrate effectiveness, the sponsor performed a Bayesian Hierarchical analysis using the Japan data as the source of observed/current data (30 patients) and data from five previous trials as the source of prior information. For its assessment of safety, FDA reviewed analyses of treatment emergent adverse events pooled from the submitted studies as well as the sponsor's postmarket surveillance database. FDA also reviewed summary data of postmarket adverse events recorded in the sponsor's postmarket surveillance database.

## Example 13. PMA - Indication Expansions of Drug-Eluting Coronary Stents Using National Registry Data [31, 32]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P070015/S128<br>P110019/S075<br>Supplements to expand indication | Abbott Vascular | XIENCE Family of Everolimus Eluting Coronary Stents | XIENCE V and XIENCE nano Everolimus Eluting Coronary Stent System<br><br>The XIENCE V and XIENCE nano Everolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease due to de novo native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.25 mm to 4.25 mm. Additionally, the XIENCE V stent system is indicated for treating de novo chronic total coronary occlusions.<br><br>Please see the Summary of Safety and Effectiveness Data for P070015/S128 and P110019/S075 for the complete indication list. | American College of Cardiology CathPCI Registry | **Premarket:** Primary (Observed/Current data in Bayesian Hierarchical Analysis with prior data from clinical trial databases) |

## Premarket Use – American College of Cardiology (ACC) CathPCI Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **XIENCE Databases (Non-RWE)**: 949 diabetic patients treated with the device(s) from SPIRIT IV, SPIRIT PRIME, XIENCE V USA Phase I, and XIENCE V USA Phase II trials<br><br>**CathPCI Registry (RWE)**: 290 diabetic patients | **Safety and Effectiveness:** 12-month target vessel failure (composite endpoint of cardiac death, target-vessel myocardial infarction (TVMI), and ischemia-driven target vessel revascularization (ID-TVR)) | 12-month data analyzed | Bayesian Hierarchical analysis |

**Narrative:**

To support expanding the indication to include treatment of patients with diabetes mellitus, the sponsor performed a Bayesian Hierarchical analysis using data from four clinical trial databases as the source of prior information, and real-world data from two registry databases (part of American College of Cardiology CathPCI registry) as the source of current data. The analysis compared the target vessel failure rate (TVF) at 12 months against a performance goal. The results of this analysis demonstrated that the performance goal and success criteria for the posterior probability were both achieved. This analysis served as the primary basis for approval of the PMA

## Example 14. PMA - Indication Expansion and Postmarket Surveillance of a DCB Percutaneous Transluminal Angioplasty Catheter Approval Using National Registry Data [33, 34, 35]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140010/S015 Supplement to expand indication | Medtronic Vascular, Inc. | IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter | The IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions with lengths up to 180 mm in superficial femoral (SFA) or popliteal arteries with reference vessel diameters of 4-7 mm. | SVS VQI Registry | **Premarket:** Primary (Control)<br><br>**Postmarket:** CoA to conduct postmarket surveillance in VQI Registry |

### Premarket Use – Society for Vascular Surgery (SVS) - Vascular Quality Initiative (VQI)

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **IN.PACT Global Study (Non-RWE):** 164 OUS Patients treated with the IN.PACT Admiral DCB at 31 sites.<br><br>**VQI Registry (RWE):** 153 patients treated with standard-of-care percutaneous, transluminal angioplasty. | **Safety:** Cumulative complications within 30, 180 and 360 days (all-cause death, target vessel revascularization, major target limb amputation, target lesion revascularization)<br><br>**Effectiveness:** 12-month target lesion revascularization (TLR). | IN.PACT:(1, 6, and 12 months then annually up to 5 years)<br><br>VQI: Standard of care | Propensity-score adjusted analysis based on 20 pre-specified variables. |

**Narrative:**

To support expanding the indication to include treatment of in-stent restenotic lesions, the sponsor performed a superiority analysis between a device cohort from the sponsor's IN.PACT Global Study and a standard-of-care percutaneous, transluminal angioplasty cohort from the SVS Vascular Quality Initiative Registry. This analysis was a prospectively-designed superiority analysis evaluating target lesion revascularization at 12 months. To account for potential differences between the populations, the sponsor performed a propensity-score adjusted analysis using 20 pre-specified variables. The propensity score results were reviewed by FDA before the sponsor performed the outcome analysis. The results of these analyses demonstrated that the success criteria were achieved--- and along with analyses of serious adverse events from the IN.PACT Global Study---was the primary basis for approval of the supplement

### Postmarket Use – Society for Vascular Surgery (SVS) - Vascular Quality Initiative (VQI)

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| 300 sequential patients from the SVS VQI Peripheral Vascular Intervention (PVI) Registry treated with the IN.PACT Admiral DCB per the standard of care | **Primary:**<br>Target lesion revascularization (TLR) within 12 months<br><br>**Secondary:**<br>All-cause mortality (12 and 24 months)<br>TLR (24 months)<br>Target vessel revascularization (TVR) (12 and 24 months)<br>Major limb amputation (12 and 24 months) | Follow-up out to 36 months post-procedure |

**Narrative**

FDA required surveillance of the IN.PACT Admiral DCB to assess its long-term safety and performance in a U.S. population. The premarket study used OUS patients treated with the device and US control patients from the SVS VQI Registry. Sequential patients (n=300), treated with the IN.PACT Admiral DCB per the standard of care, from this registry will be followed 36 months post-procedure in this surveillance. The primary endpoint is target lesion revascularization within 12 months.

## Example 15. PMA - Postmarket Surveillance of a Superficial Femoral Artery Stent Utilizing a National Registry for Condition-of-Approval [36, 37]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P070014/S037 Supplement to expand indication | Bard Peripheral Vascular, Inc. | Bard LifeStent Vascular Stent System | The Bard LifeStent Vascular Stent System is intended to improve luminal diameter in the treatment of symptomatic de novo or restenotic lesions up to 240 mm in length in the native superficial femoral artery (SFA) and popliteal artery with reference vessel diameters ranging from 4.0 – 6.5 mm. | Vascular Quality Initiative PVI Registry | **Postmarket:** CoA to use PVI Registry for postmarket surveillance. |

### Postmarket Use – Society for Vascular Surgery (SVS) Vascular Quality Initiative Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| All patients in VQI Registry with symptomatic de novo or restenotic lesions in the popliteal artery (P2/P3) that receive treatment with the Bard Life Stent; minimum of 74 patients. | **Primary Safety:** Freedom from Major Adverse Events (device and/or procedure-related death or target limb major amputation) through 12-month.<br>**Primary Effectiveness:** Freedom from target lesion revascularization and/or target vessel revascularization through 12- months. | Follow-up for 2 years |

**Narrative:**

BARD was required per the approval order to conduct surveillance and evaluate the clinical use of the LifeStent Vascular Stent System in the popliteal artery (mid and distal segments) using the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Peripheral Vascular Intervention (PVI) Registry. For surveillance, sequential patients (minimum of n=74) treated with the LifeStent in the mid and distal popliteal will be followed prospectively for 2 years. The primary endpoints are freedom from major adverse events and TLR/TVR through 12 months.

## Example 16. PMA - Postmarket Surveillance of an Endovascular Graft for Aortic Aneurysms Utilizing a National Registry for Condition-of-Approval [38, 39]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P040043/S051 Supplement to expand indication | W.L. Gore & Associates, Inc. (Gore) | GORE TAG Thoracic Endoprosthesis | The GORE TAG Thoracic Endoprosthesis is intended for endovascular repair of all lesions of the descending thoracic aorta, including:<br>• Isolated lesions in patients who have appropriate anatomy, including:<br>- Adequate iliac / femoral access<br>- Aortic inner diameter in the range of 16-42 mm<br>- ≥ 20 mm non-aneurysmal aorta proximal and distal to the lesion<br>• Type B dissections in patients who have appropriate anatomy, including:<br>- Adequate iliac / femoral access<br>- ≥ 20 mm landing zone proximal to the primary entry tear; proximal extent of the landing zone must not be dissected<br>- Diameter at proximal extent of proximal landing zone in the range of 16-42 mm | SVS VQI Registry | **Postmarket:** CoA to conduct postmarket surveillance in VQI Registry |

### Postmarket Use – Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| **One (1)-year**: All-comers (until 200 patients surveilled) treated with the device to repair Type B dissections in the descending thoracic aorta into the VQI registry during the specified enrollment period.<br><br>**Five (5)-year:** Chronic (minimum of 194) and acute (minimum of 200) patients with Device Technical Success, and treated to repair Type B dissections in the descending thoracic aorta at centers agreeing to participate in the Surveillance Project through the VQI registry.<br><br>At least 60 patients treated with the final device design of a participating manufacturer will be enrolled in each surveillance arm (i.e., acute and chronic).<br><br>If the total sample size of 200 or 194 patients has been reached for one arm (acute or chronic, respectively) of the 5-year surveillance arm, but an individual device has not met the 60 patients minimum required for that arm, enrollment will only continue for that specific device. | **Primary Safety**<br>1year arm: Freedom from dissection related mortality through 1 year<br>5year arm: Freedom from dissection related mortality at 5 years<br><br>**Primary Effectiveness**<br>1 year arm: Device technical success at the time of the procedure (successful delivery, successful and accurate deployment, and successful withdrawal of the delivery system)<br><br>5-year arm: Device technical success at the time of the procedure (successful delivery, successful and accurate deployment, and successful withdrawal of the delivery system)<br><br>Device procedural success at 30 days (device technical success with absence of the following at 30 days: major adverse events [MAE] subset, primary intimal tear false lumen perfusion, retrograde extension of the dissection, and unintentional dissection septum rupture). | 5-year population: 30 days, 1 year and then annually (5 years of surveillance)<br><br>1 year population: 30 days and 1 year |

**Narrative:**

This surveillance project will use the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry to collect surveillance data on the short-term and long-term performance of the GORE TAG Thoracic Endoprosthesis for the treatment of Type B thoracic aortic dissection. Data will also be used to identify signals and establish performance goals.

## Example 17. PMA - Postmarket Surveillance of an Endovascular Graft for Aortic Aneurysms Utilizing a National Registry for Condition-of-Approval [40, 41]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P100040/S012 Supplement to expand indication | Medtronic Vascular | Valiant Thoracic Stent Graft with Captivia Delivery System | The Valiant Thoracic Stent Graft with the Captivia Delivery System is intended for the endovascular repair of all lesions of the descending thoracic aorta (DTA) in patients having appropriate anatomy including:<br>• iliac/femoral access vessel morphology that is compatible with vascular access techniques, devices, and/or accessories;<br>• non-aneurysmal aortic diameter in the range of 18–42 mm (fusiform and saccular aneurysms/penetrating ulcers), 18 mm to 44 mm (blunt traumatic aortic injuries) or 20 mm to 44 mm (dissections) and<br>• non-aneurysmal aortic proximal and distal neck lengths ≥ 20 mm (fusiform and saccular aneurysms/penetrating ulcers), landing zone ≥20 mm proximal to the primary entry tear (BTAI, dissection). The proximal extent of the landing zone must not be dissected. | SVS VQI Registry | **Postmarket:** CoA to conduct postmarket surveillance in VQI Registry |

### Postmarket Use – Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|---|
| **One (1)-year**: All-comers (until 200 patients surveilled) treated with the device to repair Type B dissections in the descending thoracic aorta into the VQI registry during the specified enrollment period.<br><br>**Five (5)-year:** Chronic (minimum of 194) and acute (minimum of 200) patients with Device Technical Success, and treated to repair Type B dissections in the descending thoracic aorta at centers agreeing to participate in the Surveillance Project through the VQI registry.<br><br>At least 60 patients treated with the final device design of a participating manufacturer will be enrolled in each surveillance arm (i.e., acute and chronic).<br><br>If the total sample size of 200 or 194 patients has been reached for one arm (acute or chronic, respectively) of the 5-year surveillance arm, but an individual device has not met the 60 patient minimum required for that arm, enrollment will only continue for that specific device. | **Primary Safety**<br>1-year arm: Freedom from dissection related mortality through 1 year<br>5-year arm: Freedom from dissection related mortality at 5 years<br><br>**Primary Effectiveness**<br>1-year arm: Device technical success at the time of the procedure (successful delivery, successful and accurate deployment, and successful withdrawal of the delivery system).<br><br>5-year arm: Device technical success at the time of the procedure (successful delivery, successful and accurate deployment, and successful withdrawal of the delivery system).<br><br>Device procedural success at 30 days (device technical success with absence of the following at 30 days: major adverse events [MAE] subset, primary intimal tear false lumen perfusion, retrograde extension of the dissection, and unintentional dissection septum rupture). | 5-year population: 30 days, 1 year and then annually (5 years of surveillance)<br><br>1-year population: 30 days and 1 year |

**Narrative:**

This surveillance project will use the Society for Vascular Surgery Vascular (SVS) Quality Initiative (VQI) Registry to collect surveillance data on the short-term and long-term performance of the Valiant Thoracic Stent Graft with Captiva Delivery System for the treatment of Type B thoracic aortic dissection. Data will also be used to identify signals and establish performance goals.

## Example 18. PMA - Post-Approval Studies for an Implantable Cardioverter Defibrillator Utilizing a National Registry, the National Death Index, and a Sponsor Registry [42, 43, 44]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P010031/S232 | Medtronic, Inc. Cardiac Rhythm Disease Management | CONCERTO/CONCERTO II; CONSULTA; MAXIMO II; AND PROTECTA/PROTECTA XT | Please refer to approval order for full indications for use. | ACC National Cardiovascular Data Registry ICD Registry<br><br>National Death Index<br>Sponsor Registry | **Postmarket:** Post-approval study using multiple RWE data sources |

### Postmarket Use – American College of Cardiology NCDR ICD Registry, National Death Index, Sponsor Registry Used to Satisfy Post-Approval Requirements

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **PAS001, REVERSE NCDR ICD Registry Study:** Patients identified in the registry that meet the indication. Enrollment target is 1500 patients overall and 500 patients with QRS < 150ms.<br><br>**PAS002, Sponsor Registry (Product Surveillance Registry):** Patients treated with the subject device per the indication and who have a QRS duration < 150ms. Enrollment target is 500 patients. | **Primary Endpoints (PAS001):**<br>Mortality for patients identified in the ACC NCDR Registry, using the National Death Index<br><br>**Primary Endpoints (PAS002):**<br>Survival probability of freedom from centrally adjudicated heart failure hospitalization or all-cause death.<br>Survival probability of freedom from centrally adjudicated heart failure event or all cause death. | Use of multiple real-world evidence data sources including the ACC NCDR ICD Registry, a sponsor registry, and the National Death Index. |

**Narrative:**

As a condition-of-approval for this PMA supplement, the sponsor agreed to perform two post-approval studies in order to collect long-term data for patients with a prolonged QRS and who were treated with the subject device. For the first post-approval study, patients implanted with device meeting the indication were identified in the American College of Cardiology NCDR ICD Registry. Long-term mortality will be collected using the National Death Index. For the second post-approval study, additional clinical data on survival probability of freedom from adjudicated heart failure events or all-cause death will be collected from patients participating in a sponsor registry.

## Subsection B. Examples of Registries as a Source of Real-World Evidence

### Guide to Examples Leveraging Sponsor Registries for Real-World Data Collection

| | File | Sponsor | Device | Real-World Data (RWD) Source(s) | RWE Use | Key Tags |
|---|---|---|---|---|---|---|
| **19** | K163244 | CSA Medical, Inc. | truFreeze System | Sponsor Registry | **Premarket:** For this 510(k) submission to expand the indication of a cryosurgical device, the sole source of clinical evidence was the sponsor's all-comers postmarket registry. | Registry data;<br>RWE as a primary source of clinical evidence; |
| **20** | K171626 | CSA Medical, Inc. | truFreeze System | Sponsor Registry | **Premarket:** Data from the sponsor's all-comers postmarket registry served as the primary source of clinical evidence supporting an indication expansion of a cryosurgical tool. | Registry data;<br>RWE as a primary source of clinical evidence; |
| **21** | K171257 | MRI Interventions, Inc. | ClearPoint System | Registry | **Premarket:** Clinical information from a registry data was combined with published literature to support this submission modifying of the indications for use statement to include positioning of deep brain stimulator (DBS) leads. | Registry data;<br>RWE as a primary source of clinical evidence; |
| **22** | K190779 | Stryker Neurovascular | Trevo XP ProVue Retriever | Trevo Retriever Registry | **Premarket:** Data from the sponsor's registry served as the primary source of clinical evidence for modifying the labeling and instructions for use in this 510(k). | Outside-the-US;<br>Registry data;<br>RWE as a primary source of clinical evidence; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **23** | H190005 | Zimmer Biomet Spine, Inc. | The Tether - Vertebral Body Tethering System | Retrospective review of medical records used to enroll patients into a follow-up clinical study from one (1) US site under an IDE;<br><br>Postmarket registry | **Premarket:** Pediatric patients treated with the device under real-world conditions were retrospectively identified for enrollment into a prospective long-term follow-up clinical study under an IDE.<br><br>**Postmarket:** The sponsor has agreed to perform a post-approval study (PAS) that will use registry-based data collection (PAS protocol pending as of 1/02/20). | Medical records (EHR, EMR or chart review);<br>Pediatric RWE;<br>Total-Product Lifecycle Example; |
| **24** | DEN160062 | IlluminOss Medical, Inc. | IlluminOss Photodynamic Bone Stabilization System | EU Registry for the IlluminOss Bone Stabilization System | **Premarket:** Data from a postmarket EU registry study was used as a secondary source of clinical evidence to support the granting of this de novo, with medical record data collected from patients and uploaded to the sponsor's own database. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>Registry data; |
| **25** | P120017 | Medtronic, Inc. | Model 5071 Lead | Sponsor Registry, Remote-monitoring | **Premarket:** This PMA original was approved following a classification order, and the primary source of clinical evidence were data from the sponsor's postmarket surveillance registry and remote monitoring data from the sponsor's CareLink system. | Device-generated data;<br>Registry data;<br>RWE as a primary source of clinical evidence; |
| **26** | P140003 | ABIOMED, Inc. | Impella 2.5 System | Sponsor Registry | **Premarket:** In this PMA original, clinical evidence from the sponsor's USPELLA registry that captures routine care data for all device models, specifically in-hospital mortality rates, were used to supplement the submission and provide a comparison for the clinical trial data. | Registry data; |
| **27** | P150033 | Medtronic, Inc. | Micra Transcatheter Pacing System | Sponsor Registry | **Postmarket:** For this PMA original, nine years of postmarket surveillance data will be collected in the sponsor's registry as a condition-of-approval. | Registry data; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **28** | P160036 | DT MedTech, LLC | Hintermann Series H3 Total Ankle Replacement System | Outside-the-US registry<br><br>Formal meta-analysis of literature and registry data | **Premarket:** RWE was a primary source of clinical evidence for this original PMA, which relied on comparison of data abstracted from an OUS registry to a performance goal derived from a meta-analysis of published literature and registry data for a control device legally marketed in the United States.<br><br>**Postmarket:** The sponsor has agreed to conduct a post-approval study (PAS) that will follow patients included in the premarket cohort (i.e. patients from the OUS registry) to a performance goal. Similar to the PMA study, the sponsor was requested to derive the performance goal using a meta-analysis of published literature and registry data for a control device legally marketed in the United States | Outside-the-US;<br><br>Performance goal or comparator derived from RWE;<br><br>Registry data;<br><br>RWE as a primary source of clinical evidence;<br><br>Total-Product Lifecycle Example; |
| **29** | P160043 | Medtronic, Inc. | Resolute Onyx Zotarolimus-Eluting Coronary Stent System | Sponsor Registry | **Premarket:** Supplemental clinical evidence in support of this PMA original was drawn from the sponsor's international, all-comers, observational registry. | Outside-the-US;<br><br>Registry data; |
| **30** | P170011 | ABIOMED, Inc. | Impella RP | Sponsor Registry | **Postmarket:** As a condition-of-approval for this PMA converting from an HDE, the sponsor will conduct postmarket surveillance through their registry. | Registry data; |
| **31** | P140003/S004 | ABIOMED, Inc. | Impella 2.5, 5.0, CP, LD | Sponsor Registries | **Premarket:** In this indication expansion, sponsor registry data was leveraged as a supplemental source of clinical evidence and was utilized for analysis of survival-to-discharge and freedom-from-death rates, as well as other endpoints, providing supportive evidence of the effectiveness and benefit-to-risk ratio of the device.<br><br>**Postmarket:** As a condition-of-approval, postmarket surveillance will be conducted through the sponsor's registry. | Registry data;<br><br>Total-Product Lifecycle Example; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **32** | P140003/S005 | ABIOMED, Inc. | Impella 2.5, 5.0, CP, LD | Sponsor Registries | **Premarket:** For this PMA supplement, sponsor registry data served as a supplemental source of clinical evidence on freedom-from-death and adverse event rates, as well as benchmark analyses between the subject device and a comparator.<br><br>**Postmarket:** Postmarket surveillance will be conducted through the sponsor's registry as a condition-of-approval. | Registry data;<br>Total-Product Lifecycle Example; |
| **33** | P130024/S009 | Lutonix, Inc | Lutonix 035 Drug Coated Balloon PTA Catheter | Sponsor Registry | **Premarket:** In this PMA supplement for an indication expansion, RWE from the sponsor's international registry served as the primary source of clinical evidence supporting approval.<br><br>**Postmarket:** As a condition-of-approval, the sponsor will conduct postmarket surveillance through 24 months post-procedure using their OUS registry. | Outside-the-US;<br>Registry data;<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |
| **34** | P100021/S063 | Medtronic Vascular | Endurant II/Endurant IIs Stent Graft System | ANCHOR Registry | **Premarket:** Data from the sponsor's registry served as the primary source of clinical evidence supporting approval of this indication expansion.<br><br>**Postmarket:** Postmarket surveillance will be conducted through the sponsor's registry for 5 years as a condition-of-approval. | Registry data;<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |
| **35** | P100047/S090 | Medtronic, Inc. | HeartWare HVAD system | Sponsor Registry | **Postmarket:** As a condition-of-approval, the sponsor will conduct postmarket surveillance of 300 subjects for five years post-implant through the sponsor's registry. | Registry data; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **36** | P960043/S097 | Abbott Vascular Inc. | Perclose ProGlide Suture-Mediated Closure System | EVEREST II/REALISM Continued Access Registry (US and OUS) | **Premarket:** Data from the sponsor's continued access registry were extracted to serve as the sole source of clinical evidence supporting an indication expansion of their suture delivery system to include closing femoral artery access sites with sheaths up to 24F. A patient cohort from the continued access registry was selected, and their medical records were retrospectively analyzed. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>Registry data;<br>RWE as a primary source of clinical evidence; |
| **37** | P160043/S012, P110013/S088 | Medtronic Vascular | Resolute Onyx Zotarolimus-Eluting Coronary Stent System, Resolute Integrity Zotarolimus-Eluting Coronary Stent System | Global RESOLUTE Clinical Trial Program: RESOLUTE International Registry and RESOLUTE China Registry (US and OUS) | **Premarket:** Data extracted from the sponsor's registry data were pooled to form a cohort of patients treated with the subject device that was analyzed to support expansion of the indication of this family of coronary stents to include treatment of coronary chronic total occlusions.<br><br>**Postmarket:** As a condition-of-approval, the sponsor will follow patients treated with the subject device for chronic total occlusions enrolled in a PAS and OUS clinical trial for two years, with the primary endpoint being freedom from MACE. | Medical records;<br>Outside-the-US;<br>Registry data;<br>Total-Product Lifecycle Example; |

## Example 19. 510(k) - Clearance of a Cryosurgical Tool Using Sponsor Registry Data [45]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K163244 | CSA Medical, Inc. | truFreeze System | The truFreeze System is indicated for use as a cryosurgical tool in the fields of dermatology, gynecology, and general surgery, to ablate benign (e.g. Barrett's Esophagus with high grade dysplasia) and malignant lesions. | Sponsor Registry | **Premarket:** Sole-source |

## Premarket Use – Sponsor Registry

| Population | Key Elements or Endpoints from RWE Sources |
|---|---|
| **Postmarket Registry:** All-comers population of patients with Barrett's Esophagus (BE) treated using the truFreeze device. (111 patients included in the safety population analysis; 46 patients included in the efficacy population analysis). | **Safety:**<br>Stricture; Abdominal Pain; Pancreatitis; Chest Pain; GI Hemorrhage; Mucosal Lacerations event rates<br><br>**Effectiveness:**<br>Number of responders and percentage with complete eradication of dysplasia<br>Response rate by BE segment length<br>Procedural information to achieve best response (e.g. number of sessions to best response) |

**Narrative:**

To support adding "Barrett's Esophagus with high grade dysplasia" to the indications for use, the sponsor provided clinical evidence from an all-comers, postmarket registry, which collected data on patients --- including those with high-grade dysplasia --- treated using the FDA-cleared device. This study was the primary source of clinical evidence for the premarket clearance decision.

## Example 20. 510(k) - Clearance of a Cryosurgical Tool Using Sponsor Registry Data [47]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K171626 | CSA Medical, Inc. | truFreeze System | The truFreeze System is indicated for use as a cryosurgical tool in the fields of dermatology, gynecology, and general surgery, to ablate benign (e.g. Barrett's Esophagus with high grade dysplasia and/or low grade dysplasia) and malignant lesions. | Sponsor Registry | **Premarket:** Primary |

## Premarket Use – Sponsor Registry

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Postmarket Registry:** All-comers population of patients with Barrett's Esophagus (BE) treated using the truFreeze device. (111 patients included in the safety population analysis; 22 patients included in the efficacy population analysis). | **Safety Events:**<br>Stricture; Abdominal Pain; Pancreatitis; Chest Pain; GI Hemorrhage; Mucosal Lacerations event rates<br><br>**Effectiveness:**<br>Number of responders and percentage with complete eradication of dysplasia<br>Response rate by BE segment length<br>Procedural information to achieve best response (e.g. number of sessions to best response) |

**Narrative:**

The truFreeze device was previously cleared using clinical data to support adding "Barrett's Esophagus with high grade dysplasia" to the indications for use. To support adding "low-grade dysplasia" to the indications for use, the sponsor provided clinical evidence from all-comers, postmarket registry, which collected data on patients---including those with low-grade dysplasia---treated using the FDA-cleared device. This study, along with peer-reviewed literature, was the primary source of clinical evidence for the premarket clearance decision.

## Example 21. 510(k) - Modification to Indications for Use Statement for a Neurological Stereotaxic Instrument Supported by RWE from a Registry [48]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K171257 | MRI Interventions, Inc. | ClearPoint System | The ClearPoint System is intended to provide stereotactic guidance for the placement and operation of instruments or devices during planning and operation of neurological procedures within the MRI environment and in conjunction with MR imaging. The ClearPoint System is intended as an integral part of procedures that have traditionally used stereotactic methodology. These procedures include biopsies, catheter and electrode insertion, including deep brain stimulation (DBS) lead placement. The System is intended for use only with 1.5 and 3.0 Tesla MRI scanners and MR Conditional implants and devices. The user should consult the "Navigational Accuracy" section of the User's Guide to assess if the accuracy of the system is suitable for their needs. | Registry | **Premarket:** Registry data (RWE), submitted with literature, were the primary sources of clinical information. |

### Premarket Use – Registry Data

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Registry (RWE)**: Patients treated with the device in standard practice (35 institutions) | **Safety and Effectiveness:**<br>Placement accuracy<br>Procedure type |

**Narrative:**

The 510(k) was submitted to modify the indications for use statement of the system to include positioning of deep brain stimulator (DBS) leads. Clinical evidence for this 510(k) included both literature and data from a registry (35 participating institutions, 828 DBS lead placement procedures), which collected data on the device as used in standard practice. The collected data included placement accuracy data for DBS procedures. The 510(k) submission was found to be substantially-equivalent.

## Example 22. 510(k) - Modification to the Instructions for Use for a Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment Using Registry Data [49, 50]

| File | Sponsor | Device | Approved / Cleared / Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K190779 | Stryker Neurovascular | Trevo XP ProVue Retriever | 1. The Trevo Retriever is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA). Endovascular therapy with the device should start within 6 hours of symptom onset.<br><br>2. The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.<br><br>3. The Trevo Retriever is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50 cc for age < 80 years, 0-20 cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy. | Sponsor registry | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Real-world Evidence from Trevo Retriever Registry

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Trevo Retriever Registry:** 2010 ischemic stroke patients worldwide treated with subject device as initial device in mechanical neuro-thrombectomy | **Primary:**<br>Revascularization status assessment at the end of the Trevo Retriever procedure using the modified Thrombolysis in Cerebral Infarctions (TICI) score<br><br>**Secondary:**<br>Modified Rankin Score at 90 days<br><br>**Other:**<br>Device and procedure related serious adverse events at 90 days<br>All-cause mortality at 90 days<br>Neurological deterioration at 24 hours post procedure, defined as a four or more point increase in the NIH Stroke Scale from the baseline score |

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| | For additional details and complete list, please see ClinicalTrials.gov Page. |

**Narrative:**

This submission sought clearance for modifications to the labeling and instructions for use for using the subject device with an aspiration catheter (AXS Catalyst Distal Access Catheter) and aspiration pump (AXS Universal Aspiration System) as an alternative use. Clinical evidence supporting this 510(k) included real-world evidence of the subject device used in combination with catheter aspiration from the Trevo Retriever Registry along with a literature review.

## Example 23. HDE - Approval for Vertebral Body Tethering System Using RWE from a Retrospective Review of Medical Records and to Satisfy Post-Approval Requirements [51, 52, 53, 54, 55]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| H190005 | Zimmer Biomet Spine, Inc. | The Tether – Vertebral Body Tethering System | The Tether - Vertebral Body Tethering System is indicated for skeletally immature patients that require surgical treatment to obtain and maintain correction of progressive idiopathic scoliosis, with a major Cobb angle of 30 to 65 degrees whose osseous structure is dimensionally adequate to accommodate screw fixation, as determined by radiographic imaging. Patients should have failed bracing and/or be intolerant to brace wear. | **Premarket:** Patient medical records.<br><br>**Postmarket:** Harms Study Group registry | **Premarket:** Patient identification for enrollment in support of a trial using a retrospective chart review of medical records<br><br>**Postmarket:** Post-approval study |

### Premarket Use – Retrospective Review of Medical Records

| Population | Key Elements or Endpoint | Methods of Note |
|---|---|---|
| **Prospective study of patients identified from retrospective review of medical records:** 57 pediatric patients with adolescent idiopathic scoliosis that have been implanted with the subject device, identified through a retrospective review of patient medical records and enrolled in a long-term follow-up study under an investigational device exemption and followed prospectively to collect additional data | **Safety:**<br>Analysis of adverse events with adjudication by an independent Adverse Event Adjudication Committee.<br><br>**Probable Benefit:**<br>Measurement of coronal curve correction on post-operative radiographs. | Patients treated with the device under real-world conditions were retrospectively identified for enrollment into a prospective long-term follow-up clinical study. |

**Narrative:**

Approval of this HDE for a first-of-a-kind spinal tethering device for pediatric idiopathic scoliosis was supported by clinical data collected from patients after having been implanted with a device cleared for use in adults. Patients were retrospectively identified and consented to participate in a long-term study under an investigational device exemption to collect data on clinical outcomes. This is an example of using real-world evidence to identify and enroll patients treated with the device in routine practice in a follow-up clinical trial with prospective data collection.

### Postmarket Use – Post-Approval Study Using a Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| Skeletally immature patients with idiopathic scoliosis. | **Primary Safety:**<br>Serious adverse events (SAEs), and device- or procedure-related AEs.<br><br>**Primary probable benefit endpoint**:<br>Maintenance of major Cobb angle less than or equal to 40 degrees at 60-months post-surgery.<br><br>See H190005 Approval Order for additional secondary endpoints. | 5 years (60 months). |

**Narrative:**

The sponsor has agreed to conduct a post-approval study to collect additional long-term data on the performance of The Tether System in treatment of skeletally immature patients with idiopathic scoliosis. For this post-approval study, the sponsor has stated that it will partner with the Harms Study Group to create a patient registry to support the post-approval study. The full post-approval study protocol is pending as of 1/2/20.

## Example 24. De Novo - Classification of an In Vivo Cured Intramedullary Fixation Rod Using the Medical Records from Sponsor's OUS Registry [57]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN160062 | IlluminOss Medical, Inc. | IlluminOss Photodynamic Bone Stabilization System | The IlluminOss Photodynamic Bone Stabilization System (PBSS) is indicated for skeletally mature patients in the treatment of impending and actual pathological fractures of the humerus, radius, and ulna, from metastatic bone disease. | EU Registry for the IlluminOss Bone Stabilization System | **Premarket:** Secondary source of clinical evidence |

## Premarket Use – EU Registry for the IlluminOss Bone Stabilization System

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **EU Registry for the IlluminOss Bone Stabilization System:** 132 patients at three centers in Germany and four centers in the Netherlands treated with subject device for acute fractures or revision surgeries | **Safety and Effectiveness:**<br>Local or systemic device-related complications, radiographs |

**Narrative:**

For this de novo request, part of the clinical evidence submitted was an EU registry study, conducted after the device had received CE Mark approval in Europe. The EU Registry for the IlluminOss Bone Stabilization System was initiated in September 2010, with the aim of collecting technical and clinical outcomes on treated patients. Subjects were followed either until they were discharged from clinical care, or were followed for up to two years post-index surgery and medical record data was collected from patients and uploaded to the sponsor's own web-based database. The database was prospectively queried for the incidence of adverse device effects. These real-world evidence were used as a secondary source of clinical evidence to support the granting of this de novo classification request.

# Example 25. PMA - Approval of a Permanent Pacemaker Electrode Following a Classification Order Leveraging RWE from a Sponsor Registry and Device-Generated Data from Remote Monitoring [58]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P120017 | Medtronic, Inc. | Model 5071 Lead | The Medtronic Model 5071 Lead is indicated for unipolar ventricular pacing and sensing. The lead has application where permanent ventricular or dual-chamber pacing systems are indicated. Two leads may be used for bipolar pacing | Sponsor registry<br><br>Device-generated data (remote monitoring) | **Premarket:** Primary |

## Premarket Use– Sponsor Registry, Remote-Monitoring of Device-Generated Data

| Population | Key Elements or Endpoints from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| **SLS Registry (RWE):** Patients implanted with the Model 5071 lead and enrolled into the registry. 290 Model 5071 leads in 212 subjects enrolled. (First implant 2/17/94 – 1/31/2013 cut-off).<br><br>**CareLink Remote Monitoring System (RWE):** De-identified subjects implanted with Model 5071 lead and registered in CareLink system | **Primary Endpoint:**<br>Model 5071 lead related complications (Complication-free survival rate).<br><br>**Effectiveness**:<br>Summary statistics for weekly minimum and maximum pacing capture thresholds (PCT) vs time for de-identified patients followed using the sponsor's remote monitoring system (CareLink)<br><br>**Supplemental Data:** Chronic complication rates, chronic lead survival probability, and acute lead observations between Model 5071 vs Model 4965 and Model 4968 data from sponsor's Product Surveillance Registry (incorporates SLS) | Follow-up per standard care practices of their care provider. |

**Narrative:**

Approval of a PMA original following a classification order. The Model 5071 lead was originally cleared on September 26, 1990 (K902002) to be legally marketed in the United States. This application was submitted to comply with FDA-2011-N-00505 (Final rule issued July 6, 2012), which requires premarket approval for all pre-amendment Class III leads with a DTB product code.

Analysis of clinical data collected in a postmarket sponsor surveillance registry (SLS), remote monitoring data from the Medtronic CareLink System, comparative data from two previous models (4965 and 4968) collected in a sponsor postmarket surveillance registry, and data from the sponsor's complaint handling system were submitted in support of the application. The analyses were described under the Summary of Primary Clinical Study and Supplementary Clinical Data sections in the SSED and were used in the evaluation of safety and effectiveness.

## Example 26. PMA - Approval of a Ventricular Support Device Using Supplemental Sponsor Registry Data [59]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140003 | ABIOMED, Inc. | Impella 2.5 System | The Impella 2.5 System is a temporary (≤ 6 hours) ventricular support device indicated for use during high risk percutaneous coronary interventions (PCI) performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team, including a cardiac surgeon, has determined high risk PCI is the appropriate therapeutic option. Use of the Impella 2.5 System in these patients may prevent hemodynamic instability which can result from repeat episodes of reversible myocardial ischemia that occur during planned temporary coronary occlusions and may reduce peri- and post-procedural adverse events | USpella Registry (Sponsor) | **Premarket:** Supplemental source of clinical evidence |

## Premarket Use – Sponsor Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **PROTECT I trial (Non-RWE):** 20 Impella 2.5 patients; 7 sites<br><br>**PROTECT II Trial (Non-RWE)**: 216 Impella 2.5 arm patients (per-protocol) and 211 IABP arm patients (per-protocol); 112 sites<br><br>**USPELLA (RWE):** 637 Impella 2.5 patients; 49 sites | **Supplemental:** In-hospital mortality rate | **PROTECT II:** Discharge or 30-days, 90 days<br><br>**USPELLA:** Discharge | Analyses included analysis of all USPELLA patients undergoing high-risk PCI and USPELLA patients who meet the criteria for PROTECT II. |

**Narrative:**

For this PMA submission, the primary study (PROTECT II) was a randomized clinical trial with two arms (intra-aortic balloon pump arm vs Impella arm). FDA also looked at supplemental information from the sponsor's USPELLA registry (captures routine care data for all Impella device models, post 510k clearance). FDA specifically looked at the Impella 2.5 in-hospital mortality rate for all high-risk PCI patients captured in USPELLA (n=637) as well as the Impella 2.5 in-hospital mortality rate after applying the PROTECT II criteria to that USPELLA dataset (n=339).

USPELLA in-hospital mortality rates were then compared to data from the pivotal trial (n=211 IABP arm, n=216 Impella arm) to serve as a potential real-world estimate of in-hospital mortality.

## Example 27. PMA - Postmarket Surveillance of a Leadless Pacemaker Using a Sponsor Registry [60, 61, 62, 63]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P150033 | Medtronic, Inc. | Micra Transcatheter Pacing System | The Micra Transcatheter Pacing System is indicated for use in patients who have experienced one or more of the following conditions:<br>• symptomatic paroxysmal or permanent high-grade AV block in the presence of Atrial Fibrillation (AF)<br>• symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy<br>• symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.<br><br>Rate-responsive pacing is indicated to provide increased heart rate appropriate to increasing levels of activity. | Sponsor registry | **Postmarket:** CoA to use sponsor registry to collect postmarket data. |

## Postmarket Use – Sponsor Registry

| Population | Key Elements or Endpoints from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| **Micra PAS:** Patients implanted with a Micra Transcatheter Pacing System. | **Primary:**<br>1) Acute-complication rate (≤ 30 days) related to MICRA system or implant procedure<br>2) Long-term complication-free survival rate | Nine-years of follow-up. |

**Narrative:**
As a condition-of-approval, the sponsor has agreed to conduct a post-approval study using a sponsor registry.

# Example 28. PMA - Approval for a Total Ankle Replacement System using Outside-the-US RWE as a Primary Source of Clinical Evidence and RWE for a Post-Approval Study [64, 65]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160036 | DT MedTech, LLC | Hintermann Series H3 Total Ankle Replacement System | The Hintermann Series H3 Total Ankle Replacement System is indicated for use as a non-cemented implant to replace a painful arthritic ankle joint due to primary osteoarthritis, post-traumatic osteoarthritis or arthritis secondary to inflammatory disease.<br><br>The device system is for prescription use. | Outside-the-US Registry<br><br>Performance goal derived from a meta-analysis that included published literature and registry data | **Premarket:** Primary source of clinical evidence<br><br>**Postmarket:** Post-approval study |

## Premarket Use –Outside-the-US Registry

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **H3 Registry:** Retrospective analysis of patients treated with the subject device who met the inclusion criteria for enrollment in the retrospective analysis. The H3 Registry is a single-site registry in Switzerland. The H3 system has been commercially available in Europe since 2003. | **Primary Endpoints (Co-primary)**<br>• American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Score at 2 years or later.<br>• Survivorship (absence of revision/removal) within 5 years<br>• Occurrence of a Serious Device-Related Adverse Event (SADE), as determined by the independent Clinical Events Committee) other than a removal/revision within 2 years<br><br>**Safety:**<br>• Serious device related adverse event rates compared against a performance goal derived from literature and registry data |

**Narrative:**

For this PMA application, the sponsor performed a retrospective analysis that compared data abstracted from an outside-the-US registry (H3 Registry) against a performance goal. The performance goal was derived from literature and registry data for a control device legally-marketed in the United States. The subject device has been commercially available in Europe since 2003. The sponsor also performed a safety analysis comparing adverse event data from the registry against adverse event data extracted from published literature and national joint registries. These analyses served as the primary basis supporting approval of the PMA.

## Postmarket Use – Post-approval study

| Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|
| **Primary Safety:** Significant adverse events, device or procedure-related adverse events.<br><br>**Primary Probable Benefit:** Maintenance of major Cobb angle less than or equal to 40 degrees at 60 months post-surgery | 10 years |

**Narrative:**

As a condition-of-approval, the sponsor has agreed to conduct a post-approval study (PAS) that will follow patients included in the premarket cohort (i.e. patients from the OUS registry). The results will be compared against a performance goal. Similar to the PMA study, the sponsor was requested to derive the performance goal using a meta-analysis of published literature and registry data for a control device legally marketed in the United States.

## Example 29. PMA - Approval of a Coronary Drug-Eluting Stent Leveraging Supplemental OUS Sponsor Registry Data [67, 68, 69, 70]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160043 | Medtronic, Inc. | Resolute Onyx Zotarolimus-Eluting Coronary Stent System | The Resolute Onyx Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to de novo lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 5.0 mm. | RESOLUTE International Registry | **Premarket**: Supplemental |

### Premarket Use– Sponsor Registry

| Population | Key Elements or Endpoints from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| **RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study (Non-RWE):** Single-arm, open-label trial, 75 enrolled patients<br><br>**Supplemental Clinical Studies (Non-RWE excluding RESOLUTE INTERNATIONAL Study):**<br>RESOLUTE INTEGRITY US PAS: Resolute Integrity post-approval study<br>RESOLUTE US: Prospective, non-randomized, historically controlled trial<br>RESOLUTE AC: Prospective, all-comers randomized trial (randomized 1:1 to XIENCE V or Resolute); 2292 patients.<br>RESOLUTE FIM: Single-arm trial (139 patients)<br>RESOLUTE Japan: Prospective, single arm trial (100 patients)<br>RESOLUTE Asia 38 mm Cohort: Prospective, non-randomized study (38mm Resolute stent); 109 patients<br>**RESOLUTE INTERNATIONAL (RWE):** Prospective, all-comers, real-world observational study; 2349 patients. | **Primary endpoint:** Composite endpoint of cardiac death or target vessel myocardial infarction at 12 months | Baseline, 30 days, 6 months, 1, 2 and 3 years |

**Narrative:**

The RESOLUTE ONYX Core (2.25mm-4.0mm) Clinical Study was the primary source of clinical evidence for the approval. FDA also reviewed clinical data from prior clinical investigations of stents in the Resolute device family, including clinical data collected in the RESOLUTE INTERNATIONAL, an all-comers, observational registry with subjects treated per local, routine practice. These prior clinical studies provided additional information on the safety and effectiveness performance of the Resolute stent family

## Example 30. PMA - Postmarket Surveillance of a Ventricular Support Device Using Sponsor Registry Data [71]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P170011 Conversion from HDE | ABIOMED, Inc. | Impella RP System | The Impella RP® System is indicated for providing temporary right ventricular support for up to 14 days in patients with a body surface area ≥1.5 $m^2$, who develop acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery. | cVAD Registry (Sponsor) | **Postmarket:** PAS to be conducted using cVAD registry (former USPELLA) |

## Postmarket Use– Sponsor Registry

| Population | Key Elements or Endpoints from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| **IMPELLA RP – Real-world Evidence Evaluation:** 60 consecutively treated patients (age ≥ 18 years old) treated with IMPELLA RP. Data collected through the cVAD registry.<br><br>**IMPELLA RP – Pediatric Real-world Evidence Evaluation:** 15 consecutively treated pediatric patients (under 18 years of age) or all pediatric patients under 18 years of age treated over a 5-year period (whichever comes first). Data collected using the cVAD registry. | **Primary (Both populations):**<br>Survival rate at 30 days post-explant or discharge (whichever is longer)<br>Bleeding, hemolysis, and pulmonary embolism at 30 days or discharge (whichever is longer)<br>Device malfunction, central venous pressure, cardiac index, and LVAD flow<br><br>Pediatric Population: Survival rate at 180 days | Age ≥ 18: Post-discharge data at 30 days, 90 days and 1 year.<br><br>Under 18 years of age: Post-discharge data at 30 days and 180 days. |

**Narrative:**

As a condition-of-approval, the sponsor has agreed to collect RWE on patients treated with the IMPELLA RP using the cVAD registry. Patients are treated and followed in the cVAD registry per standard of care and institution guidelines. Post-discharge data will be collected by telephone contact and review of medical records.

## Example 31. PMA - Approval of an Indication Expansion and Postmarket Surveillance of a Ventricular Support Device Leveraging Sponsor Registry Data [72, 73]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140003/S004 Supplement to expand indication and to include additional device catheters | ABIOMED, Inc. | Impella Ventricular Support Systems (Impella 2.5, 5.0, CP, LD) | The Impella 2.5, Impella CP, Impella 5.0, and Impella LD catheters, in conjunction with the Automated Impella Controller, are temporary ventricular support devices intended for short term use (< 4 days for the Impella 2.5 and Impella CP, and ≤ 6 days for Impella 5.0 and LD) and indicated for the treatment of ongoing cardiogenic shock that occurs immediately (< 48 hours) following acute myocardial infarction or open heart surgery as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures.* The intent of the Impella system therapy is to reduce ventricular work and to provide the circulatory support necessary to allow heart recovery and early assessment of residual myocardial function.<br><br>**optimal medical management and conventional measures include volume loading, use of pressors and inotropes support with or without IABP* | Sponsor registries (e.g. USPELLA, cVAD) | **Premarket:** Supplemental<br><br>**Postmarket:** PAS to be conducted using cVAD registry |

## Premarket Use – Sponsor Registries (e.g. USPELLA Registry)

| Population | Key Elements or Endpoints from RWE Sources | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **ISAR-SHOCK trial (Non-RWE):** 13 intra-aortic balloon pump arm and 13 Impella 2.5 patients with acute myocardial infarction with cardiogenic shock (AMICS)<br><br>**USPELLA (RWE):** 324 Impella patients with AMICS (Impella 2.5, Impella 5.0/LD, and Impella CP)<br><br>**AB5000 (RWE):** 115 AB5000 patients with AMICS | **Supplemental:** Freedom-from-death; duration-of-support; 30-day survival rate; survival-to-discharge; Adverse events (e.g. death, stroke/CVA, TIA, acute renal dysfunction, acute hepatic failure, bleeding, infection, hemolysis, MSOF, respiratory failure/dysfunction, supraventricular arrhythmia) | ISAR-SHOCK: Up to six months.<br><br>USPELLA: Discharge, 30-day | Analyses included analysis of all UPSELLA patients as well as a sub-analysis of patients stratified by those who may qualify for ISAR-SHOCK and a population who would likely be excluded from ISAR-SHOCK. |

**Narrative:**

The primary clinical study (ISAR-SHOCK) was a randomized clinical trial with two arms (intra-aortic balloon pump arm vs Impella 2.5 arm).

FDA also reviewed supplemental analyses of freedom-from-death and 30-day survival rate, survival-to-discharge rate, duration-of-support and adverse events from AMICS patients from the sponsor's USPELLA registry, including data from device models (e.g. Impella 5.0/LD and Impella CP) not in the pivotal ISAR-SHOCK trial. FDA also reviewed survival-to-discharge rates (the primary effectiveness outcome of interest) between two UPSELLA cohorts: patients who may have qualified for ISAR-SHOCK and a higher-risk

cohort that would likely not qualify. Finally, FDA also reviewed supplemental analyses of freedom-from-death and survival-to-discharge rate between matched patients supported with the Impella device family and a temporary ventricular assist device comparator (AB5000).

These analyses provided supportive evidence on the effectiveness and benefit-to-risk of the device as well as additional clinical evidence on device catheters (e.g., Impella 5.0/LD, Impella CP) not evaluated in the pivotal trial

## Postmarket Use– Sponsor Registry (cVAD Registry)

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|---|
| **cVAD Registry (RWE)**: Minimum of 276 patients supported with Impella devices for the indication of AMICS with revascularization and enrolled in the cVAD registry | **Primary:** Survival rates (longer between discharge or 30 days)<br><br>**Secondary:** Adverse event rates (longer between discharge or 30 days). Technical and implant success rate (exit from catheterization laboratory or operation room). | 30 days, 90 days, 1 year post implant follow ups |

**Narrative:**

As a condition-of-approval, the sponsor has agreed to conduct a post-approval study evaluating the safety and effectiveness of Impella devices in a real-world population using data through the cVAD registry.

## Example 32. PMA - Approval of an Indication Expansion and Postmarket Surveillance of a Ventricular Support Device Leveraging Sponsor Registry Data [74, 75]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140003/S005 Supplement to expand indication and include additional device catheters | ABIOMED, Inc. | Impella Ventricular Support Systems (Impella 2.5, 5.0, CP, LD) | The Impella 2.5, Impella CP, Impella 5.0, and Impella LD catheters, in conjunction with the Automated Impella Controller, are temporary ventricular support devices intended for short term use (≤ 4 days for the Impella 2.5 and Impella CP, and ≤ 6 days for Impella 5.0 and LD) and indicated for the treatment of ongoing cardiogenic shock that occurs immediately (< 48 hours) following acute myocardial infarction or open heart surgery as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures.* The intent of the Impella system therapy is to reduce ventricular work and to provide the circulatory support necessary to allow heart recovery and early assessment of residual myocardial function.<br><br>**optimal medical management and conventional treatment measures include volume loading and use of pressors and inotropes, with or without IABP.* | Sponsor registries (e.g. USPELLA, cVAD)) | **Premarket:** Supplemental<br><br>**Postmarket:** PAS to be conducted using cVAD registry |

### Premarket Use– Sponsor Registry (e.g. UPSELLA Registry)

| Population | Key Elements or Endpoints from RWE sources | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **RECOVER I trial (Non-RWE):** Single-arm study of 15 Impella 5.0/LD patients met inclusion/exclusion criteria.<br><br>**USPELLA (RWE):** 77 post-cardiotomy cardiogenic shock (PCCS) Impella patients (Impella 2.5, Impella 5.0/LD, and Impella CP)<br><br>**AB5000 (RWE):** 79 AB5000 patients with PCCS (benchmark for comparison) | **Supplemental:** Freedom-from-death (survival to 30 days); Adverse events (e.g. death, stroke/CVA, TIA, acute renal dysfunction, acute hepatic failure, bleeding, infection, hemolysis, multi-system organ failure, acute hepatic failure, supraventricular arrhythmia, sepsis, respiratory failure/dysfunction) | RECOVER I: 30 days,60 days,180 days, 1-year<br><br>USPELLA/AB5000: Discharge/30 days | Analyses included analysis of all UPSELLA patients as well as two sub-analyses of patients. The first sub-analysis analyzed USPELLA data based on ascending risk of mortality. The second sub-analysis---requested by FDA---analyzed data from UPSELLA patients supported by Impella before, during and after surgery. |

**Narrative:**

The primary clinical study (RECOVER I) was a single-arm clinical trial which evaluated outcomes of cardiogenic shock or low-cardiac output syndrome patients supported using Impella 5.0/LD.

FDA reviewed supplemental analyses of freedom-from-death and adverse events from PCCS patients from the sponsor's USPELLA registry, including data from device models (Impella 2.5 and Impella CP) not in the pivotal trial. FDA also reviewed analyses of freedom-from-death for patients categorized by risk-of-mortality and those supported with

the device before, during and after surgery. Finally, FDA also reviewed supplemental benchmark analyses between the Impella device family and a temporary ventricular assist device comparator (AB5000).

These analyses provided supportive evidence on the effectiveness and benefit-to-risk of the device as well as additional clinical evidence on device catheters not evaluated in the pivotal study.

## Postmarket Use– Sponsor Registry (cVAD Registry)

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|---|
| **cVAD Registry:** Minimum of 44 patients supported with Impella devices for post-cardiotomy cardiogenic shock (PCCS) and enrolled in the cVAD registry. | **Primary:** Survival rates (longer between discharge or 30 days)<br><br>**Secondary:** Adverse event rates (longer between discharge or 30 days). Technical and implant success rate (exit from catheterization laboratory or operation room). | 30 days, 90 days, 1 year post implant follow ups |

**Narrative:**
The sponsor has agreed to conduct a post-approval study evaluating the safety and effectiveness of Impella devices in a real-world population using the cVAD registry.

# Example 33. PMA - Indication Expansion and Postmarket Surveillance of a Drug-Eluting Peripheral Transluminal Angioplasty Catheter Leveraging OUS Sponsor Registry Data [76, 77]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P130024/S009 Supplement to expand indication | Lutonix, Inc. | Lutonix 035 Drug Coated Balloon PTA Catheter | The Lutonix 035 Drug Coated Balloon PTA Catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic or in-stent restenotic lesions up to 300mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm. | Global SFA Registry (Sponsor Registry) | **Premarket:** Primary |

## Premarket Use– Sponsor Registry (GLOBAL SFA Registry)

| Population | Key Elements or Endpoints from RWE Sources | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **GLOBAL SFA Registry (RWE):** OUS registry. 691 patients (38 sites) treated with the device for stenotic or obstructive femoropopliteal arteries including those with in-stent restenotic lesions (ISR).<br><br>**SFA ISR Study (Non-RWE):** Randomized clinical trial. 82 patients randomized 2:1 to Lutonix DCB or standard balloon angioplasty for treatment of femoropopliteal in-stent restenosis.<br><br>**Long-Lesion SFA Study (Non-RWE):** Single-arm study; 118 patients (14 sites) treated with device and presenting with long-lesions ( ≥ 14cm) | **Primary Safety:** Composite endpoint of freedom at 30 days from target vessel revascularization (TVR), major index limb amputation, and device- and procedure-related death<br><br>**Primary Effectiveness:** Freedom from target lesion revascularization (TLR) at 12 months | GLOBAL SFA Registry: 1, 6, 12 and 24 months. | Sub-analyses by gender, long-lesions >140mm), ISR lesions |

**Narrative:**

The primary clinical studies submitted in support of the PMA included a real-world registry, a randomized clinical trial, and a single arm study. RWE from the GLOBAL SFA Registry was used in the primary assessment of effectiveness and safety for both the ISR and long-lesion (up-to 300mm in length) indication expansions.

FDA's review of clinical effectiveness for treatment of ISR included assessments of twelve-month freedom-from-TLR and twelve-month primary patency data from the GLOBAL SFA Registry (RWE) and twelve-month patency data and freedom from clinically-driven-TLF data from the SFA ISR Study. FDA's review of clinical safety included assessments of composite endpoints from the GLOBAL SFA Registry (RWE) and SFA ISR Study.

FDA's review of clinical effectiveness for treatment of lesions up-to-300mm in length with the device included assessments of twelve-month freedom-from-TLR and twelve-month primary patency data from the long-lesion subset in the GLOBAL SFA Registry (RWE) and twelve-month primary patency and twelve-month freedom from clinically-driven TLR from the Long-lesion SFA Study. FDA's review of clinical safety included assessments of composite endpoints from the GLOBAL SFA Registry (RWE) and Long-Lesion SFA Study.

## Postmarket Use– Sponsor Registry (GLOBAL SFA Registry)

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|---|
| **Global SFA Registry:** Continued follow-up of the ISR and long-lesion cohorts in the GLOBAL SFA Registry | **Primary:** Composite of freedom from all-cause peri-procedural death (≤30 days). 12-month and 24-month freedom from index limb amputation, index limb re-intervention, index limb-death, and TLR. | Through 24-months post-procedure. |

**Narrative:**

As a condition-of-approval, the sponsor has agreed to conduct a post-approval study following SFA and long-lesion cohorts (through 24-months post-procedure) in the GLOBAL SFA Registry.

# Example 34. PMA - Indication Expansion and Postmarket Surveillance of an Endovascular Graft for Aortic Aneurysms Leveraging Sponsor Registry Data [78]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P100021/S063 Supplement to expand indication | Medtronic Vascular | Endurant II/Endurant IIs Stent Graft System | The Endurant II/IIs bifurcated stent grafts are indicated for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. They may be utilized in conjunction with the Heli-FX EndoAnchor System when augmented radial fixation and/or sealing is required; in particular, in the treatment of abdominal aortic aneurysms with short (> 4 mm and < 10 mm) infrarenal necks. The Endurant II aorto-uni-iliac (AUI) stent graft is indicated for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms in patients whose anatomy does not allow the use of a bifurcated stent graft. The Endurant II/IIs Stent Graft System is indicated for use in patients with the following characteristics: [See approval order for full list] | ANCHOR Registry | **Premarket:** Sole-source of primary clinical information<br><br>**Postmarket**: CoA to conduct postmarket data collection utilizing same registry. |

## Premarket Use– ANCHOR Registry

| Population | Key Elements or Endpoints from RWE sources | Follow-up / Duration | Methods of Note |
|---|---|---|---|
| **ANCHOR Registry:** 70 patients enrolled into the registry who were treated with Endurant or Endurant II/IIs Stent Graft Systems and met enrollment criteria. (22 sites, 19 in US, 3 OUS) | **Primary Safety:** No primary safety endpoint, but supportive data collected on morbidity and mortality.<br><br>**Primary Effectiveness:** Technical success rate; Type Ia endoleak rate at 1 month and 12 months; re-intervention rate through 12 months. | Follow-up per local standard of care.<br><br>Data collected at baseline and up to 5 years post-procedure. | Imaging data is collected per standard of care and is evaluated by an imaging core lab (per-protocol).<br><br>Broadly-defined analysis time windows (due to collection of data per standard of care and to include as many subjects as possible) |

**Narrative:**

The ANCHOR Registry collects clinical data from patients treated with the Heli-FX EndoAnchor system and endovascular grafts from several manufacturers, including the graft in the submission. RWE from this real-world registry were the sole-source of primary clinical evidence used in the assessment of safety and effectiveness for the proposed indication (FDA also reviewed supplemental clinical information from literature).

Specifically, for effectiveness, FDA reviewed analyses of technical success rate (successful delivery and successful and accurate deployment of the graft), Type Ia endoleak rates at 1 and 12 months, and re-intervention rates through 12 months. For safety, FDA reviewed aneurysm-related mortality, aneurysm rupture through 30 days and 12 months, major adverse events through 30 days, and renal insufficiency and failure through 30 days. FDA also reviewed all-cause mortality, major adverse events and serious adverse events through 12 months.

## Postmarket Use– ANCHOR Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|---|
| **ANCHOR Registry (RWE):** Continued follow-up of the short-neck cohort in the ANCHOR Registry. | **Primary:** Aneurysm-related mortality, aneurysm rupture, aneurysm expansion, Type Ia endoleak, migration, Type III endoleak, re-intervention, device-related adverse events, and device integrity. | Five-year follow-up with data analyzed annually. |

**Narrative:**

As a condition-of-approval, the sponsor has agreed to conduct a post-approval study following the PMA cohort (through 5 years post-procedure) in the ANCHOR Registry.

## Example 35. PMA - Postmarket Surveillance of a Ventricular Assist Device Leveraging a Sponsor Registry [79]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P100047/S090 Supplement to expand indication | Medtronic, Inc. | HeartWare HVAD System | The HeartWare™ HVAD™ System is indicated for hemodynamic support in patients with advanced, refractory left ventricular heart failure; either as a bridge to cardiac transplantation (BTT), myocardial recovery, or as destination therapy (DT) in patients for whom subsequent transplantation is not planned. | Sponsor registry | **Postmarket:** CoA to use sponsor registry to collect postmarket data. |

### Postmarket Use– Sponsor Registry

| Population | Key Elements or Endpoints from RWE sources | Follow-up/Duration (RWE) |
|---|---|---|
| **ENDURANCE Supplemental PAS:** 300 subjects enrolled and followed using the sponsor's Product Surveillance Registry (PSR). | **Primary Endpoint:** Survival free of disabling stroke or device malfunction requiring exchange, explant, or urgent transplant.<br><br>Secondary: Observed early stroke rate (≤2 years post-implant) and stroke risk factors; late stroke rate (>2 years post-implant) and late stroke risk factors, and stroke severity. | Through five-years post implant. |

**Narrative:**
As a condition-of-approval, the sponsor has agreed to conduct a post-approval study using a sponsor registry

## Example 36. PMA - Modification to Indications for Use Statement for a Vascular Hemostasis Device Using the Sponsor's Registry Study [80]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P960043/S097 | Abbott Vascular Inc. | Perclose ProGlide Suture-Mediated Closure System | The Perclose ProGlide SMC System is indicated for the percutaneous delivery of suture for closing the common femoral artery and vein access site of patients who have undergone diagnostic or interventional catheterization procedures. The Perclose ProGlide SMC System is used without or, if required, with adjunctive manual compression:<br>- For access sites in the common femoral artery using 5F to 21F sheaths<br>- For access sites in the common femoral vein using 5F to 24F sheaths.<br>- For arterial and venous sheath sizes greater than 8F, at least two devices and the pre-close technique are required. | EVEREST II/REALISM Continued Access Registry Study for Abbott MitraClip device | **Premarket:** Sole source of clinical evidence |

## Premarket Use – Analysis of Retrospectively Collected Data from EVEREST II/REALISM Continued Access Registry Study

| Population | Key Elements or Endpoints from RWE source |
|---|---|
| **ProGlide Cohort from EVEREST II/REALISM Continued Access Registry Study:** 159 patients in whom the subject device was used as the primary method for large bore venous access-site closure with or without secondary closure methods during the MitraClip index procedure with the MitraClip 24Fr vascular sheath, and who were enrolled in the five (5) REALISM sites identified as high frequency users of vessel closure devices and utilized the subject device for vessel closure | **Primary:**<br>Rate of freedom from major femoral vein access-site related complications at 30-days post MitraClip index procedure<br><br>See Summary of Safety and Effectiveness Data for additional details and complete list. |

**Narrative:**

For this PMA panel track supplement, data from the sponsor's continued access registry for a different device were utilized to expand the indication of their suture delivery system to include closing femoral artery access sites using sheaths up to 24F, increased from 21F in the previous indication. A patient cohort from the continued access study that received the suture delivery system was selected based on usage of the subject device across the sites in the continued access study, and their medical records were retrospectively analyzed for safety and efficacy. This supplement was exempted from going to the Circulatory Systems Devices Panel, and the submitted real-world evidence served as the sole support for supplement approval.

## Example 37. PMA - Modification for Indications for Use Statement for Two Coronary Drug-Eluting Stents Using Sponsor Registry Data and a Post-Approval Study [81, 82, 83, 84]

| File | Sponsor | Devices | Approved / Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160043/S012, P110013/S088 | Medtronic Vascular | Resolute Onyx Zotarolimus-Eluting Coronary Stent System, Resolute Integrity Zotarolimus-Eluting Coronary Stent System | Please see Approval Orders for P160043/S012 and P110013/S088. | PERSPECTIVE Study<br><br>Global RESOLUTE Clinical Trial Program: RESOLUTE International Registry & RESOLUTE China Registry | **Premarket**: Primary source of clinical evidence<br><br>**Postmarket:** CoA to collect postmarket data in sponsor PAS and RCT. |

## Premarket Use – Sponsor Registry Data (US and OUS)

| Population | Key Elements or Endpoints from RWE source |
|---|---|
| **PERSPECTIVE Study – Resolute CTO Cohort (RWE):** 183 patients who underwent attempted percutaneous chronic total occlusion revascularization treated with the Resolute Integrity stent at a single center in US<br><br>**Global RESOLUTE Clinical Trial Program – RESOLUTE International Registry & RESOLUTE China Registry (RWE):** 358 patients treated with Resolute DES for chronic total occlusions | **Safety and Effectiveness:**<br>Occurrence of major adverse cardiac events (MACE) defined as: death, myocardial infarction (MI) (ARC defined), and clinically-driven target lesion revascularization at one-year post-procedure<br>Lesion success defined as: attainment of <50% residual stenosis of the target lesion using any percutaneous method<br>Device success defined as: attainment of <50% residual stenosis of the target lesion using only the assigned device<br>Procedure success defined as: attainment <50% residual stenosis of the target lesion and no in-hospital MACE<br><br>Please see Summary of Safety and Effectiveness Data for P160043/S012 and P11013/S088 for additional details and complete list. |

**Narrative:**

These bundled panel track PMA supplements are in support of an indication expansion for the Resolute family of stents to include treatment of patients with coronary chronic total occlusions. The sponsor submitted real-world evidence in the form of a US single-center prospective/retrospective observational study collecting data from medical records and US and OUS sponsor registry data pooled for analysis of a cohort of patients treated with the subject devices. These data were used to support approval of these supplements.

## Post-market Use – Post-approval study

| Population | Key Elements or Endpoints from RWE source | Follow-up |
|---|---|---|
| **RESOLUTE ONYX CTO Post-Approval Study (PAS001):** Lesion- and patient-level meta-analyses of approximately 100 subjects with chronic total occlusions treated with subject devices enrolled in the RESOLUTE ONYX CTO Post-Approval Study and ONYX ONE OUS randomized clinical trial.<br><br>Please see the Resolute Onyx PAS pages (P160043/S012, P110013/S088, P160043/S001)) for additional details. | **PAS001 Endpoints:**<br>**Primary:**<br>Freedom from MACE (death, myocardial infarction, and clinically-driven target lesion revascularization) at 30 days<br>**Secondary:**<br>Acute success (device, lesion, and procedure), cardiac death, target vessel MI, TLR, TLF, TVF, stent thrombosis | Two years |

**Narrative:**

As a condition-of-approval for these bundled PMA supplements, the sponsor is required to conduct a post-approval study following patients with chronic total occlusions treated with the subject devices enrolled in the RESOLUTE ONYX CTO Post-Approval Study and ONYX ONE OUS randomized clinical trial in order to demonstrate the generalizability of the performance the Resolute family of drug-eluting stents for the treatment of chronic total occlusions (CTOs) in a real-world setting. Approximately 100 patients will be followed for two years, with the primary safety and effectiveness endpoint being freedom from MACE.

# Appendix Section II. Examples Leveraging Administrative Claims Data for Real-World Data Collection

## Guide to Examples Leveraging Administrative Claims Data for Real-World Data Collection

| | File | Sponsor | Device | Real-World Data (RWD) Source(s) | RWE Use | Key Tags |
|---|---|---|---|---|---|---|
| **38** | P180035 | CooperVision, Inc. | MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear | Retrospective review of medical records from seven (7) US clinics<br><br>Electronic health-records and claims data | **Premarket:** RWE in addition to clinical trial data was a primary source of clinical evidence for this original PMA.<br><br>**Postmarket**: The sponsor has agreed to conduct a post-approval study (PAS) that proposes to use RWE from electronic health records and claims data from integrated health care and coverage providers or integrated optometry/ophthalmology practices (PAS protocol pending as of 1/2/20). | Administrative claims data;<br>Medical records (EHR, EMR or chart review);<br>Pediatric RWE;<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |
| **39** | P040020/S049 | Alcon Research, Ltd | AcrySof IQ ReSTOR +3.0 D Multifocal Toric Intraocular Lens | CMS Medicare Beneficiary Encrypted Files | **Postmarket:** For this indication expansion of a multifocal intraocular lens, the post-approval study will utilize Medicare Beneficiary Encrypted Files as part of a retrospective study of all cataract surgeries in the Medicare population from 2011-2013, comprising approximately 180,000 surgeries, in order to estimate the background rate of post-surgical intraocular inflammation to compare to the subject device. | Administrative claims data; |

## Example 38. PMA - Approval for a Daily Wear Soft Contact Lens to Reduce the Progression of Myopia Using Retrospective Review of Medical Records and RWE for a Post-Approval Study [85, 86, 87]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P180035 | CooperVision, Inc. | MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear | MiSight 1 Day (Omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear are indicated for the correction of myopic ametropia and for slowing the progression of myopia in children with non-diseased eyes, who at the initiation of treatment are 8-12 years of age and have a refraction of -0.75 D to -4.00 D (spherical equivalent) with ≤ 0.75 diopters of astigmatism. The lens is to be discarded after each removal. | **Premarket:** Retrospective review of medical records from community optometry clinics<br><br>**Postmarket:** RWE from electronic health-records and claims data from integrated health care and coverage providers or integrated optometry/ophthalmology practices | **Premarket:** Primary source of clinical evidence<br><br>**Postmarket**: Post-approval study |

## Premarket Use – Retrospective Review of Medical Records from Community Clinics

| Population | Key Elements or Endpoints from RWE source |
|---|---|
| **MiSight Randomized Controlled Study (MIST-401) (Non-RWE)**: Two-arm, randomized, controlled trial (n=187)<br><br>**Retrospective Review of Medical Records (RWE):** 2134 patient-years from 782 US pediatric patients with soft contact lens, age 8-12. | **Safety:**<br>Rate of Microbial Keratitis (no higher than 0.4% per patient-year)<br><br>**Effectiveness:**<br>Assessed in a separate clinical trial |

**Narrative:**

MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear are indicated for the correction of myopic ametropia and for slowing the progression of myopia in children. For this original PMA, the sponsor provided clinical evidence from a randomized, controlled trial. In addition---to satisfy the premarket requirement---the sponsor was required to demonstrate that the rate of Microbial Keratitis (MK), a potential vision-threatening adverse event, is no higher than 0.4% per patient-year. This risk has not been extensively evaluated in pediatric populations and requires a sample size greater than the pivotal trial to estimate because of the low prevalence.

To meet the FDA premarket requirement, the sponsor conducted a retrospective study investigating real-world soft contact lens use among children. In this study, the sponsor conducted a retrospective analysis of medical records of 782 pediatric patients, age 8 – 12, wearing commercially available soft contact lens from seven (7) US community clinics. SAEs and MK were identified through chart review conducted by an adjudication committee consisted of three independent ophthalmologists and optometrists. In total, two MK were identified (both were resolved), and a rate of 9.4/10,000 patient-years were established (95% CI: [2.3 to 37.7 per 10,000]), with the upper bound of 95% CI lower than the 0.4%/patient-year requirement.

## Postmarket Use – Post-approval study with RWE from electronic health-records and claims data from integrated health care and coverage providers or integrated optometry/ophthalmology practices

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|---|
| Consecutive subjects receiving the device who consent to the use and release of their health encounter data for this PAS. | Microbial keratitis,<br>Incidence of loss of best-corrected visual acuity<br>Incidence of non-infectious infiltrative keratitis<br>Peripheral noninfectious ulcers | Three-years (post-fitting) |

**Narrative:**

As a condition-of-approval, the sponsor agreed to conduct a post-approval to provide additional long-term data on the safety and effectiveness of the device. The sponsor agreed to evaluate the rate of MK among those who use the MiSight against a performance goal of 0.2%/patient-year. This endpoint would be difficult to assess in a traditional clinical trial due to its low-prevalence. Instead, the sponsor has agreed to conduct this post-approval study within integrated health care and coverage organization systems or integrated (optometry/ophthalmology) eyecare practices. Outcome data will come from electronic health records and administrative claims. The full post-approval study protocol is pending as of 1/2/2020.

## Example 39. PMA - Postmarket Surveillance of a Multifocal Intraocular Lens Utilizing Data from Medicare Beneficiary Encrypted Files (CMS) [88]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P040020/S049 Supplement to expand indication | Alcon Research, Ltd. | AcrySof IQ ReSTOR +3.0 D Multifocal Toric Intraocular Lens | The AcrySof IQ ReSTOR +3.0 D Multifocal Toric Posterior Chamber Intraocular Lens (IOL) is indicated for primary implantation in the capsular bag of the eye for the visual correction of aphakia and pre-existing corneal astigmatism secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision, reduction of residual refractive cylinder and increased spectacle independence. The lens is intended to be placed in the capsular bag. | CMS Medicare Beneficiary Encrypted Files | **Postmarket:** Multi-center surveillance study that will also use data from Medicare Beneficiary Encrypted Files (BEF) to estimate background rate of post-surgical intraocular inflammation |

## Postmarket Use – Post-approval study leveraging CMS Medicare Beneficiary Encrypted Files

| Population | Key Elements or Endpoints from RWE source | Follow-up | Methods of Note |
|---|---|---|---|
| Data from all cataract surgeries in the Medicare population (from 2011-2013) will be used to estimate the background rate of the outcome of interest. (Estimated to contain 180,000 surgeries)<br><br>Sponsor is also collecting data on the device patients in a separate study phase. (3000 eyes) | **Primary:**<br>Rate of post-surgical intraocular inflammation (using associated coding for endophthalmitis, uveitis, postsurgical intraocular inflammation or other related codes). | Primary rates to be estimated from a 180-day period following intraocular lens implantation | Using Medicare beneficiary files for a retrospective study to estimate the background rate of post-surgery ocular inflammation, which will be used to compare with the observed rate in the device group (for which new data collection will take place). |

**Narrative:**

The post-approval study will evaluate the rate of post-surgical intraocular inflammation between a device cohort against the rate of post-surgical intraocular inflammation extracted from ICD-9 codes in 2011-2013 Medicare Beneficiary Encrypted Files (BEF). The study consists of two phases. Phase A involves new data collection from 3000 eyes implanted with the AcrySof IQ ReSTOR +3.0 D Toric IOL for up to 180 days. The second phase is the analysis of 2011-2013 Medicare Beneficiary Encrypted Files (BEF) to determine the background post-surgical intraocular inflammation rate.

# Appendix Section III. Examples Leveraging Both National Registries and Administrative Claims Data for Real-World Data Collection

## Guide to Examples Leveraging Both National Registries and Administrative Claims Data for Real-World Data Collection

| | File | Sponsor | Device | Real-World Data (RWD) Source(s) | RWE Use | Key Tags |
|---|---|---|---|---|---|---|
| **40** | P130013 | Boston Scientific Corporation | WATCHMAN LAA Closure Technology | ACC LAAO Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | As a condition-approval, postmarket surveillance will be performed through the ACC Left Atrial Appendage Occlusion (LAAO) Registry in an all-comers population. Longer-term outcomes in interest will be collected by linkage to CMS. | Administrative claims data;<br>Registry data; |
| **41** | P140031 | Edwards Lifesciences, LLC | SAPIEN 3 Transcatheter Heart Valve | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | For this original PMA, postmarket surveillance will be conducted through the STS/ACC TVT Registry with linkage to CMS as a condition-of-approval. | Administrative claims data;<br>Registry data; |
| **42** | P110042/S077 | Boston Scientific Corporation | EMBLEM S-ICD Subcutaneous Electrode, Model 3501 | ACC NCDR: ICD Registry; LATITUDE NXT Patient Management System; CMS Claims Database; Truven MarketScan; National Death Index | As a condition-of-approval, the sponsor agreed to conduct postmarket surveillance using RWE from multiple real-world data sources including a national registry, public and private claims, remote monitoring of device generated data, and the National Death Index. | Administrative claims data;<br>Registry data; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **43** | P140031/S028 | Edwards Lifesciences, LLC | SAPIEN 3 Transcatheter Heart Valve | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | For this PMA supplement seeking an indication expansion, clinical evidence from the STS/ACC registry served as the sole support for approval, and was utilized, with additional linkage to CMS for long-term outcomes, for postmarket surveillance as a condition-of-approval. | Administrative claims data;<br>Registry data;<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |
| **44** | P130009/S034 | Edwards Lifesciences, LLC | SAPIEN XT Transcatheter Heart Valve | Sponsor Registry, STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database | RWE from a sponsor registry served as supplemental evidence for this PMA supplement for an indication expansion, and postmarket surveillance will be performed through the STS/ACC TVT Registry with linkage to CMS as a condition-of-approval. | Administrative claims data;<br>Registry data;<br>Total-Product Lifecycle Example; |
| **45** | P130021/S010 | Medtronic CoreValve LLC | CoreValve System | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database | For this indication expansion, postmarket surveillance will be conducted through the STS/ACC TVT registry with linkage to CMS for long term outcomes of up to five years post-implantation. | Administrative claims data;<br>Registry data; |
| **46** | P130009/S057 | Edwards Lifesciences, LLC | SAPIEN XT Transcatheter Heart Valve | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | Postmarket surveillance will be conducted through the STS/ACC TVT Registry with linkage to CMS for longer-term outcomes for this PMA supplement for an indication expansion. | Administrative claims data;<br>Registry data; |
| **47** | P130021/S033 | Medtronic CoreValve | CoreValve System | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | For this PMA supplement to expand indication, postmarket surveillance will be conducted through the STS/ACC TVT Registry with linkage to CMS as a condition-of-approval. | Administrative claims data;<br>Registry data; |
| **48** | P140031/S010 | Edwards Lifesciences, LLC | SAPIEN 3 Transcatheter Heart Valve | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | Postmarket surveillance will be conducted through the STS/ACC TVT Registry with linkage to CMS for this PMA supplement for indication expansion. | Administrative claims data;<br>Registry data; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **49** | P100009/S028 | ABBOTT VASCULAR INC | MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | For this PMA supplement for an indication expansion, postmarket surveillance will be conducted through the STS/ACC TVT Registry with linkage to CMS as a condition-of-approval. | Administrative claims data;<br>Registry data; |
| **50** | P130021/S058 | Medtronic CoreValve LLC | Medtronic CoreValve Evolut R System, Medtronic CoreValve Evolut PRO System | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | Postmarket surveillance will be conducted through the STS/ACC TVT Registry with linkage to CMS for this PMA supplement for an indication expansion. | Administrative claims data;<br>Registry data; |
| **51** | P140031/S085 | Edwards Lifesciences LLC | Edwards SAPIEN 3 Transcatheter Heart Valve System, Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | For this PMA supplement for an indication expansion, postmarket surveillance will be performed using the STS/ACC TVT Registry with linkage to CMS. | Administrative claims data;<br>Registry data; |
| **52** | NCT02687035 | Edwards Lifesciences, LLC | SAPIEN 3 Transcatheter Heart Valve | STS/ACC TVT Registry<br><br>Centers for Medicare and Medicaid Services (CMS) claims database. | For this continued-access program, data will be collected using the STS/ACC TVT Registry with linkage to CMS. | Administrative claims data;<br>Registry data; |

## Example 40. PMA - Postmarket Surveillance of a Left Atrial Appendage Closure Device Utilizing a National Registry and Claims Data for Condition-of-Approval [89, 90]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P130013 | Boston Scientific Corporation | WATCHMAN LAA Closure Technology | The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:<br>*Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc1 scores and are recommended for anticoagulation therapy;<br>*Are deemed by their physicians to be suitable for warfarin; and<br>*Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin | ACC LAAO Registry<br><br>CMS | **Postmarket:** CoA to use LAAO Registry with linkage to CMS for postmarket surveillance. |

### Postmarket Use – American College of Cardiology (ACC) Left Atrial Appendage Occlusion (LAAO) Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| Minimum of 2000 patients, (all-comers population) | **Primary:**<br>Implant success rate; Procedural safety; Effective Closure of left-atrial appendage; Composite Stroke and all-cause mortality; Ischemic stroke or systemic embolism; Peri-procedural events | Five years of surveillance | Linkage to CMS for longer-term outcomes of interest |

**Narrative:**

This hypothesis-driven, post-approval surveillance project was designed to evaluate several performance goals in an all-comers population. Some of the performance goals are related to longer-term outcomes (stroke, systemic embolism, etc.). The enrollees are being followed per standard of care for two years in the registry, and then specific outcomes of interest are being collected via linkage to CMS claims data for follow-up years three through five.

## Example 41. PMA - Postmarket Surveillance of a Transcatheter Heart Valve Utilizing a National Registry for Condition-of-Approval [91, 92, 93, 94]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140031 | Edwards Lifesciences, LLC | SAPIEN 3 Transcatheter Heart Valve | The Edwards SAPIEN 3 Transcatheter Heart Valve (THV), model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). | STS/ACC TVT Registry<br><br>CMS | **Postmarket:** CoA to use TVT Registry with linkage to CMS for postmarket surveillance. |

### Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| All implanted patients (as described in the approved indication) in the STS/ACC TVT Registry within 5 years of device approval | **Primary:**<br>(1) Device success (intra-procedure);<br>(2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy, acute events associated with index TAVR procedure), peri- procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological (non- stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months;<br>(4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) annually through 5-year post implantation | Five years of surveillance | Linkage to CMS for longer-term outcomes of interest |

**Narrative:**

Surveillance will be conducted in the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the SAPIEN 3 THV in implanted patients (at high or greater risk for open surgical therapy) within 5 years of device approval. Follow up of these patients will be conducted through linkage to the CMS database for long-term surveillance through 5 years post implantation.

## Example 42. PMA - Postmarket Surveillance of an Implantable Cardioverter-Defibrillator Utilizing National Registries and Claims Data for Condition-of-Approval [95, 96, 97, 98]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P110042/S077 | Boston Scientific Corporation | EMBLEM S-ICD Subcutaneous Electrode, Model 3501 | The S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmia in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing. | • ACC NCDR: ICD Registry;<br>• LATITUDE NXT Patient Management System<br>• CMS Claims Database<br>• Truven MarketScan<br>• National Death Index (linkage to NCDR patients). | Postmarket – CoA post-approval study utilizing multiple RWE data sources |

### Postmarket Use – Post-Approval Study with Data Collected Using American College of Cardiology - National Cardiovascular Data Registry (NCDR) ICD Registry, CMS Claims, Truven MarketScan, National Death Index, and Remote-Monitoring

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| US consecutive patients implanted with EMBLEM S-ICD Electrode Model 3501 whose data are captured in one of the databases utilized for this study.<br><br>• NCDR ICD Registry (N=2,100)<br>• National Death Index linkage to NCDR patients (N=2,100).<br>• LATITUDE NXT Patient Management System (N=2,000);<br>• CMS Claims Database (N=2,100) | **Primary:**<br>• NCDR: The first primary endpoint evaluates the rate of Model 3501 implant and periprocedural complications.<br>• Remote Monitoring (LATITUDE NXT): The second primary endpoint evaluates the five-year rate of Model 3501 EMBLEM S-ICD Electrode integrity alerts.<br>• Administrative Claims (CMS): The third primary endpoint evaluates the five-year rate of Model 3501 EMBLEM S-ICD Electrode complications requiring reoperation or hospitalization.<br>• National Death Index: The fourth primary endpoint evaluates the five-year rate of Model 3501 EMBLEM S-ICD Electrode patient deaths from any cause.<br><br>**Secondary:**<br>• Administrative Claims (Truven): The secondary endpoint evaluates the five-year rate of Model 3501 EMBLEM S-ICD Electrode complications requiring reoperation or hospitalization. | 5 years of surveillance | Use of multiple real-world evidence data sources including registries and device remote monitoring, as well as linkages with claims data and the National Death Index. |

**Narrative:**

This surveillance study marks a significant advancement on the methodologies used to monitor long-term performance of ICDs where multiple real-world data sources will be leveraged to monitor multiple aspects of real-world device safety and effectiveness. Usually, a new enrollment study requiring direct follow-up of patients of up to 5 years would have been required. For this approval, the postmarket study will leverage an existing national registry, remote monitoring of device-generated data, claims data from public and private payers, and the national death index, using only data collecting during routine-care.

# Example 43. PMA - Indication Expansion and Postmarket Surveillance for a Transcatheter Heart Valve Using a National Registry [99, 100, 101, 102]

| Fil | Sponsor | Device | Approved / Cleared / Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140031/S028<br>Supplement to expand indication | Edwards Lifesciences LLC | SAPIEN 3 Transcatheter Heart Valve | The Edwards SAPIEN 3 Transcatheter Heart Valve (THV), Model 9600TFX, and accessories are indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator). | STS/ACC Transcatheter Valve Therapy (TVT) Registry<br><br>Centers for Medicare and Medicaid Services (CMS) database | **Premarket:** Sole-Source of clinical evidence (STS/ACC TVT Registry)<br><br>**Postmarket:** CoA to use TVT Registry with linkage to CMS for postmarket surveillance. |

## Premarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **TVT Registry (Aortic Population) (RWE):** Patients treated with SAPIEN 3 (314) for failed surgical aortic prosthesis (aortic valve-in-valve)<br><br>**TVT Registry (Mitral Population) (RWE):** Patients treated with SAPIEN XT (241) or SAPIEN 3 (70) for failed surgical mitral prosthesis (mitral valve-in-valve) | **Safety:** All-cause mortality, cardiac mortality, stroke, transient ischemic attack (TIA), aortic valve intervention, mitral valve intervention<br><br>**Effectiveness:** Echocardiographic performance, NYHA classification, 5-meter walk test (aortic valve dataset), 6-minute walk test (mitral valve dataset), length of stay and quality of life score (KCCQ) | TVT Registry captures data at discharge, 30-days and 1 year.<br><br>Data in this submission analyzed at baseline, discharge, and 30-days. | Adverse event adjudication (readmission for heart failure, stroke/TIA and aortic and mitral valve reinterventions) performed per TVT Registry Coder's Data Dictionary |

**Narrative:**

The device is used in transcatheter aortic valve replacement. FDA reviewed analyses of real-world use of the device captured in the Society of Thoracic Surgeons / American College of Cardiology Transcatheter Valve Therapy (TVT) registry for this supplement seeking to expand the indication (to include treatment of patients with failed surgical bioprosthetic aortic or mitral valves and in high-risk patients). Analyses included both safety endpoints at discharge and 30-days (all-cause mortality, cardiac mortality, stroke, TIA, re-intervention) and effectiveness endpoints at baseline, discharge and 30-days (echo-derived gradient data, regurgitation, NYHA classification, 5-meter or 6-minute walk test, quality of life score, and length of index hospitalization stay) from aortic or mitral valve-in-valve patients. These analyses were the primary basis for approval of the PMA.

## Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| All mitral or aortic SAPIEN 3 Valve in Surgical Valve patients over 2 years post approval (June 5, 2017 to June 4, 2019). | **Aortic Indication Endpoints**: (1) Device success (intra-procedure);<br>(2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological (nonstroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months;<br>(4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction at 2-5 year post-implantation<br><br>**Mitral Indication Endpoints:**<br>**(**1) all-cause mortality, heart failure rehospitalization, and mitral valve reintervention at 30 days and 12 months;<br>(2) 6-minute walk distance, KCCQ, and change in NYHA functional class at 30 days and 12 months;<br>(3) device- or procedure-related adverse events, major bleeding complications, stroke and other cerebrovascular events, myocardial infarction, new requirement for dialysis, new onset atrial fibrillation, and other events or complications<br>[See Approval Order for full list] at 30 days and 12 months<br>(4) mitral valve hemodynamics at 30 days and 12 months;<br>(5) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction at 2-5 years post implantation | Surveillance through five-years post implantation | Linkage to CMS for long-term outcomes |

**Narrative:**

This surveillance plan will use the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the SAPIEN 3 Transcatheter Heart Valve in patients with a failed surgical bioprosthetic aortic or mitral valve for two years following device approval. Follow up of these patients will be performed through linkage to the CMS database for long-term surveillance through 5 years post implantation.

# Example 44. PMA - Indication Expansion and Postmarket Surveillance for a Transcatheter Heart Valve with National Registry Data [104, 105, 106]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P130009/S034 Supplement to expand indication | Edwards Lifesciences, LLC | SAPIEN XT Transcatheter Heart Valve | The Edwards SAPIEN XT Transcatheter Heart Valve is indicated for patients with symptomatic heart disease due to either severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). | SOURCE XT (Sponsor Registry, Premarket)<br><br>STS/ACC TVT Registry (Postmarket), w/ CMS | **Premarket:** Supplemental<br><br>**Postmarket:** CoA to use TVT Registry with linkage to CMS for postmarket surveillance. |

## Premarket Use – Supplemental RWE from SOURCE XT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration |
|---|---|---|
| **PARTNER II Nested Studies (Non-RWE):** Single-arm study and continued access study nested in PARTNER II Trial (197 attempted implant; 195 patients implanted, pooled across the original population and continued-access population). Included patients met the device sizing requirements (23mm or 26mm SAPIEN XT THV).<br><br>**SOURCE XT (RWE):** OUS post-approval registry collecting data on consecutive patients treated with the SAPIEN XT THV. 2688 patients enrolled in SOURCE XT; 57 of those underwent a "TAV-in-SAV" procedure (the proposed indication), using 23, 26 or 29mm valve sizes. | **Safety:**<br>All-cause death (30 days, 1 year, 2 years)<br>Cardiac death (30 days, 1 year, 2 years)<br>Stroke (All, Major stoke; 30 days, 1 year, 2 years)<br>Repeat hospitalization (30 days, 1 year, 2 years)<br>Other events (i.e. MI, See Summary of Safety and Effectiveness data for full list.)<br><br>**Effectiveness:**<br>Valve hemodynamics: Doppler velocity index, mean gradient, total aortic regurgitation at baseline, discharge, 30 days, 1 year, 2 years<br>Quality-of-life (ED-5Q) at baseline, 30 days, 1 year, 2 years<br>NYHA Classification change (baseline to 30 days, 1 year, 2 years) | SOURCE XT: Discharge, 30 days, and 12 months post-implant, and annually thereafter for up to 5 years. |

**Narrative:**
The primary source for clinical evidence and basis for approval for this supplement was from the PARTNER II nested clinical studies for "TAV-in-SAV" indications and included clinical evidence on two device sizes (23, 26mm). FDA also reviewed supplemental clinical information from the SOURCE XT Registry, which provided additional clinical evidence for all three valve sizes (23, 26 and 29mm), including an additional valve size (29mm) not evaluated in the PARTNER II nested studies. FDA approved the indication expansion for all three valve sizes (23, 26 and 29mm).

## Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| All implanted SAPIEN XT patients with symptomatic heart disease, due to either severe native calcific aortic stenosis or failure of a surgical bioprothesis valve who are at high or greater risk for open surgical therapy | **Primary endpoints**:<br>(1) Device success (intra-procedure);<br>(2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy, acute events associated with index TAVR procedure), peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months;<br>(4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) annually through 5 year post implantation | Five years of surveillance | Linkage to CMS for long-term outcomes (through 5 years) |

**Narrative:**

This Surveillance Plan will use the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the SAPIEN XT Transcatheter Heart Valve in patients with either severe native calcific aortic stenosis or failure of a surgical bioprosthetic aortic valve that are at high or greater risk for open surgical therapy. Follow up of these patients will be linked to the CMS database for long-term surveillance through 5 years post implantation**.**

## Example 45. PMA - Postmarket Surveillance of a Transcatheter Heart Valve Utilizing a National Registry and Claims Data for Condition-of-Approval [94, 107, 108]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P130021/S010 Supplement to expand indication | Medtronic CoreValve LLC | CoreValve System | The Medtronic CoreValve system is indicated for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). | STS/ACC TVT Registry<br><br>CMS | **Postmarket:** CoA to use TVT Registry with linkage to CMS for postmarket surveillance. |

### Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| All implanted patients (as described in the approved indication) in the STS/ACC TVT Registry within 5 years of device approval | **Primary:**<br>(1) Device success (intra-procedure)<br>(2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological, vascular and quality of life outcomes at 30 days and 12 months;<br>(4) all-cause mortality, neurological and vascular outcomes annually through 5-year post implantation. | Five years of surveillance | Linkage to CMS for longer-term outcomes of interest |

**Narrative:**

Surveillance will be conducted in the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the CoreValve system in implanted patients within 5 years of device approval. Follow up of these patients will be conducted through linkage to the CMS database for long-term surveillance through 5 years' post implantation.

## Example 46. PMA - Postmarket Surveillance of a Transcatheter Heart Valve Utilizing a National Registry and Claims Data for Condition-of-Approval [94, 109, 110]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P130009/S057 Supplement to expand indication | Edwards Lifesciences, LLC | SAPIEN XT Transcatheter Heart Valve | The Edwards SAPIEN XT transcatheter heart valve (THV), model 9300TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator). | STS/ACC TVT Registry<br><br>CMS | **Postmarket:** CoA to use TVT Registry with linkage to CMS for postmarket surveillance. |

### Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up / Duration | Methods of note |
|---|---|---|---|
| All implanted patients, with intermediate or greater risk for open surgical therapy, in the TVT-registry within five years of the device approval | **Primary:**<br>(1) Device success (intra-procedure);<br>(2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological complications (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months;<br>(4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-5 years post implantation | Five years of surveillance | Linkage to CMS for longer-term outcomes of interest |

**Narrative:**

Surveillance will be conducted in the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the SAPIEN XT THV in implanted patients (at intermediate or greater risk for open surgical therapy) within 5 years of device approval. Follow up of these patients will be conducted through linkage to the CMS database for long-term surveillance through 5 years post implantation

## Example 47. PMA - Postmarket Surveillance of a Transcatheter Heart Valve Utilizing a National Registry and Claims Data for Condition-of-Approval [111]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P130021/S033 Supplement to expand indication | Medtronic CoreValve LLC | CoreValve System | The Medtronic CoreValve, CoreValve Evolut R, CoreValve Evolut PRO systems are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator). | STS/ACC TVT Registry<br><br>CMS | **Postmarket:** CoA to use TVT Registry with linkage to CMS for postmarket surveillance. |

## Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up / Duration | Methods of Note |
|---|---|---|---|
| All implanted patients, with intermediate or greater risk for open surgical therapy, in the TVT-registry | **Primary:**<br>(1) Device success (intra-procedure);<br>(2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological complications (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months;<br>(4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-5 years post implantation. | Five years of surveillance | Linkage to CMS for longer-term outcomes of interest |

**Narrative:**

Surveillance will be conducted in the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the CoreValve system in implanted patients (at intermediate or greater risk for open surgical therapy). Follow up of these patients will be conducted through linkage to the CMS database for long-term surveillance through 5 years post implantation

## Example 48. PMA - Postmarket Surveillance of a Transcatheter Heart Valve Utilizing a National Registry and Claims Data for Condition-of-Approval [94, 112, 113]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140031/S010 | Edwards Lifesciences, LLC | SAPIEN 3 Transcatheter Heart Valve | The Edwards SAPIEN 3 Transcatheter Heart Valve (THV), model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator) | STS/ACC TVT Registry<br>CMS | **Postmarket**: CoA to use TVT Registry with linkage to CMS for postmarket surveillance. |

## Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up | Methods of note | Population |
|---|---|---|---|---|
| All implanted patients, with intermediate or greater risk for open surgical therapy, in the TVT registry within five-years of the device approval | **Primary endpoints**:<br>(1) Device success (intra-procedure)<br>(2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological complications (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months;<br>(4) all-cause mortality, all stroke and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-5 years post implantation. | Five years of surveillance | Linkage to CMS for longer-term outcomes | All implanted patients, with intermediate or greater risk for open surgical therapy, in the TVT registry within five-years of the device approval |

**Narrative:**

This surveillance plan will use the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the SAPIEN 3 Transcatheter Heart Valve in patients at intermediate or greater risk for open surgical therapy. Follow up of these patients will be performed through linkage to the CMS database for long-term surveillance through 5 years post implantation.

## Example 49. PMA - Postmarket Surveillance of a Mitral Valve Repair Device Utilizing a National Registry and Claims Data for Condition-of-Approval [114, 115]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P100009/S028 | Abbott Vascular Inc. | MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System | The MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), are indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease. | STS/ACC TVT Registry Centers for Medicare and Medicaid Services (CMS) claims database. | **Postmarket:** Post-approval study using STS/ACC TVT Registry with linkage to CMS |

### Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up / Duration | Methods of Note |
|---|---|---|---|
| **STS/ACC TVT Registry:** Continued follow-up of patients enrolled in the continued access protocol and consecutive patients treated with the subject device for the indication | **Primary Endpoints:**<br>Clinical data up-to-one year collected using the TVT Registry. Follow-up data will include All-cause mortality, Stroke, Repeat-procedure for mitral valve-related dysfunction, and Hospitalization. | Five years | Linkage to CMS claims data for follow-up data |

**Narrative:**

The sponsor submitted this PMA supplement to modify the indications for use statement to include secondary mitral regurgitation. As a condition-of-approval, the sponsor will perform a post-approval study that will use the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the MitraClip System and to collect annual, follow-up data of subjects enrolled in the continued access protocol study. Follow-up of these patients will be performed through linkage to the CMS database for long-term surveillance through 5 years post-implantation

## Example 50. PMA - Postmarket Surveillance of a Transcatheter Heart Valve Utilizing a National Registry and Claims Data for Condition-of-Approval [116]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P130021/S058 | Medtronic CoreValve LLC | Medtronic CoreValve Evolut R System, Medtronic CoreValve Evolut PRO System | The Medtronic CoreValve Evolut R System and Medtronic CoreValve Evolut PRO System are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy. | STS/ACC TVT Registry CMS | **Postmarket:** Post-approval study using STS/ACC TVT Registry with linkage to CMS |

### Postmarket use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up / Duration | Methods of Note |
|---|---|---|---|
| **STS/ACC TVT Registry:** Continued follow-up of patients enrolled in the continued access protocol and consecutive patients treated with the subject device for the low-risk indication | **Primary Endpoints:**<br>(1) Device success (intra-procedure);<br>(2) All-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months; and<br>(4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-10 years post implantation. | Ten years | Linkage to CMS claims data for follow-up data |

**Narrative:**

The sponsor submitted this PMA supplement to modify the indications for use statement to include patients at low-risk for surgical aortic valve replacement (SAVR). As a condition-of-approval, the sponsor will perform a post-approval study that will use the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the CoreValve Evolute R and PRO system. Follow up of these patients will be performed through linkage to the CMS database for long-term surveillance through ten years post implantation. Additionally, the post-approval study will continue to follow subjects enrolled in the continued-access protocol study using the STS/ACC TVT Registry for data collection.

# Example 51. PMA - Postmarket Surveillance of a Transcatheter Heart Valve Utilizing a National Registry and Claims Data for Condition-of-Approval [117]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140031/S085 | Edwards Lifesciences LLC | Edwards SAPIEN 3 Transcatheter Heart Valve System, Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System | The Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy. | STS/ACC TVT Registry CMS | **Postmarket:** Post-approval study using STS/ACC TVT Registry with linkage to CMS |

## Postmarket Use – STS/ACC TVT Registry

| Population | Key Elements or Endpoints from RWE source | Follow-up | Methods of Note |
|---|---|---|---|
| **STS/ACC TVT Registry:** Continued follow-up of patients enrolled in the continued access protocol and consecutive patients treated with the subject device for the low-risk indication | **Primary endpoints**:<br>(1) Device success (intra-procedure)<br>(2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months;<br>(3) neurological complications (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months;<br>(4) all-cause mortality, all stroke and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-10 years post implantation. | Ten years | Linkage to CMS for longer-term outcomes |

**Narrative:**

The sponsor submitted this PMA supplement to modify the indications for use statement to include patients at low-risk for surgical aortic valve replacement (SAVR). As a condition-of-approval, the sponsor will perform a post-approval study that will use the STS/ACC TVT Registry to monitor long term durability, safety and effectiveness of the SAPIEN 3 and SAPIEN 3 Ultra systems. Follow up of these patients will be performed through linkage to the CMS database for long-term surveillance through ten years post implantation. Additionally, the post-approval study will continue to follow subjects enrolled in the continued-access protocol study using the STS/ACC TVT Registry for data collection.

## Example 52. Continued-Access Program Leveraging National Registry and Claims Data for Data Collection [45, 118]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| NCT02687035 | Edwards Lifesciences, LLC | SAPIEN 3 | The Edwards SAPIEN 3 Transcatheter Heart Valve (THV), model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator) | STS/ACC TVT Registry<br>CMS | Continued-access program leveraging TVT Registry and CMS databases for data collection |

### Continued Access Protocol – STS/SCC TVT Registry

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **PARTNER II S3iCAP Using the TVT Registry:** Severe aortic stenosis patients at intermediate risk for standard aortic valve replacement. (1822 patients, continued-access program). Data to be entered into STS/ACC TVT Registry. | **Primary:**<br>Stroke (30 days)<br>Aortic valve reintervention (30 days)<br>Death (30 days) | STS/ACC TVT Registry (screening to one year)<br><br>Five-year follow-up (through CMS linkage) | Data entered into STS/ACC TVT Registry with linkage to CMS for longer-term outcomes |

**Narrative:**

The PARTNER II S3iCAP is a continued-access program to provide continued access of the device to patients. Data will be collected in the STS/ACC TVT Registry with linkage to CMS.

# Appendix Section IV. Examples Utilizing Medical Records as Real-World Evidence

## Guide to Examples Utilizing Medical Records as Real-World Evidence

| | File | Sponsor | Device | Real-World Data (RWD) Source(s) | RWE Use | Key Tags |
|---|---|---|---|---|---|---|
| **53** | K171120 | TransEnterix, Inc. | Senhance Surgical System | Retrospective review of medical records | **Premarket:** Data extracted from a retrospective medical chart review was compared to performance drawn from published literature to support the clearance of this new robotically assisted surgical device. | Medical records (EHR, EMR or chart review);<br>RWE as a primary source of clinical evidence; |
| **54** | K172959 | PeraHealth, Inc. | PeraServer and PeraTrend System | Medical record data used for validation of software as a medical device (SaMD) product | **Premarket:** Three publications were submitted for this 510(k), in which the subject software as a medical device (SaMD) product was tested on data from retrospective medical records of adult and pediatric patients. | Digital Health Example;<br>Medical records (EHR, EMR or chart review);<br>RWE as a primary source of clinical evidence; |
| **55** | K180111 | Pursuit Vascular, Inc. | ClearGuard HD Antimicrobial Barrier Cap | Data abstraction from electronic health records and National Healthcare Safety Network (NHSN) Dialysis Event forms of patients from forty (40) dialysis centers in the US | **Premarket:** RWE was a primary source of clinical evidence supporting modifying the indications for use statement to include information related to reduction of bloodstream infection. The sponsor performed a cluster-randomized, multi-arm, unblinded study that analyzed routinely-collected blood infection surveillance data from 40 dialysis centers in the US. | Medical records (EHR, EMR or chart review);<br>RWE as a primary source of clinical evidence; |
| **56** | K180163 | TransEnterix, Inc. | Senhance Surgical System | Retrospective review of medical records from four (4) OUS sites | **Premarket:** Data extracted from retrospective medical chart reviews on the performance of the subject device was compared to data from published literature on laparoscopic procedures, and used as the primary support to expand the indication of this robotically assisted surgical device to include inguinal hernia repair and cholecystectomy procedures. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>RWE as a primary source of clinical evidence; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **57** | K180894 | Levita Magnetics International Corp. | Levita Magnetic Surgical System | Retrospective review of medical records from one (1) US site | **Premarket:** Data extracted from a retrospective review of medical records were used to support modifications to the indications for use statement to include use to retract the liver in bariatric procedures and an expansion of the Body Mass Index (BMI) range for patients. | Medical records (EHR, EMR or chart review);<br>RWE as a primary source of clinical evidence; |
| **58** | K180986 | XableCath, Inc. | XableCath Support Catheter Product Family | Retrospective review of OUS medical records | **Premarket:** RWE was the sole source of clinical evidence, with data from a retrospective medical records review of patients treated OUS supporting the determination of substantial equivalence. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>RWE as a primary source of clinical evidence; |
| **59** | K181323 | C. R. Bard, Inc. | Atlas Gold PTA Dilatation Catheter | Retrospective review of medical records from one (1) US site | **Premarket:** Data extracted from a retrospective review of medical records were used to support expansion of the indications for use for the device to include use in the venous system. | Medical records (EHR, EMR or chart review);<br>RWE as a primary source of clinical evidence; |
| **60** | K191173 | Abbott Vascular | Emboshield NAV$^{6}$ Embolic Protection System | Retrospective review of medical records from one (1) US site | **Premarket:** Data extracted from a retrospective review of medical records were used to support modifications to the indications for use statement to include use while performing atherectomy in lower extremity arteries. | Medical records (EHR, EMR or chart review);<br>RWE as a primary source of clinical evidence; |
| **61** | DEN170001 | Vapotherm, Inc. | Precision Flow HVNI | Vermont Oxford Network Database | **Premarket:** RWE was the sole source of evidence for the pediatric and neonate population for this submission. The sponsor submitted a retrospective study of medical chart data of patients treated with the subject device for high velocity nasal infusion that was compared to neonate outcome data with CPAP treatment from the Vermont Oxford Network. | Medical records (EHR, EMR or chart review);<br>Pediatric RWE; |
| **62** | DEN170015 | Wilson-Cook Medical, Inc. | Hemospray Endoscopic Hemostat | Three (3) outside-the-US postmarket studies | **Premarket:** RWE was a primary source of clinical evidence for this de novo, which included a registry study with data submitted by physicians to a database and two postmarket studies, all conducted OUS. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>RWE as a primary source of clinical evidence; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **63** | DEN170064 | Rapid-Medical Ltd | Comaneci Embolization Assist Device | Retrospective review of medical records from two (2) OUS sites | **Premarket:** The primary source of clinical evidence for this de novo was a retrospective case series of patients treated OUS, with data collected from the patients' medical records using a prespecified data collection form. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>RWE as a primary source of clinical evidence; |
| **64** | DEN170073 | Viz.AI, Inc | ContaCT | Radiology reports and Real-world Literature | **Premarket:** This is a radiological computer aided triage and notification software. A secondary RWE analysis compared the standard-of-care notification time extracted from radiologist reports against a comparable metric from standalone testing. | Digital Health Example;<br>Medical records (EHR, EMR or chart review);<br>Performance goal or comparator derived from RWE; |
| **65** | P160022 | Zoll Medical Corporation | X Series, R Series, AED Pro, AED 3 BLS Professional Defibrillators, Pro-Padz Radiotransparent Electrode, etc. (See Approval Order for full list) | Device-generated and clinical data from out-of-hospital use, medical records | **Premarket:** Prior clinical trial data and real-world evidence, including device-generated data and clinical data recorded by the AEDs during routine field use, were used to support approval after call for premarket approval applications for AEDs.<br><br>**Postmarket:** Post-approval study will collect ECG waveform and device data from devices used to treat patients in cardiac arrest during routine use. These data will then be analyzed to compare the performance of the device's algorithm against expert annotation | Device-generated data;<br>Medical records;<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |
| **66** | P140010/S037 | Medtronic Vascular, Inc. | IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter | IN.PACT Admiral DCB Long Lesion Sub-Cohort Clinical Evaluation (US and OUS) | **Premarket:** RWE was the primary source of clinical data supporting expanding the indication to include treatment of long lesions of up to 410 mm. The RWE consisted of a retrospective analysis of the Long Lesion Sub-Cohort from the sponsor's global study of the subject device. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>RWE as a primary source of clinical evidence; |
| **67** | P140017/S005 | Medtronic, Inc. | Melody TPV | Real-world study (medical records, 10 sites) | **Premarket:** For this indication expansion, the primary source of clinical evidence was from medical records collected across 10 sites and pooled with data from two post-approval studies for analysis. | Medical records;<br>RWE as a primary source of clinical evidence; |

## Example 53. 510(k) - Clearance of New Robotically Assisted Surgical Device Using a Retrospective Review of Medical Records [119]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K171120 | TransEnterix, Inc. | Senhance Surgical System | The Senhance Surgical System is intended to assist in the accurate control of laparoscopic instruments for visualization and endoscopic manipulation of tissue including grasping, cutting, blunt and sharp dissection, approximation, ligation, electrocautery, suturing, mobilization and retraction in laparoscopic colorectal surgery and laparoscopic gynecological surgery. The system is indicated for adult use. It is intended for use by trained physicians in an operating room environment in accordance with the Instructions for Use. | Retrospective review of medical records<br><br>Real-world Literature | **Premarket:** Primary source of clinical evidence |

### Premarket Use – Retrospective Review of Medical Records

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **Gynecological Laparoscopic Surgery (Non-RWE)**: Prospective non-randomized open-label clinical trial of gynecological laparoscopic surgical patients (n=150) treated with the subject device.<br><br>**Colorectal Laparoscopic Surgery (RWE):** Retrospective review of medical records of colorectal surgical patients (n=45) treated with the subject device. | **Key Elements:** Surgical complication, post-surgical adverse events, reoperation, readmission, mortality, transfusion, conversion to standard laparoscopy, operative time, hospital length of stay.<br><br>See 510(k) Summary for additional details and complete list | Results from surgeries with subject device were compared to results from published literature of the predicate device (some of which were drawn from real-world use). |

**Narrative:**

Clinical data were provided to support use of this device in laparoscopic colorectal surgery and laparoscopic gynecological surgery. For use in gynecological procedures, data were drawn from a prospective non-randomized clinical trial for 150 patients undergoing surgery with the Senhance system. These data were compared to results from published literature of the predicate device (8 publications, more than 8,000 gynecological operations). For use in colorectal laparoscopic surgery, data were from a retrospective case series review of 45 patients undergoing colorectal procedures using the Senhance system. These data were compared to results from published literature of the predicate device (11 publications, more than 5,000 colorectal operations).

## Example 54. 510(k) - Clearance of a New Adjunct to Multiparameter Patient Monitor Using Data from Electronic Medical Records for Validation [120, 121, 122, 123]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K172959 | PeraHealth, Inc. | PeraServer and PeraTrend System | The Rothman Index uses commonly recorded vital sign, nursing assessment, and lab data to compute a patient status index. The Rothman Index is a single measure of a patient's physiologic condition based on the aggregate statistical mortality risk associated with the values of the patient's vital signs, nursing assessments, and selected lab values.<br><br>PeraServer is indicated for use wherever there is interest in generating Rothman Index (RI) scores and/or associated configurable warnings.<br><br>PeraTrend is indicated for use by healthcare providers whenever there is need for displaying and/or trending RI scores and displaying associated configurable warning states as an adjunct to clinical decision support.<br><br>PeraServer/PeraTrend is intended for the care of patients throughout the hospital setting (e.g., in the emergency department, on the wards, in intensive care units).<br><br>The Rothman Index score is validated for use with neonatal, pediatric, and adult patients. It is an adjunct-to and is not intended to replace vital signs monitoring and is not intended for use in the Neonatal Intensive Care Unit. | Electronic medical records | **Premarket:** Validation using data from electronic medical records |

## Premarket Use –Data from Patient Medical Records Used for Validation

| Population | Methods of Note |
|---|---|
| **Adult (RWE)**: Model development and validation using data calculated from the electronic medical records of adult patients (n~170,000 patients)<br><br>**Pediatric (RWE)**: Model development and validation using data calculated from the electronic medical records of pediatric patients (105,470 patient visits)<br><br>**Modified Early Warning Score Comparison (RWE)**: Comparison between the Rothman Index and the modified early warning score using data calculated from the electronic medical record (32,472 patient visits) | The Rothman Index (RI) score was validated in adult and pediatric patients using data and outcomes derived from electronic medical records. Additionally, real-world literature was provided describing a comparison between the RI score and the modified early warning score using data derived from the electronic medical record (32,472 patient visits) |

**Narrative:**
The subject device is a software platform that extracts data from the electronic medical record to compute a Rothman Index score (and associated warnings), which are then

displayed to the user. For this 510(k), the sponsor demonstrated the validity of the RI score by providing data from three publications. Two publications described the validation of the RI score calculated using data and outcomes retrospectively derived from the electronic medical records of adult and pediatric patients. The third publication provided a comparison between the RI score and the modified early warning score calculated using data derived from the electronic medical records. This submission is an example of using real-world data from the electronic medical or health record as source data for validating a software-only device.

## Example 55. 510(k) - Modification to Indications for Use Statement for a Hemodialysis Catheter End Cap Using a Cluster-Randomized Trial with Data Abstracted from Electronic Health Records and National Healthcare Safety Network (NHSN) Dialysis Event Forms of Patients [124, 125, 126, 127]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K180111 | Pursuit Vascular, Inc. | ClearGuard HD Antimicrobial Barrier Cap | ClearGuard HD Antimicrobial Barrier Cap is indicated for use with hemodialysis catheter hubs.<br><br>Using in vitro methods, the antimicrobial treatment on the ClearGuard HD Antimicrobial Barrier Cap has been shown to be effective at reducing microbial colonization in hemodialysis catheter hubs against the following microorganisms: Enterococcus faecium (VRE), Enterococcus faecalis (VRE), Acinetobacter baumannii, Escherichia coli, Staphylococcus aureus (MRSA), Staphylococcus aureus, Staphylococcus epidermidis (MRSE), Pseudomonas aeruginosa, Candida albicans and Candida parapsilosis and has not been shown to be effective against Candida paratropicalis and Klebsiella pneumoniae.<br><br>Using Postmarket clinical surveillance data, use of the ClearGuard HD Antimicrobial Barrier Cap has been shown to reduce the incidence of central-line associated bloodstream infections (CLABSI) in hemodialysis patients with catheters. Note: CLABSI was defined as a positive blood culture (PBC) not related to an alternative source of infection per the National Healthcare Safety Network (NHSN) surveillance definition. Alternative sources were excluded if dialysis sites attributed the PBC to vascular access on the dialysis event form. The actual reduction in CLABSI rates may be less substantial as the evaluation for alternative PBC sources was not pre-specified, nor standardized between patients and clinical sites, and supplemental data evaluating for alternative sources were not available for review.<br><br>The subject device is not intended to be used for the treatment of existing infections. The antimicrobial is only present within the hub of the catheter and does not migrate to distal portions of the catheter. | Cluster-randomized, multi-arm, unblinded study using routinely collected data at 40 dialysis centers throughout the US. | **Premarket:** Primary source of clinical evidence |

### Premarket Use – Prospective Study of Hemodialysis Centers Participating in the CDC National Healthcare Safety Network

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **DaVita Dialysis Centers Participating in the CDC National Healthcare Safety Network (RWE):** The US Centers for Disease Control and Prevention (CDC) maintains the National Healthcare Safety Network (NHSN) to track healthcare-associated infection (HAI) in Ambulatory Surgery Centers, Acute and long-term Care Hospitals and Facilities, Outpatient Dialysis Facilities and other healthcare facilities. As participants in the NHSN, DaVita routinely collects information on patients receiving hemodialysis. During the study, 1,671 subjects participated. | **Primary:**<br>The pre-specified primary study endpoint was the rate of positive blood culture. An additional exploratory ad-hoc analysis was conducted to explore the possible reduction of Central Line-Associated Bloodstream Infection (CLABSI). | This submission included the results of a cluster-randomized prospective open-label study that took advantage of existing public-health data collection for the NHSN.<br><br>Data were abstracted from the electronic health record and from the NHSN Dialysis Event form. |

**Narrative:**

In K180111, the sponsor sought to modify the indications for use statement to include information related to reduction of bloodstream infection. The clinical data used to support clearance of the modification were generated from a cluster-randomized prospective open-label study conducted in 40 dialysis centers across the US, randomized to use either the subject device or a comparator in a 1:1 ratio. The variables collected for this study were those routinely collected by dialysis centers as part of participation in the CDC's NHSN for routine blood infection surveillance. In this study, patients were treated according to the local standard of care, which included blood culture specimen collection for routine blood infection surveillance. Blood cultures were analyzed by a clinical laboratory and the results were entered into the patient's electronic health record (EHR) and to the NHSN Dialysis Event form for reporting to the NHSN. Data were then abstracted for the purposes of the study. The information was considered sufficient to support adding to the indications for use a statement that addressed reduction in CLABSI for dialysis patients treated with the subject device.

## Example 56. 510(k) - Modification to Indications for Use Statement for a Robotic Surgical System Using Retrospective Reviews of Medical Records [128]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K180163 | TransEnterix, Inc. | Transenterix Senhance Surgical System | The Senhance Surgical System is intended to assist in the accurate control of laparoscopic instruments for visualization and endoscopic manipulation of tissue including grasping, cutting, blunt and sharp dissection, approximation, ligation, electrocautery, suturing, mobilization and retraction. The Senhance Surgical System is intended for use in laparoscopic gynecological surgery, colorectal surgery, cholecystectomy, and inguinal hernia repair. The system is indicated for adult use. It is intended for use by trained physicians in an operating room environment in accordance with the Instructions for Use. | Retrospective review of medical records (OUS) | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Retrospective Review of Medical Records

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **Cholecystectomy Case Series (RWE)**: Two retrospective chart reviews of 40 patients who had robotic cholecystectomy procedures performed with the subject device<br><br>**Inguinal Hernia Repair Surgery Data (RWE):** Retrospective chart review of 64 patients who had robotic transabdominal preperitoneal inguinal hernia repair performed with subject device | **Key Elements:** Conversion to laparoscopy, conversion to open technique, intraoperative and postoperative complications, reoperations, readmissions related to procedure, transfusion, operative time, mortality<br><br>See 510(k) Summary for additional details and complete list. | Results from surgeries with subject device were compared to results from published literature of the predicate device. |

**Narrative:**

For this 510(k) submission, the sponsor sought to expand the subject device indication to include laparoscopic inguinal hernia repair and cholecystectomy (gallbladder removal) procedures. The sponsor submitted clinical evidence consisting of two retrospective chart reviews of robotic cholecystectomies performed with the subject device that were compared to clinical data on use of the predicate robotic device and conventional laparoscopic procedures derived from published literature. For the inguinal hernia procedure, they submitted a retrospective chart review study of patients who underwent surgery with the subject device, that was also compared to clinical literature on procedures performed with the predicate robotic device and with conventional laparoscopy. This real-world evidence, along with the cited literature, was used to support a decision of substantial equivalence.

# Example 57. 510(k) - Modification to Indications for Use and Labeling for Magnetic Surgical Instrument System Using a Retrospective Review of Medical Records [129]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K180894 | Levita Magnetics International Corp. | Levita Magnetic Surgical System | The Magnetic Surgical System is designed to grasp and retract the body and the fundus of the gallbladder in laparoscopic cholecystectomy procedures and the liver in bariatric procedures to facilitate access and visualization of the surgical site. The device is indicated for use in patients with a BMI range of 20-60 kg/$m^2$. | Retrospective review of medical records | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Retrospective Review of Medical Records

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Retrospective Review of Medical Records (RWE):** A retrospective clinical study of 73 subjects with ten participating surgeons<br><br>**Outside-the-US Prospective Study (Non-RWE)**: An OUS prospective clinical study of 30 subjects with three participating surgeons. | **Primary:**<br>Successful completion of laparoscopic bariatric surgery using the device<br>Mean operative times<br>Adverse Events, including intraoperative complications, morbidity and mortality at follow-up. |

**Narrative:**

In this submission, real-world evidence was provided to support modification to the indications for use statement and labeling of a magnetic surgical device intended aid in retraction and visualization of specific organs during surgical procedures. The modification includes use to retract the liver in bariatric procedures and an expansion of the BMI range for patients. Two different studies provided clinical data supporting this submission: real-world evidence from a retrospective evaluation of patients treated with the subject device and a prospective open-label study conducted OUS. The information from these studies was used to support a substantial equivalence determination.

## Example 58. 510(k) - Clearance of an Updated Percutaneous Catheter with Active Tip Using a Retrospective Review of OUS Medical Records [130]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K180986 | XableCath, Inc. | XableCath Support Catheter Product Family | The XableCath catheter is intended to be used to facilitate access to discrete regions of the peripheral vasculature in conjunction with steerable guidewires. This device may be used to facilitate placement and exchange of guidewires and other interventional devices. | OUS retrospective chart review | **Premarket:** Sole source of clinical evidence |

## Premarket Use – Retrospective Review of Medical Records

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Real-World Validation Study:** 26 patients who underwent angiography of the lower extremity through various arterial access sites including femoral, brachial, and radial locations, with therapeutic vascular deployment performed with subject device | **Safety and Effectiveness:**<br>Procedural complications<br>Thrombosis<br>Arterial rupture<br>Distal embolization<br>Complication at mean follow-up of 53 days post-procedure |

**Narrative:**

For this special 510(k) submission, the clinical evidence submitted was OUS data obtained from an extension of their product validation assessment, including a review of patients' medical records, which were analyzed for successful device use and adverse event occurrence in the real-world validation study cohort. The submitted real-world evidence served as the sole support for the determination of substantial equivalence.

# Example 59. 510(k) - Modification to Indications for Use Statement and Labeling for 510(k) Dilation Catheter Using a Retrospective Review of Medical Records [131, 132, 133]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K181323 | C. R. Bard, Inc. | Atlas Gold PTA Dilatation Catheter | The Atlas Gold PTA Dilatation Catheter is indicated for use in Percutaneous Transluminal Angioplasty of the peripheral vasculature, including the iliac arteries and iliac and femoral veins, and for the treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae. This device is also indicated for post-dilatation of stents and stent grafts in the peripheral vasculature. This catheter is not for use in coronary arteries. | Retrospective review of medical records | **Premarket:** Primary source of clinical evidence |

## Premarket Use –Retrospective Review of Medical Records

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Retrospective Review of Medical Records:** Patients treated with illiofemoral vein compression (61 with the device post-stent dilation and 20 pre-dilation). | **Primary Endpoint:** Intra-procedural freedom from major adverse events (acute thrombosis, perforation, or device-related complications). |

**Narrative:**

The sponsor submitted this 510(k) submission to modify the indications of use to include use in the venous system and include a summary of the retrospective study results in the labeling. To support the submission, the sponsor provided clinical evidence from a retrospective analysis of medical records, and a literature review to support an expansion of the indication for the device. For the retrospective study, patients treated with illiofemoral vein compression from September 1, 2013 to May 30, 2017 were identified during the medical chart review and data were abstracted from the patient's medical chart. The primary safety endpoint used in the analysis was intra-procedural freedom from major adverse events, which was compared to a benchmark. These data, along with the literature review, supported FDA's decision of substantial equivalence.

## Example 60. 510(k) - Modification to Indications for Use Statement for Embolic Protection System Using a Retrospective Review of Medical Records [134]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K191173 | Abbott Vascular | Emboshield NAV Embolic Protection System | The Emboshield NAV Embolic Protection System is indicated for use as a guide wire and embolic protection system to contain and remove embolic material (thrombus/debris) while performing angioplasty and stenting procedures in carotid arteries and while performing atherectomy, during standalone procedures or together with PTA and/or stenting, in lower extremity arteries. The diameter of the artery at the site of the Filtration Element placement should be between 2.5 and 7.0 mm. | Retrospective review of medical records | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Retrospective Review of Medical Records

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Retrospective Review of Medical Records:** Patients (n=162) undergoing atherectomy procedures using embolic protection devices for treatment of lower extremity lesions. | **Primary:** 30-day freedom from major adverse events, a composite of death, myocardial infarction (MI), thrombosis, dissection (grade C or greater), distal embolization (DE), perforation at the level of the filter, unplanned amputation and target vessel revascularization (TVR). This endpoint was compared against a performance goal (83%). |

**Narrative:**

The submission sought to modify the indications for use statement for the previously cleared device, to include use while performing atherectomy in lower extremity arteries (LEA). Associated updates were made to contraindications, warnings, precautions and adverse events. The clinical data supporting this modification came from retrospective review of medical records from the Mt Sinai Health Center of patients treated for lower extremity lesions using the subject device under the practice of medicine. These patients presented lesions representative of complex PAD, and the rate of freedom from major adverse events after use of the subject device was considered to be sufficient to demonstrate substantial equivalence.

# Example 61. De Novo - Classification of High Velocity Nasal Insufflation Device for Neonates Using a Retrospective Review of Medical Records [22, 135, 136]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN170001 | Vapotherm, Inc. | Precision Flow HVNI | Precision Flow HVNI is intended for use to add warm moisture to breathing gases from an external source for administration to a neonate/infant, pediatric and adult patients in the hospital and subacute institutions settings. It adds heat and moisture to a blended medical air/ oxygen mixture and assures the integrity of the precise air/oxygen mixture via an integral oxygen analyzer. The flow rates may be from 1 to 40 liters per minute via nasal cannula.<br><br>Precision Flow HVNI provides high velocity nasal insufflation (HVNI) with simultaneous oxygen delivery to augment breathing of spontaneously breathing patients suffering from respiratory distress and/or hypoxemia in the hospital setting. Precision Flow HVNI is not intended to provide total ventilatory requirements of the patient and not for use during field transport. | Retrospective review of medical records | **Premarket:** One of the sources of clinical evidence supporting neonate population indication |

## Premarket Use – Retrospective Review of Medical Records

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Vermont Oxford Network Database Retrospective EMR Review (RWE)**: 1,363 very low birth weight infants (<1500 g) with respiratory failure treated at critical care centers<br><br>**Randomized Clinical Trial in Adult Patient Population (Non-RWE):** 204 adult patients presenting with respiratory failure not requiring intubation | **Safety and Effectiveness:**<br>Pneumothorax<br>Nosocomial infection<br>Oxygen use (28 days, 36 weeks, and at home)<br>Retinopathy of prematurity<br>Intraventricular hemorrhage<br>Length of hospital stay |

**Narrative:**

For this De Novo classification request, the sponsor was seeking an indication for their device in adult, pediatric, and neonate populations. They performed a randomized clinical trial for the adult population and submitted a literature review for the neonate population. The sponsor submitted four studies in neonates, including three small prospective studies, and one retrospective study. The retrospective study analyzed medical chart data from patients treated at five centers and compared it to neonate outcome data from the Vermont Oxford Network to show safety and efficacy for high velocity nasal infusion compared to CPAP. These data supported the granting of the classification request for a neonatal indication.

# Example 62. De Novo - Classification of a Hemostatic Device for Intraluminal Gastrointestinal Bleeding Using Medical Records from OUS Postmarket Studies [15, 137]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN170015 | Wilson-Cook Medical, Inc. | Hemospray Endoscopic Hemostat | The COOK Hemospray Endoscopic Hemostat is used for hemostasis of non-variceal gastrointestinal bleeding. | OUS postmarket studies<br><br>Peer-reviewed real-world literature | **Premarket:** Primary source of clinical evidence |

## Premarket Use – OUS Postmarket Studies

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Premarket Pilot Study (Non-RWE):** OUS early feasibility study of 20 patients with peptic ulcers.<br><br>**SEAL Registry Study (RWE):** 89 patients with upper GI bleeds including peptic ulcers, bleeding after endoscopic mucosal resection or dissection, diffuse bleeding from gastric malignancy, Mallory-Weiss tears, and upper-GI post-polypectomy bleeding<br><br>**APPROACH Study (RWE):** OUS postmarket trial of 50 adult patients with nonvariceal lower gastrointestinal bleeding<br><br>**Peer-Reviewed Literature with Select Studies Conducted Using RWD Sources:** 30 studies identified in literature search comprising the treatment of 522 patients with the subject device, with 12 studies utilizing data from registries. See Summary of Safety and Effectiveness Data for additional details. | **Safety and Effectiveness:**<br>Successful hemostasis achieved by device<br>Rebleeding within 72 hours<br>Recurrent bleeding<br>Device-related adverse events<br><br>**Secondary:**<br>Initial hemostasis, clinical success, early recurrent bleed, late recurrent bleed, serious adverse GI events with 30 days of procedure, serious adverse events within 30 days of procedure, 30 day all-cause mortality |

**Narrative:**

For this de novo submission, the clinical evidence submitted included a pilot clinical trial in Hong Kong and three postmarket investigations outside the US: the SEAL registry survey in Europe and Canada, the HALT Study in Europe and Canada, and the APPROACH study in Canada. The SEAL survey collected clinical data on cases of device use by having physicians enter case information in a database. The HALT and APPROACH studies, both sponsored by the submitter, were prospective, single-arm studies to assess safety and effectiveness. These data as well as a literature review were used to support the granted De Novo classification request.

# Example 63. De Novo - Classification of a Temporary Coil Embolization Assist Device Using Real-World Evidence from Retrospective OUS Case Series [138]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN170064 | Rapid-Medical Ltd | Comaneci Embolization Assist Device | The Comaneci Embolization Assist Device is indicated for use in the neurovasculature as a temporary endovascular device used to assist in the coil embolization of wide-necked intracranial aneurysms with a neck width ≤ 10 mm. A wide-necked intracranial aneurysm defines the neck width as ≥ 4 mm or a dome-to-neck ratio < 2. | Patient medical records | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Data from Patient Medical Records Used for Validation

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **Medical Records:** 63 consecutively-treated patients with intracranial aneurysms treated with the subject device at two outside-the-US sites | Adverse events<br>Technical success<br>Please see Decision Summary for complete list and for additional details. | Data was abstracted from patient medical records using a pre-specified data collection form |

**Narrative:**

For this de novo classification request, the sponsor provided clinical evidence from a retrospective case series of patients consecutively treated between March and December 2017 from two outside-the-US sites. Data were abstracted using a prespecified data collection form and the analysis included assessment by an independent imaging lab and as well as independent event adjudication. These data were the primary source of clinical evidence supporting the submission. To meet the premarket requirement, the sponsor will also conduct a postmarket study to collect additional data on the device as used in the US population.

## Example 64. De Novo - Classification of a Radiological Computer-Assisted Triage and Notification Software Using A Secondary Analysis of Medical Records and Real-world Literature [139, 140]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN170073 | Viz.AI, Inc | ContaCT | ContaCT is a notification-only, parallel workflow tool for use by hospital networks and trained clinicians to identify and communicate images of specific patients to a specialist, independent of standard of care workflow.<br><br>ContaCT uses an artificial intelligence algorithm to analyze images for findings suggestive of a prespecified clinical condition and to notify an appropriate medical specialist of these findings in parallel to standard of care image interpretation. Identification of suspected findings is not for diagnostic use beyond notification. Specifically, the device analyzes CT angiogram images of the brain acquired in the acute setting, and sends notifications to a neurovascular specialist that a suspected large vessel occlusion has been identified and recommends review of those images. Images can be previewed through a mobile application.<br><br>Images that are previewed through the mobile application are compressed and are for informational purposes only and not intended for diagnostic use beyond notification. Notified clinicians are responsible for viewing non-compressed images on a diagnostic viewer and engaging in appropriate patient evaluation and relevant discussion with a treating physician before making care-related decisions or requests. ContaCT is limited to analysis of imaging data and should not be used in-lieu of full patient evaluation or relied upon to make or confirm diagnosis. | Patient medical records (radiology reports)<br><br>Real-world Literature | **Premarket:** Support a secondary analysis in standalone testing |

## Premarket Use – Secondary Analysis of Medical Records and Real-World Literature

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **CT Imaging Datasets and Radiologist Reports:** (300) CT angiogram (CTA) images (studies) were obtained from two clinical sites in the U.S along with the corresponding radiologist reports. | **Safety and Effectiveness:** Standard-of-care notification time | Real-world data (notification-time) extracted from radiologist reports |

**Narrative:**

This device is an adjunctive workflow and notification tool (software as a medical device) that analyzes CT angiogram images of the brain and notifies a neurovascular specialist when a large vessel occlusion has been identified for further image review. The sponsor conducted standalone performance testing evaluating the performance of their algorithm on CT images from two sites against expert-established ground truth. The primary analysis evaluated the sensitivity and specificity of the device's algorithm. A

secondary analysis (RWE) compared the standard-of-care notification time (extracted from the standard-of-care final radiologist report documenting when results were communicated to a specialist) against a comparable metric from the standalone testing of the device. FDA also considered non real-world and real-world literature (e.g. from the STRATIS Registry) describing the potential patient benefit from earlier endovascular treatment, time from presentation to reperfusion and time to stroke center notification. This is an example of leveraging real-world data on clinical workflow and notification time to assess the benefit of a SaMD that is used as a parallel workflow and notification tool**.**

## Example 65. PMA - Approval for Automated External Defibrillator Using Device-Generated Data and for a Post-Approval Study After Call for PMA [141, 142, 143, 144]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160022 | ZOLL MEDICAL CORPORATION | X Series, R Series, Propaq MD, AED Pro, AED 3 BLS Professional Defibrillators, ProPadz Radiotransparent Electrode, SurePower Battery Pack, SurePower II Battery Pack, AED Pro Non-Rechargeable Lithium Battery Pack, AED 3 Battery Pack, SurePower Charger, and SurePower Single Bay Charger | For full indication, please see Summary of Safety and Effectiveness Data. | Device and clinical data from out-of-hospital use, medical records | **Premarket:** Primary source of clinical evidence<br><br>**Postmarket:** CoA with Postmarket RWE collection |

## Premarket Use – Device Generated Data and Real-World Evidence Supporting a PMA Submitted in Response to a Classification Order

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **Randomized Multi-Center In-Hospital Clinical Trial for VF/VT Defibrillation (Non-RWE):** 192 patients enrolled in this clinical trial comparing shock efficiency of the device's rectilinear biphasic waveform against a monophasic damped sine waveform.<br><br>**In-Hospital Study (Non-RWE):** Patients undergoing coronary artery bypass graft (CABG) surgery (n=20).<br><br>**Published Literature (RWE):** Out-of-hospital cardiac patients with VF treated with the rectilinear biphasic waveform (n=94). | **Safety and Effectiveness:**<br>Initial Shock Success<br>Subsequent Shock Success<br>Return of spontaneous circulation | Device-generated data extracted from AED devices used commercially in the field. |

**Narrative:**

This PMA was submitted to fulfil requirements imposed by a Final Order (Docket FDA-2013- N-0234) issued on January 29, 2015, which required premarket approval of Class III Automated External Defibrillators (AED). The devices in this PMA were first cleared under K112432, K060559, and K041892. For this PMA, FDA reviewed clinical data from three prior studies, including a published observational study of out-of-hospital use by responding EMTs. This study included analyses of device data from the AED following use by EMTs and survival data of patients transported to treating hospitals.

# Postmarket Use – Post-Approval Study Supported by Real-World Data Collection (Device-Generated Data)

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration |
|---|---|---|
| **Device-Generated Data:** Device and clinical data recorded by the AED from patients in cardiac arrest and who receive attempted resuscitation using the device. | **Primary Endpoints:**<br>Accuracy of the device's algorithm compared to expert, annotation of ECG data files captured by the device during routine use of the device. | N/A |

**Narrative:**

For this post-approval study, the sponsor will collect ECG waveform and device data from devices used to treat patients in cardiac arrest during routine use. These data will then be analyzed to compare the performance of the device's algorithm against expert annotation. This example illustrates the use of real-world and device-generated data collection to help support a post-approval study.

# Example 66. PMA - Modification to Indications for Use Statement for a Drug-Eluting Peripheral Transluminal Angioplasty Catheter Supported by a Retrospective Review of Medical Records from the Sponsor's Database [145]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140010/S037 | Medtronic Vascular, Inc. | IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter | The IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions with lengths up to 360 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm | IN.PACT Admiral DCB Long Lesion Sub-Cohort Clinical Evaluation (US and OUS) | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Sponsor Registry (US and OUS)

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **IN.PACT Admiral DCB Long Lesion Sub-Cohort Clinical Evaluation (RWE):** 227 subjects with lesion length > 180 mm based on angiographic core lab assessment, Rutherford Clinical Category 2-4, single unilateral treated lesion confirmed by angiographic core lab and site reported procedure information | **Primary Safety Endpoint:** Freedom from device- and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target vessel revascularization (CD-TVR) within 12 months post-index procedure<br><br>**Primary Effectiveness Endpoint:** Primary patency within 12 months post-index procedure, defined as: freedom from clinically-driven target lesion revascularization (CD-TLR), and freedom from restenosis as determined by Doppler Ultrasound Peak Systolic Velocity Ratio (PSVR)<br><br>See Summary of Safety and Effectiveness Data for additional details and complete list of secondary endpoints. |

**Narrative:**

In this PMA panel track supplement, the sponsor was seeking to expand its indication beyond the 180 mm lesion length previously indicated. The primary clinical evidence submitted came from analysis of data from patients meeting the retrospectively applied inclusion criteria, comprising the Long Lesion Sub-Cohort from the IN.PACT DCB Global Study database. These RWD supported the effectiveness for lesion lengths up to 360 mm and served as the primary source of clinical evidence supporting the approval of this PMA panel track supplement.

# Example 67. PMA - Approval of an Indication Expansion for a Transcatheter Pulmonary Valve Using Medical Record Data [146]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140017/S005 Supplement to expand indication | Medtronic, Inc. | Melody Transcatheter Pulmonary Valve | The Melody TPV is indicated for use in the management of pediatric and adult patients who have a clinical indication for intervention on a dysfunctional RVOT conduit or bioprosthetic pulmonary valve that has ≥ moderate regurgitation and/or a mean RVOT gradient ≥ 35 mm Hg | Real-world study (medical records, 10 sites) | **Premarket:** RWD was pooled with non-RWD and analyzed descriptively to support expanded indication |

## Premarket Use – Real-World Study

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration (RWE) | Methods of Note |
|---|---|---|---|
| **Melody TPV Long-Term Follow-up PAS (Non-RWE):** Long-term follow-up of HDE IDE population (8 patients)<br><br>**Melody TPV New Enrollment PAS (Non-RWE):** Post-approval study following HDE approval (17 patients)<br><br>**Retrospective Analysis (RWE):** of 100 consecutive patients (10 sites) implanted with a Melody TPV within a dysfunctional bioprosthetic pulmonary valve. Patients were treated between 1/25/2010 and 6/1/2015. | **Safety:**<br>Procedure-related serious adverse events<br>Device-related serious adverse events<br>All-cause mortality<br><br>**Effectiveness**:<br>Procedural success; TPV dysfunction; Reoperation on the TPV; Catheter re-intervention on the TPV; Hemodynamic performance | Baseline, implant procedure, discharge, 6 months, and then annually. | Data were pooled for analysis |

**Narrative:**

Real-world data collected from 10 sites was pooled with data from two post-approval studies. Safety and effectiveness outcomes from this pooled analysis were the primary source of clinical evidence for the supplement. For assessment of safety, FDA reviewed analyses of freedom from all-cause mortality, stent-related major fracture and endocarditis as well as procedure and device related serious adverse events. For assessment of effectiveness, FDA reviewed procedural success, freedom from TPV dysfunction, freedom from TPV reoperation, freedom from catheter TPV re-intervention, and hemodynamic performance. This analysis was used to expand the indications to include pulmonary valve-in-valve.

# Appendix Section V. Examples Utilizing Other Sources of Real-World Evidence

## Guide to Examples Utilizing Other Sources of Real-World Evidence

| | File | Sponsor | Device | Real-World Data (RWD) Source(s) | RWE Use | Key Tags |
|---|---|---|---|---|---|---|
| **68** | DEN160014 | Ovesco Endoscopy AG | RemOVE System | OUS compassionate use data | **Premarket:** OUS compassionate use data served as the sole source of clinical evidence supporting this de novo classification request. | Outside-the-US;<br>RWE as a primary source of clinical evidence; |
| **69** | DEN140018 | Advanced Cooling Therapy, LLC | ESOPHAGEAL COOLING DEVICE | OUS Clinical case summaries and chart data | **Premarket:** OUS clinical case summaries and patient body temperature charts served as the primary source of clinical evidence for this de novo classification request. | Medical records (EHR, EMR or chart review);<br>Outside-the-US;<br>RWE as a primary source of clinical evidence; |
| **70** | DEN150010 | DIGNITANA AB | DIGNICAP SCALP COOLING SYSTEM | OUS Postmarket surveillance data | **Premarket:** For this de novo classification request, OUS postmarket surveillance data served as a supplemental source of clinical evidence. | Outside-the-US; |
| **71** | DEN160006 | TVA Medical, Inc. | everlinQ endoAVF System | Global everlinQ endoAVF System Clinical Program | **Premarket:** Real-world evidence in the form of OUS commercial use data was submitted in support of this de novo classification request, serving as a secondary source of clinical evidence for long term endpoints. | Outside-the-US; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **72** | DEN170052 | Natural Cycles Nordic AB | Natural Cycles | Outside-the-US data from a web and mobile-based standalone software application for conception | **Premarket:** This is a web and mobile-based standalone software application for conception. For this submission, the sponsor performed a retrospective analysis of data from approximately 15,000 users of the mobile application. This was a primary source of clinical evidence supporting the De Novo classification request. | Digital Health Example; Outside-the-US; Patient-generated or patient-entered data; RWE as a primary source of clinical evidence; |
| **73** | P120024 | Aesculap Implant Systems, Inc. | activL Artificial Disc | Explant analysis, medical records | **Postmarket:** As a condition-of-approval for this PMA original, the sponsor will conduct an explant analysis retrieval study over 10 years, including medical records from each explant case. | Medical records (EHR, EMR or chart review); |
| **74** | P160012 | Physio-Control, Inc. | LIFEPAK CR Plus Defibrillator, LIFEPAK EXPRESS Defibrillator, and CHARGEPAK Battery Charger | Device-generated data collected during field-use of the AEDs, medical record review (US and OUS) | **Premarket:** Real-world evidence from two postmarket studies analyzing device-generated data and clinical details of out-of-hospital use of the subject device in adult and pediatric patients were used to support this premarket approval submitted in response to a classification order for AEDs. | Device-generated data; Outside-the-US; Pediatric RWE; RWE as a primary source of clinical evidence; |
| **75** | P160032 | Defibtech, LLC | Lifeline/ReviveR DDU-100, Lifeline/ReviveR AUTO DDU-120, Lifeline/ReviveR VIEW DDU-2300, Lifeline/ReviveR VIEW AUTO DDU-2200, Lifeline/ReviveR ECG DDU-2450, and Lifeline/ReviveR ECG+ DDU-2475 Automated External Defibrillators | Device-generated and clinical data collected during field-use of the AEDs (US and OUS) | **Premarket:** Real-world evidence from studies of out-of-hospital use of the AEDs, including device-generated data and clinical data recorded by the subject devices in adult and pediatric populations (US and OUS) were used to support approval after a call for premarket approval applications for AEDs following a classification order. | Device-generated data; Outside-the-US; Pediatric RWE; RWE as a primary source of clinical evidence; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **76** | P160033 | Cardiac Science Corporation | Powerheart AED G3, Powerheart AED G3 Plus, and Powerheart AED G5 | Device-generated and clinical data collected during field-use of the AEDs (includes US and OUS use) | **Premarket:** Prior clinical trial data and real-world evidence, including device-generated data and clinical data recorded by the AEDs during routine field use (includes US and OUS use), were used to support approval after call for premarket approval applications for AEDs. | Device-generated data;<br>Outside-the-US;<br>RWE as a primary source of clinical evidence; |
| **77** | P100022/S020 | Cook Medical, Inc. | Zilver PTX Drug-Eluting Peripheral Stent | OUS Postmarket surveillance data | **Premarket:** For this indication expansion, postmarket surveillance data from Japan served as a supplemental source of clinical evidence. | Outside-the-US; |
| **78** | P010030/S056 | ZOLL Manufacturing Corporation | LifeVest Wearable Cardioverter Defibrillator | Sponsor Database, Device-generated data, Real-world Literature | **Premarket:** This PMA supplement for an indication expansion was solely supported by RWE, including device-generated and clinical data in the sponsor's database, as well as real-world literature analyzing device-generated and clinical data form pediatric populations.<br><br>**Postmarket:** As part of the condition-of-approval, the sponsor will collect additional device-generated and clinical data on patients meeting the approved indication in the sponsor's database. | Device-generated data;<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |
| **79** | P050023/S087 | Biotronix, Inc. | PROMRI FULL BODY SCAN (FBS) ICD SYSTEM | Device-generated data; home/remote monitoring system | **Postmarket:** Postmarket surveillance as a condition-of-approval will be conducted through a remote monitoring system to analyze device-generated data from patients with a post-MRI VF episode. | Device-generated data;<br>Registry data; |
| **80** | P120005/S041 | Dexcom, Inc. | Dexcom G5 Mobile Continuous Glucose Monitoring System | Device-generated data during home-use | **Postmarket:** As a condition-of-approval, the sponsor will perform a home use study of device-generated data and patient-reported data. | Device-generated data;<br>Patient-generated or patient-entered data; |
| **81** | P930016/S044 | AMO Manufacturing USA | STAR S4 IR Excimer Laser System iDesign Advanced WaveScan Studio System | Retrospective studies (Published Literature) | **Premarket:** For this indication expansion, real-world literature from two OUS retrospective studies of de-identified patient data extracted from a LASIK provider's medical record database. | Outside-the-US; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **82** | P020050/S023 | Alcon Laboratories, Inc. | WaveLight EX500 Excimer Laser System, ALLEGRETTO WAVE EYE-Q Excimer Laser System | Retrospective studies (RWE Literature) | **Premarket:** Real-world literature in the form of two single-site retrospective studies served as a supplemental source of clinical evidence for this indication expansion. | |

# Example 68. De Novo - Classification of an Endoscopic Electroscopic Clip Cutting System Using OUS Compassionate Use Data [147]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN160014 | Ovesco Endoscopy AG | remOVE System | The remOVE System consists of the DC Impulse and the DC Cutter Set.<br><br>The remOVE DC Impulse is a medical electrical device for fragmentation of OTSC (endoscopic device for effective treatment of hemorrhage and acute or chronic wall defects in the GI tract) and FTRD (endoscopic device for full-thickness resection of colorectal wall lesions) clips made by Ovesco Endoscopy AG for the digestive tract.<br><br>The remOVE DC Cutter Set is a set of instruments for use in flexible endoscopy. It consists of a bipolar DC instrument for the fragmentation of OTSC (endoscopic device for effective treatment of hemorrhage and acute or chronic wall defects in the GI tract) and FTRD (endoscopic device for full-thickness resection of colorectal wall lesion) clips from Ovesco Endoscopy AG, a pair of forceps and a cap for removal of these fragmented clips. | OUS compassionate use data | **Premarket:** Sole source of clinical evidence |

## Premarket Use – OUS Compassionate Use Data

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **European Compassionate Use Data (RWE):** 11 patients in Europe who underwent OTSC removal with the subject device<br><br>**OUS Compassionate Use Data (RWE):** 74 patients (including 11 patients in above study) who underwent OTSC removal with subject device | **Safety and Effectiveness:**<br>Retrieval of clip fragment<br>Adverse events |

**Narrative:**

For this de novo request, the clinical evidence submitted consisted of retrospective studies of compassionate use cases in Europe prior to commercial market launch, including a retrospective case series. RWE from the compassionate use cases served as the sole source of clinical evidence supporting the granting of this de novo classification request. The de novo submission was ultimately approved.

## Example 69. De Novo - Classification of an Esophageal Cooling Device Using OUS Clinical Case Summaries and Temperature Charts [148]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN140018 | Advanced Cooling Therapy, LLC | Esophageal Cooling Device | The Esophageal Cooling Device is a thermal regulating device, intended to:<br>• connect to a Gaymar Medi-Therm III Conductive Hyper/Hypothermia System to control patient temperature, and<br>• provide gastric decompression and suctioning | OUS clinical case summaries and patient body temperature charts | **Premarket:** Primary, supportive |

### Premarket Use – OUS Clinical Case Summaries and Patient Body Temperature Charts

| Population | Key Elements from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| **OUS Clinical Summaries:** Clinical data summaries and patient body temperature charts (n=16 patients, 10 reports w/ body temperature charts) of the device used commercially outside of US. | **Elements:**<br>Target temperature<br>Body temperature vs time data | N/A |

**Narrative:**

A formal clinical study was not requested by FDA. Assessment of device risk was based on the provided non-clinical and animal studies, while assessment of probable benefit was based on the provided non-clinical and clinical data.

| Population | Key Elements from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| **OUS clinical summaries:** Clinical data summaries and patient body temperature charts (n=16 patients, 10 reports w/ body temperature charts) of the device used commercially outside of US. | **Elements:**<br>Target temperature<br>Body temperature vs time data | N/A |

**Narrative:**

A formal clinical study was not requested by FDA. Assessment of device risk was based on the provided non-clinical and animal studies, while assessment of probable benefit was based on the provided non-clinical and clinical data.

## Example 70. De Novo - Classification of a Scalp Cooling System Using Supplemental RWE from OUS Postmarket Surveillance Study [149]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN150010 | DIGNITANA AB | DigniCap Scalp Cooling System | The DigniCap Scalp Cooling System is indicated to reduce the likelihood of chemotherapy-induced alopecia in women with breast cancer. | Postmarket surveillance study | **Premarket:** Supplemental |

## Premarket Use – OUS Postmarket Surveillance

| Population | Key Elements from RWE Sources |
|---|---|
| **Feasibility Study (Non-RWE):** Patients with stage I breast cancer receiving adjuvant chemotherapy treatment<br><br>**Pivotal Study (Non-RWE):** Non-randomized, multi-center trial<br><br>**Dignitana Postmarket Surveillance (RWE):** Postmarket surveillance of approximately 6000 patients | **Elements:**<br>Adverse events |

**Narrative:**

The primary source of clinical evidence for the submission was based on two studies of the Dignicap, which collected patient efficacy and safety data of the device from patients with early-stage breast cancer. FDA also reviewed postmarket surveillance data provided by the sponsor on device-use outside-the-US, which provided additional data on the risk of scalp metastasis.

## Example 71. De Novo - Classification of a Percutaneous Catheter for Creation of an Arteriovenous Fistula for Hemodialysis Access Using OUS Commercial Use Data [150]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN160006 | TVA Medical, Inc. | everlinQ endoAVF System | The everlinQ endoAVF System is indicated for the creation of an arteriovenous fistula (AVF) using the ulnar artery and ulnar vein in patients with minimum artery and vein diameters of 2.0 mm and less than 2.0 mm separation between the artery and vein at the fistula creation site who have chronic kidney disease and need hemodialysis. | Outside-the-US commercial use in Europe | **Premarket:** Supplemental source of clinical evidence for long term endpoint |

## Premarket Use – OUS Commercial Use Data

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **COMM Commercial Use Dataset:** 79 patients with chronic kidney disease requiring hemodialysis, treated under open-label commercial use of the 6Fr version of the subject device | **Safety and Effectiveness:**<br>Serious adverse events<br>Procedure success defined as proportion of subjects who achieved successful endoAVF creation as confirmed by intraprocedural angiography/fistulogram or duplex ultrasound verification performed post-procedure<br><br>Please see Decision Summary for additional details and complete list. | Open-label commercial use of the subject device was reported by physicians to the sponsor through the sponsor's form that excluded personal data on patients |

**Narrative:**

For this de novo classification request, part of the clinical evidence submitted was a pooled dataset with postmarket commercial data on open-label use of the device in Europe. The sponsor generated a form for physicians to report data on patients being treated with the device. This real-world evidence supported granting of the classification request by serving as a secondary source of clinical evidence for long term endpoint data.

## Example 72. De Novo - Classification of a Web and Mobile-Based Software Application for Contraception Using Real-World Evidence from a Software Application with Patient-Entered/Patient-Generated Data [151, 152]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN170052 | Natural Cycles Nordic AB | Natural Cycles | Natural Cycles is a stand-alone software application, intended for women 18 years and older, to monitor their fertility. Natural Cycles can be used for preventing a pregnancy (contraception) or planning a pregnancy (conception). | Real-world evidence from a web and mobile-based software application with patient-entered/patient-generated data | **Premarket:** Primary source of clinical evidence |

### Premarket Use – Analysis of Real-World Evidence from a Web and Mobile-Based Software Application, Including Patient-Entered/Patient-Generated Data

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Web and Mobile-Based Software Application with Patient-Entered/Patient-Generated Data:** 15,570 women age 18-45 (average 29) that registered in the software application from September 2017 to October 2017. | **Effectiveness of Pregnancy Prevention:**<br>Method failure rate<br>Pearl Index (perfect-use)<br>Pearl Index (typical-use)<br><br>Please see the De Novo Summary for additional details. |

**Narrative:**

Natural Cycles is a web and mobile-based software application for contraception. To support the De Novo classification, outside-the-US data was collected from 15,570 women (age 18-45, average 29 years old) who had registered in the software application between September to October 2017. These women were prospectively followed until April 30, 2018. Along with pregnancy tests or follow-up by email, pregnancy status was determined by the application's algorithm. Patient data were retrospectively analyzed to validate the accuracy of the algorithm in identifying ovulation by temperature and luteinizing hormone (LH). Additionally, a subgroup analysis was performed on women who had recently used (or had not used) hormonal contraception. Please see the De Novo Summary for additional details.

## Example 73. PMA - Postmarket Surveillance of an Intervertebral Disc Prosthesis Using an Explant Retrieval Study [153]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P120024 | Aesculap Implant Systems, Inc. | activL Artificial Disc | The activL Artificial Disc (activL) is indicated for reconstruction of the disc at one level (L4-L5 or L5-S1) following single-level discectomy in skeletally mature patients with symptomatic degenerative disc disease (DDD) with no more than Grade I spondylolisthesis at the involved level. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, physical examination, and radiographic studies. The activL Artificial Disc is implanted using an anterior retroperitoneal approach. Patients receiving the activL Artificial Disc should have failed at least six months of nonoperative treatment prior to implantation of the device. | Clinical data from patient medical records | **Postmarket:** Explant retrieval study, enhanced surveillance |

### Postmarket Use – Explant Retrieval Study

| Population | Key Elements or Endpoints from RWE Sources |
|---|---|
| **Explant Analysis:** All patients with explanted device | **Primary Elements:**<br>Detailed clinical narrative, copies of the original implant operative report, copies of all subsequent surgical operative reports, copies of the operative report from the explant/removal surgery, copies of all pathology reports, results of the explant analysis. |

**Narrative:**

As part of the condition-of-approval, the sponsor agreed to conduct an explant analysis retrieval study over a ten-year period. For all explanted devices, the sponsor agreed to provide a clinical narrative, copies of operative reports from the original surgery, copies of operative reports from subsequent surgeries as well as the explant surgery, copies of pathology reports, and conduct an explant analysis.

## Example 74. PMA - Approval for Automated External Defibrillator Using Device-Generated Data as a Primary Source of Clinical Evidence After Call for PMA [154, 155, 156, 157]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160012 | Physio-Control, Inc. | LIFEPAK CR Plus Defibrillator, LIFEPAK EXPRESS Defibrillator, and CHARGEPAK Battery Charger | Please see Approval Order. | Device-generated data collected during field-use of the AEDs<br><br>Medical chart review | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Device-Generated Data and Real-World Evidence Supporting a PMA Submitted in Response to a Classification Order

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **In-hospital Prospective Randomized Trial of Monophasic vs. Biphasic Waveforms (Non-RWE):** 154 patients in which VVF was induced (See Higgins et al for additional information)<br><br>**Postmarket Out-of-Hospital Study of Adult Waveform in the Netherlands (RWE):** 120 patients with witnessed and un-witnessed cardiac arrest and ventricular fibrillation as initial recorded rhythm, in whom the first shock was delivered using the subject device by non-medical first responders<br><br>**Postmarket Surveillance Study of Infant/Child Electrodes (RWE):** 19 patients, most uses appropriate to age/weight labeling of up to 8 years or up to 25 kg (55 lbs.), 2 patients in upper end of age range exceeding weight range | **Primary:**<br>Success of first shock: termination of ventricular fibrillation into an organized rhythm within 1 minute after shock delivery<br><br>**Secondary:**<br>Termination of ventricular fibrillation at 5 seconds after first shock<br><br>Please see Summary of Safety and Effectiveness Data for additional details and complete list. | Device-generated data extracted from AED devices used commercially in the field. Study data collectors traveled to the scene when EMS were called for cardiac arrest and recorded data on the circumstances of the cardiac arrest, interviewed witnesses, and collected data from the AED and the manual defibrillators. |

**Narrative:**

This PMA was submitted in response to the Final Order (Docket FDA-2013- N-0234) issued on January 29, 2015, which required premarket approval of marketed pre-amendment Class III Automated External Defibrillators. In this PMA submission, the sponsor submitted two postmarket studies that analyzed device-generated data and clinical details of out-of-hospital use of the subject devices. The first was a prospective, randomized, out-of-hospital study in the Netherlands of the subject devices' use in adults, with ECG and shock data obtained from the AEDs and data obtained from medical records and study data collectors' interviews of witnesses at the scene. The sponsor also submitted results from a postmarket surveillance study of the use of the device with Infant/Child electrodes in a pediatric population. These data supported exemption of this submission from review by the Circulatory System Devices Panel, since it was previously reviewed by this panel on January 25, 2011 as part of the 515(i) process, and also supported approval of the PMA.

## Example 75. PMA - Approval for Automated External Defibrillator Using Device-Generated Data as a Primary Source of Clinical Evidence After Call for PMA [158, 159, 160, 161]

| File | Sponsor | Device | Approved/Cleared Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160032 | Defibtech, LLC | Lifeline/ReviveR DDU-100, Lifeline/ReviveR AUTO DDU-120, Lifeline/ReviveR VIEW DDU-2300, Lifeline/ReviveR VIEW AUTO DDU-2200, Lifeline/ReviveR ECG DDU-2450, and Lifeline/ReviveR ECG+ DDU-2475 Automated External Defibrillators | Please see Approval Order. | Device-generated data collected during field-use of the AEDs | **Premarket:** Sole source of clinical evidence |

## Premarket Use – Device-Generated Data and Real-World Evidence Supporting a PMA Submitted in Response to a Classification Order

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **Postmarket Out-of-Hospital Study of Adult Waveform in Europe (RWE):** 115 patients who weighed ≥36 kg with known or suspected sudden cardiac arrest out-of-hospital, attended by emergency medical services and treated with AED<br><br>**Observational Postmarket Study of Pediatric Pads (RWE):** 27 pediatric patients 0 – 8 years old or up to 25 kg (55 lbs.) treated with subject device with pediatric pads that reduces AED waveform from 150J to 50J | **Safety and Effectiveness:**<br>Percentage of patients with ventricular fibrillation as the initial monitored rhythm who were defibrillated in the first series of ≤3 shocks<br>Survival to hospital admission and discharge<br>Return of spontaneous circulation (ROSC)<br><br>See Summary of Safety and Effectiveness Data for additional details and complete list. | Device-generated data extracted from AED devices used commercially in the field. |

**Narrative:**

This PMA was submitted in response to the Final Order (Docket FDA-2013- N-0234) issued on January 29, 2015, which required premarket approval of marketed pre-amendment Class III Automated External Defibrillators (AED). For this PMA submission, the sponsor submitted real-world evidence in the form of two postmarket studies that analyzed device-generated data as well as clinical details of out-of-hospital use of the subject devices. The first was a prospective, randomized, out-of-hospital study in Europe of the sponsor's AED in adults, with ECG and shock data obtained from the AED recording system and patient data collected from incidence and follow-up reports. The second was a US and OUS postmarket observational study of the pediatric pads for the device that asked users to submit ECG and shock data from the AEDs in addition to details about the patient and event. These data were used to support FDA's evaluation of safety, effectiveness, and benefit-risk for this PMA. They also supported exemption of the subject devices from review by the Circulatory System Devices Panel, since it was previously reviewed by this panel on January 25, 2011 as part of the 515(i) process.

## Example 76. PMA - Approval for Automated External Defibrillator Using Device-Generated Data as a Primary Source of Clinical Evidence After Call for PMA [162, 163]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160033 | Cardiac Science Corporation | Powerheart AED G3, Powerheart AED G3 Plus, and Powerheart AED G5 | Please see approval order. | Device-generated and clinical data collected during field-use of the AEDs | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Device-Generated Data and Real-World Evidence Supporting a PMA Submitted in Response to a Classification Order

| Population | Key Elements or Endpoints from RWE Source | Methods of Note |
|---|---|---|
| **RhythmX ECG Analysis IDE G920078 (Non-RWE)**: Randomized, controlled trial (156 patients) with two arms.<br><br>**Postmarket Performance of the RhythmX Analysis Algorithm (RWE):** Retrospective analysis of rescue data from the AED as used in the field from December 1999 to December 2016.<br><br>**Adult Defibrillation Waveform (Non-RWE)**: STAR Biphasic Waveform IDE G970230: Randomized, controlled trial (118 patients) with two arms.<br><br>**Postmarket Performance of the STAR Biphasic Waveform (RWE):** Retrospective analysis of rescue data from the AED as used in the field from December 1999 to December 2016. | **Safety and Effectiveness:**<br>Shock success<br>Restoration of spontaneous circulation (ROSC)<br>Restoration of an organized rhythm (ROR) | Device-generated data extracted from AED devices used commercially in the field. |

**Narrative:**

This PMA was submitted to fulfill requirements imposed by a Final Order (Docket FDA-2013- N-0234) issued on January 29, 2015, which required premarket approval of Class III Automated External Defibrillators (AED). The devices in this PMA have been available in the US since 2003. For this PMA, FDA reviewed prior clinical trial data and real-world evidence including analyses of device-generated data and clinical data recorded by the AEDs during routine, field use in the US and OUS. These data, in addition to the clinical trial data, were used to support FDA's evaluation of safety, effectiveness, and benefit-risk for the PMA.

# Example 77. PMA - Approval of an Indication Expansion of a Superficial Femoral Artery Drug-Eluting Stent Using Supplemental OUS Postmarket Surveillance Data [164, 165]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P100022/S020 Supplement to expand indication | Cook Medical, Inc. | Zilver PTX Drug-Eluting Peripheral Stent | The Zilver PTX Drug-Eluting Stent is indicated for improving luminal diameter for the treatment of de novo or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 300 mm per patient. | OUS postmarket surveillance | **Premarket:** Supplemental |

## Premarket Use – OUS Postmarket Surveillance Data

| Population | Key Elements or Endpoints from RWE Sources |
|---|---|
| **Zilver PTX Single Arm Study Analysis (Non-RWE)**: Retrospective analysis of patient data from Zilver PTX single arm clinical trial (30 outside-the-US sites, 787 patients enrolled, 665 patients with 755 lesions in analysis population).<br><br>The population included three analysis sub-groups: 493 patients (lesion length ≤ 140 mm); 110 patients (lesion-length > 140 mm to 240 mm); 62 patients (lesion length > 240mm to 300mm).<br><br>**Japan Postmarket Surveillance (Non-RWE):** Postmarket surveillance study with no inclusion/exclusion criteria and consecutive enrollment of patients treated with the Zilver PTX stent (905 patients; 717 patients with 842 lesions included in analysis population).<br><br>The population included three analysis sub-groups: 391 patients with 494 lesions (lesion length up to 140mm); 183 patients with 201 lesions (lesion length > 140 mm to 240 mm); and 143 patients with 147 lesions (lesion length > 240 mm to 300 mm in length) | **Outcomes Included in Supplemental Analysis:**<br>Freedom from target lesion revascularization at 1, 2, and 3 years<br>Primary patency at one year |

**Narrative:**

The primary source of clinical evidence for the submission was an analysis of patient data from the Zilver PTX Single Arm Study, an OUS study with clinical sites in Europe, Canada and Korea.

FDA also reviewed Japanese postmarket surveillance data from patients treated with the Zilver PTX Stent, with no inclusion / exclusion criteria. Patients were treated per standard of care. Specifically, FDA reviewed analyses of 1, 2 and 3-year freedom from target lesion vascularization and primary patency at one year.

## Example 78. PMA - Approval of an Indication Expansion and Postmarket Surveillance for a Wearable Automated External Defibrillator Using Device-Generated Data, Sponsor Database, and Real-World Literature [166, 167, 168, 169, 170, 171]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P010030/S056 | ZOLL Manufacturing Corporation | LifeVest Wearable Cardioverter Defibrillator | The LifeVest system is indicated for patients 18 years of age and older who are at risk for sudden cardiac arrest and are not candidates for or refuse an implantable defibrillator.<br>The LifeVest system is indicated for patients under 18 years of age who are at risk for sudden cardiac arrest and are not candidates for or refuse an implantable defibrillator. Patients must have a chest circumference of 26 inches (66 centimeters) or greater and a<br>weight of 18.75 kilograms (41.3 pounds) or greater. | Sponsor database<br><br>Device-generated data<br><br>Real-world literature | **Premarket:** Primary source of clinical evidence<br><br>**Postmarket**: CoA with postmarket RWE collection |

### Premarket Use – Sponsor Database, Device-Generated Data and Real-World Literature

| Population | Key Elements or Endpoints from RWE Sources | Methods of Note |
|---|---|---|
| **Zoll Database (RWE):** Clinical database of patients prescribed and fitted with device.<br><br>**Study 1 (RWE Literature):** Retrospective analysis of sponsor's database (81 patients 9-18 years of age, 103 patients aged 19-21 years of age).<br><br>**Study 2 (RWE Literature):** Retrospective analysis of all patients prescribed WCD (January 1, 2007 to June 30, 2009) at a single site (4 patients, l18 years of age or younger)<br><br>**Study 3 (Literature) (Non-RWE):** Case report | **Zoll Database:** Patient demographics; Wear duration; Indication for use; Before and after treatment ECG waveform data; Treatment summary (appropriate vs inappropriate); Energy Delivered; reason for ending device use.<br><br>**Study 1**: Patient demographics; diagnoses and reason for device use; wear compliance, device discharge data, and reason for ending use.<br><br>**Study 2:** Patient demographics; Diagnosis and LVEF; Indication for ICD; Wear duration and compliance; Device discharge data<br><br>**Study 3:** Case report | Device generated data |

**Narrative:**

The device is a prescription device that also collects device-generated data (e.g. electrocardiograms (ECG)) recorded before and after delivery of therapy. Patients can also record their ECG data manually with the device. These device-generated data can be uploaded to the sponsor's database and reviewed by the patient's physician. For this submission seeking to expand the indication to include patients under 18 years of age (and who meet specified chest-circumference and weight requirements), FDA reviewed clinical and device-generated data collected in the sponsor's database. FDA also reviewed published analyses of device-generated data and clinical data from pediatric populations. FDA relied on this data during its assessment of benefit-risk, device safety and effectiveness.

## Postmarket Use – Sponsor Database, Device-Generated Data

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Zoll Database:** Data collection from patients under 18 years of age who meet the approved indication. Data will be collected from the sponsor's medical order database, device-generated data, and call reports for device use (150 patients). | **Effectiveness:** Compliance with use, duration of use, appropriate therapy delivery, ECG data, call reports<br><br>**Safety:** Inappropriate therapy, ECG data, call reports and adverse events. |

**Narrative:**

As part of a condition-of-approval for the PMA, the sponsor agreed to collect additional clinical and device data routinely collected in the sponsor's databases from patients who meet the approved indication. The final, corrected report for the study was received by FDA on September 7, 2016. On April 25th, 2017, FDA approved an update of the labeling to include the results of the completed post-approval study.

## Example 79. PMA - Postmarket Surveillance of Implantable Cardioverter Defibrillators Using Remote Monitoring [172, 173]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P050023/S087 | Biotronik, Inc. | PROMRI FULL BODY SCAN (FBS) ICD SYSTEM | Iforia 7/Iperia/Inventra ICDs<br>The Iforia 7/Iperia/Inventra Families of Implantable Cardioverter Defibrillators (ICDs) are intended to provide ventricular anti tachycardia pacing and ventricular defibrillation, for automated treatment of lifethreatening ventricular arrhythmias. The VR-T DX ICDs are part of a system that includes both a BIOTRONIK DX ICD lead and an Iforia 7 DX/Iperia DX/Inventra DX ICD.<br><br>Linox/Protego DF-1 ICD Leads<br>The Linox/Protego DF-1 8F steroid-eluting, bipolar, IS-1 transvenous lead system is intended for use in the right ventricle of patients for whom implantable cardioverter defibrillators are indicated. The Linox S DX/Protego DF-1 S DX lead is indicated for use as a system that includes both the Linox S DX/Protego DF-1 S DX and a BIOTRONIK DX ICD.<br><br>Protego ICD Leads<br>The Protego 8F steroid-eluting, bipolar, DF4 transvenous lead system is intended for use in the right ventricle of patients for whom implantable cardioverter defibrillators are indicated.<br><br>Setrox S/Safio S Pacing Leads<br>BIOTRONIK's Setrox S/Safio S transvenous, steroid-eluting, active fixation endocardial leads are indicated for permanent pacing and sensing. Active fixation pacing leads with a bipolar (BP) IS-1 connector configuration are designed for use in conjunction with implantable pulse generators with IS-1 headers. The leads may be used with single or dual chamber pacing systems, dual chamber ICDs, CRT-Ps and CRT-Ds. The Setrox S/Safio S lead models are intended for placement in either the right atrium or right ventricle. | Sponsor Registry (Home monitoring system) | **Postmarket:** CoA to collect de-identified patient and device data using remote/home monitoring system. |

### Postmarket Use – Sponsor Database

| Population | Key Elements or Endpoints from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| All subjects implanted with a ProMRI ICD/CRT-D system enabled with the home/remote monitoring system. | **Primary:**<br>Freedom from VF delays<br><br>**Secondary:**<br>User compliance to requirement to restore the tachycardia detection and ICD therapy settings after the MRI scan | Through five years post-approval (or 25 patients with a post-MRI VF episode) |

**Narrative:**

As part of the condition-of-approval, the sponsor will collect de-identified patient data through a home/remote monitoring system and analyze data from subjects who have had a post-MRI VF episode.

# Example 80. PMA - Postmarket Surveillance of a Glucose Sensor Using Device-Generated and Patient-Reported Data [174, 175]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P120005/S041 | Dexcom, Inc. | Dexcom G5 Mobile Continuous Glucose Monitoring System | The Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5) is a glucose monitoring system indicated for the management of diabetes in persons age 2 years and older. The Dexcom G5 is designed to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G5 results should be based on the glucose trends and several sequential readings over time. The Dexcom G5 also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. The Dexcom G5 is intended for single patient use and requires a prescription. | Device data (Continuous Glucose Monitoring) and patient-collected data during home-use | Postmarket |

## Postmarket Use – Patient Home Use Study of Continuous Glucose Monitor (CGM)

| Population | Key Elements or Endpoints from RWE Sources |
|---|---|
| **Post-approval study:**<br>1110 participants (2 years of age or older with Type I Diabetes or insulin-requiring Type 2 diabetes).<br><br>Each participant will also serve as their own control. | **Primary Elements:**<br>Average number of hypoglycemic (hypo) events per patient.<br><br>**Secondary elements**:<br>Hemoglobin A1c<br>Other hypoglycemia metrics<br>Diabetic ketoacidosis (DKA) metrics<br>Patient reported outcomes (PROs).<br>CGM average glucose<br>CGM standard deviation<br>Time-in-range and time-above/below-range metrics<br>CGM use frequency at 6 months vs. 1 month and change in SMBG frequency. |

**Narrative:**

As a condition-of-approval, the sponsor agreed to conduct a post-approval study evaluating the safety of non-adjunctive use of the Dexcom G5 CGM against standard glucose meters. Patients will use a glucose meter for six months followed by six months of using the CGM. In this example, data is collected from patients in a home-use setting. The data for this study are generated both by the device (CGM data) and by the patients (including patient-reported outcomes). It should be noted that this CGM is an electronic monitoring system that is used to determine the delivery of insulin by patients (as opposed to medical professionals).

Similar example: P160030

# Example 81. PMA - Approval of an Indication Expansion for an Excimer Laser System Using Supplemental Real-World Literature [176, 177, 178]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P930016/S044 Supplement to expand indication | AMO Manufacturing USA, LLC. | STAR S4 IR Excimer Laser System iDesign Advanced WaveScan Studio System | The STAR S4 IR Excimer Laser System and iDesign Advanced WaveScan Studio System is indicated for wavefront-guided laser assisted in situ keratomileusis (LASIK) in patients:<br>▪ with myopia as measured by the iDesign Advanced WaveScan Studio system up to -11 D spherical equivalent with up to -5 D cylinder<br>▪ with agreement between manifest refraction (adjusted for optical infinity) and iDesign Advanced WaveScan Studio System refraction as follows:<br>• Spherical Equivalent: Magnitude of the difference is less than 0.625 D.<br>• Cylinder: Magnitude of the difference is less than or equal to 0.5 D.<br>▪ 18 years of age or older, and<br>▪ with refractive stability (a change of ≤1.0 D in sphere or cylinder for a minimum of 12 months prior to surgery). | Retrospective studies (data extracted from provider medical record database) | **Premarket:** Supplemental |

## Premarket Use – Published Literature

| Population | Key Elements or Endpoints from RWE sources | Follow-up/Duration (RWE) |
|---|---|---|
| **Primary Clinical Study (Non-RWE):** Prospective, multicenter, open-label, non-randomized (170 patients, 334 treated eyes, 12 US sites)<br><br>**RWE Study 1:** RWE Literature describing a retrospective study of de-identified patient data extracted from electronic medical records of a LASIK provider.<br><br>**RWE Study 2:** RWE Literature describing a retrospective study of de-identified patient data extracted from electronic medical records of a LASIK provider. | **Elements:**<br>Visual outcomes (e.g. UDVA and CDVA)<br>Refractive outcomes<br>Patient satisfaction | **Study 1**: Follow-up through one-month<br><br>**Study 2**: Baseline, one-week, one-month, 3 months |

**Narrative:**

The primary source of clinical evidence for the submission was a prospective open-label investigation of the device. FDA also reviewed supplemental real-world literature from two outside-the-US studies, which were retrospective studies of de-identified patient data extracted from the electronic medical record database of a LASIK provider. These studies provided additional safety and effectiveness data for the device during the early post-operative period.

# Example 82. PMA - Approval of an Indication Expansion for an Excimer Laser System Using Supplemental Real-World Literature [179, 180, 181]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P020050/S023 (Supplement expansion to include PRK treatment indication) | Alcon Laboratories | WaveLight EX500 Excimer Laser System, ALLEGRETTO WAVE EYE-Q Excimer Laser System | The WaveLight EX500 Excimer Laser System and ALLEGRETTO WAVE Eye-Q Excimer Laser Systems are indicated for use in Photorefractive Keratectomy (PRK) treatments for:<br>• the reduction or elimination of up to -6.0 diopters (D) of spherical equivalent myopia or myopia with astigmatism, with up to -6.0 D of spherical component and up to -3.0 D of astigmatic component at the spectacle plane,<br>• patients who are 18 years of age or older and,<br>• patients with documentation of a stable manifest refraction defined as ≤ 0.5 D preoperative spherical equivalent shift over one year prior to surgery. | Peer-reviewed real-world literature (retrospective studies with chart review) | **Premarket:** Supplemental |

## Premarket Use – Real-World Literature

| Population | Key Elements from RWE Sources | Follow-up/Duration (RWE) |
|---|---|---|
| **Primary Clinical Study (Non-RWE):** Prospective, multicenter, open-label, non-randomized study with two stages.<br><br>**RWE Study 1:** RWE Literature describing a retrospective review of all consecutive patients treated with PRK between February 2004 and January 2006 (64 patients, 128 eyes)<br><br>**RWE Study 2:** RWE Literature describing a retrospective review of all consecutive patients treated with PRK between April 2009 and January 2010 (151 patients, 222 eyes) | **Study 1 Elements:**<br>Refractive and visual outcomes, adverse events, post-operative complications<br><br>**Study 2 Elements:**<br>Refractive and visual outcomes, complications | **Study 1**: 1 month, 3 months, 6 months and 12 months<br><br>**Study 2**: 3 days, 1 month, 3 months and 6 months |

**Narrative:**

The primary source of clinical evidence for the submission was a prospective open-label investigation of the device. FDA also reviewed supplemental real-world literature from two single-site retrospective studies and non-real-world literature from a third study (randomized study of tomography guided vs wavefront optimized PRK). These two RWE studies provided additional data on refractive and visual outcomes as well as complications.

| Population | Key Elements from RWE sources | Follow-up/Duration (RWE) |
|---|---|---|
| **Primary Clinical Study (Non-RWE):** Prospective, multicenter, open-label, non-randomized study with two stages.<br><br>**RWE Study 1:** RWE Literature describing a retrospective review of all consecutive patients treated with PRK between 2/2004 and 1/2006 (64 patients, 128 eyes)<br><br>**RWE Study 2:** RWE Literature describing a retrospective review of all consecutive patients treated with PRK between 4/2009 and 1/2010 (151 patients, 222 eyes) | **Study 1 Elements:**<br>Refractive and visual outcomes, adverse events, post-operative complications<br><br>**Study 2 Elements:**<br>Refractive and visual outcomes, complications | **Study 1**: 1 month, 3 months, 6 months and 12 months<br><br>**Study 2**: 3 days, 1 month, 3 months and 6 months |

**Narrative:**

The primary source of clinical evidence for the submission was a prospective open-label investigation of the device. FDA also reviewed supplemental real-world literature from two single-site retrospective studies and non-real-world literature from a third study (randomized study of tomography guided vs wavefront optimized PRK). These two RWE studies provided additional data on refractive and visual outcomes as well as complications.

## Appendix Section VI. Examples of Real-World Evidence Use for In Vitro Diagnostics

# Guide to Examples of Real-World Evidence Use for In Vitro Diagnostics

| | File | Sponsor | Device | Real-World Data (RWD) Source(s) | RWE Use | Key Tags |
|---|---|---|---|---|---|---|
| **83** | K132750 | Illumina, Inc. | Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay | CFTR2 Database | **Premarket:** Information from the CFTR2 Database, a publicly-maintained Next Generation Sequencing database, was used as the sole source of evidence supporting this 510(k) for a cystic fibrosis indication for the subject IVD. | Next-generation sequencing;<br>RWE as a primary source of clinical evidence; |
| **84** | K124006 | Illumina, Inc. | Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay | CFTR2 Database | **Premarket:** Clinical evidence from the CFTR2 Database, a publicly-maintained Next Generation Sequencing database, was used as the sole source of evidence supporting this 510(k) for a cystic fibrosis variant assay. | Next-generation sequencing;<br>RWE as a primary source of clinical evidence; |
| **85** | DEN150035 | Baebies, Inc. | SEEKER System | Missouri State Public Health Laboratory and Missouri Department of Health and Senior Services (MDHSS) Surveillance Program | **Premarket:** This de novo classification request was solely supported by a pivotal trial embedded in a state-run routine screening program testing newborn dried blood samples and actively surveilling for false negatives. | Pediatric RWE;<br>RWE as a primary source of clinical evidence; |
| **86** | DEN140010 | Wallac Oy | EnLite Neonatal TREC Kit | Danish Newborn Screening Biobank<br>Danish medical records | **Premarket:** This de novo classification request was primarily supported by a pivotal trial that analyzed and linked samples from an international biobank to data from medical records systems. | Medical records (EHR, EMR or chart review);<br>Pediatric RWE;<br>RWE as a primary source of clinical evidence; |

| | | | | | | |
|---|---|---|---|---|---|---|
| **87** | DEN160026 | 23andMe | 23andMe Personal Genome Service (PGS) | Real-world literature | **Premarket:** To support this de novo classification request, peer-reviewed real-world literature was submitted for each of the 10 conditions included in the Genetic Health Risk tests. | RWE as a primary source of clinical evidence; |
| **88** | DEN170058 | Memorial Sloan-Kettering Cancer Center | MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) | Retrospective review of medical records from one (1) US site | **Premarket:** This is a next generation sequencing based tumor profiling test. RWE extracted from a retrospective review of medical records was used to estimate somatic mutation prevalence, to validate a cut-off, and to support evaluation of a claim for this De Novo classification request. | Medical records (EHR, EMR or chart review);<br>Next-generation sequencing;<br>RWE as a primary source of clinical evidence; |
| **89** | P140020 | Myriad Genetic Laboratories | BRACAnalysis CDx | Sponsor database | **Postmarket:** As a condition-of-approval, the sponsor is required to collect data on all IVD results during commercial use. | |
| **90** | P160052 | QIAGEN, Inc. | PartoSure Test | Observational clinical study with follow-up data collected from medical records | **Premarket:** To support this PMA, the primary clinical evidence submitted was an observational study of pregnant patients tested with the subject device to detect preterm delivery, with follow-up data on pregnancy and delivery outcomes collected from the patients' medical records.<br><br>**Postmarket:** As a condition-of-approval, the sponsor agreed to conduct a confirmatory study to collect additional data from medical records of pregnant women presenting with signs and symptoms of preterm labor, with the sponsor following up with study participants up to 39 weeks of gestation to collect outcome data. | Medical records (EHR, EMR or chart review);<br>RWE as a primary source of clinical evidence;<br>Total-Product Lifecycle Example; |

## Example 83. 510(k) - Clearance of an IVD Using a Publicly Maintained Next Generation Sequencing Database [182, 183, 184]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K132750 | Illumina, Inc. | Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay | The Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay is a targeted sequencing in vitro diagnostic system that re-sequences the protein coding regions and intron/exon boundaries of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood specimens collected in K2EDTA. The test detects single nucleotide variants, and small InDels within the region sequenced, and additionally reports on two deep intronic mutations and two large deletions. The test is intended to be used on the Illumina MiSeqDx Instrument. The test is intended to be used as an aid in the diagnosis of individuals with suspected cystic fibrosis (CF). The test is most appropriate when the patient has an atypical or non-classic presentation of CF or when other mutation panels have failed to identify both causative mutations. The results of the test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available information including clinical symptoms, other diagnostic tests, and family history. This test is not indicated for use for stand-alone diagnostic purposes, fetal diagnostic testing, for pre-implantation testing, carrier screening, newborn screening, or population screening. | CFTR2 Database | **Premarket**: (Sole-source) for indications |

## Premarket Use – Next Generation Sequencing Database – CFTR2 Database

**Narrative:**

The clinical sensitivity and specificity was estimated based on the information from the CFTR2 database (as of August 2013) as published in Sosnay PR et al., "Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene" Nat. Genet., published online on 25 August 2013. The CFTR2 database provides additional information on genetic variants in the cystic fibrosis (CF) gene and was used as a source of valid scientific evidence to establish which variants were disease-causing.

## Example 84. 510(k) - Clearance of an IVD Using a Publicly Maintained Next Generation Sequencing Database [183, 184, 185]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| K124006 | Illumina, Inc. | Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay | The Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay is a qualitative in vitro diagnostic system used to simultaneously detect 139 clinically relevant cystic fibrosis disease causing mutations and variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA isolated from human peripheral whole blood -specimens. The variants include those recommended in 2004 by the American College of Medical Genetics (ACMG) and in 2011 by the American College of Obstetricians and Gynecologists (ACOG). The test is intended for carrier screening in adults of reproductive age, in confirmatory diagnostic testing of newborns and children, and as an initial test to aid in the diagnosis of individuals with suspected cystic fibrosis. The results of this test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available laboratory and clinical information.<br><br>This test is not indicated for use for newborn screening, fetal diagnostic testing, pre-implantation testing, or for standalone diagnostic purposes. The test is intended to be used on the Illumina MiSeqDx instrument. | CFTR2 Database | **Premarket**: (sole-source) for indications |

## Premarket Use – Next Generation Sequencing Database – CFTR2 Database

**Narrative:**

The clinical sensitivity and specificity was estimated based on the information from the CFTR2 database (as of August 2013) as published in Sosnay PR et al., "Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene" Nat. Genet., published online on 25 August 2013. The CFTR2 database provides additional information on genetic variants in the cystic fibrosis (CF) gene and was used as a source of valid scientific evidence to establish which variants were disease-causing.

## Example 85. De Novo - Classification of a Newborn Screening IVD Using Clinical Evidence from a Pivotal Trial Leveraging Real-World Data Collection in a State Public Health Laboratory [186, 187]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN150035 | Baebies, Inc. | SEEKER System | The SEEKER System, including the SEEKER Instrument and the SEEKER LSD Reagent Kit IDUA\|GAA\|GBA\|GLA for use on the SEEKER Instrument, is intended for quantitative measurement of the activity of α-L-iduronidase, α-D-glucosidase, β-glucocerebrosidase and α-D-galactosidase A from newborn dried blood spot specimens as an aid in screening newborns for Mucopolysaccharidosis Type I, Pompe, Gaucher and Fabry diseases. Reduced activity of these enzymes may be indicative of these lysosomal storage diseases. The enzymes measured using the SEEKER LSD Reagent KitIDUA\|GAA\|GBA\|GLA and their associated lysosomal storage diseases are listed below.<br><br>Enzyme (abbreviation) — Disease<br>α-L-iduronidase (IDUA); — Mucopolysaccharidosis Type I (MPS I);<br>α-D-glucosidase (GAA) — Pompe<br>β-glucocerebrosidase (GBA) — Gaucher<br>α-D-galactosidase A (GLA) — Fabry | Missouri Department of Health and Senior Services (MDHSS) Surveillance Program<br><br>Missouri State Public Health Laboratory (MSPHL) | **Premarket:** Sole-Source |

## Premarket Use – Missouri State Public Health Laboratory, Missouri Department of Health and Senior Service Surveillance Program

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **MSPHL:** All newborn dried blood samples submitted to the MSPHL for routine newborn screening between 1/11/13 and 1/14/15. Samples from 105,089 newborns (babies born on or after 8/27/13) were screened and included in the pivotal phase analysis. The pilot phase included samples from babies born before 8/27/13.<br><br>**MDHSS:** Routine active surveillance program to check for false negatives during study and for fifteen months after study completion. | **Performance:**<br>Total Number of samples where 1st test is below borderline<br>Total average test result below high risk.<br>Total not referred after risk assessment<br>Total Presumed Affected<br>True Positives<br>Total Refused/Moved<br>Total presumptive false positives<br>Presumptive False Positive Rate<br>Presumptive False Negative Rate | 15 months of active surveillance monitoring to check for false negatives following study completion. | Pivotal trial protocol utilized MSPHL's study protocol for new screening tests. |

**Narrative:**

The clinical performance of the IVD was evaluated in a clinical trial in collaboration with the MSPHL as part of their routine screening program. All dried-blood spot specimens submitted to the MSPHL for routine newborn screening between January 11, 2013 and January 14, 2015 were included in the study. Babies born after or on 8/27/13 were included in the pivotal trial phase.

A Missouri Department of Health and Senior Services (MDHSS) active surveillance program used to track false negative reports and confirm diagnosis for routine screening was also used to check for false negatives in this study. Briefly, the active surveillance program checks for false negatives reported to the state's contracting metabolic centers.

This is an example of embedding a pivotal IVD clinical trial in routine practice. Note that the pivotal phase of the trial does not use presumed normal banked bio-specimens enriched with known positive samples but instead evaluates IVD performance on all samples submitted to a state lab for routine screening.

# Example 86. De Novo - Classification of an IVD Using Clinical Evidence from a Pivotal Trial Leveraging Real-World Data Collection from an International Biobank and Medical Records [135, 188]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN140010 | Wallac Oy | EnLite Neonatal TREC Kit | The EnLite Neonatal TREC Kit is an in vitro diagnostic device intended for the semiquantitative determination of TREC (T-cell receptor excision circle) DNA in blood specimens dried on filter paper. The test is for use on the VICTOR EnLite instrument. The test is indicated for use as an aid in screening newborns for severe combined immunodeficiency disorder (SCID).<br><br>This test is not intended for use as a diagnostic test or for screening of SCID-like Syndromes, such as DiGeorge Syndrome, or Omenn Syndrome. It is also not intended to screen for less acute SCID syndromes such as leaky-SCID or variant SCID. | Danish Newborn Screening Biobank<br><br>Danish medical records | **Premarket:** Primary |

## Premarket Use – Danish Newborn Screening Biobank, Danish Medical Records

| Population | Key Elements or Endpoints from RWE Source | Follow-up/Duration | Methods of Note |
|---|---|---|---|
| **Cut-Off Study (RWE):** 3243 archived dried blood spot samples from the Danish Newborn Screening Biobank (DNSB) to establish clinical cut-off values.<br><br>**Pivotal Study (RWE):** 6389 consecutive, archived dried blood spot samples from the DNSB, enriched with 17 confirmed positive SCID samples, 9 low-level TREC samples, and 56 normal samples (to mask identification of the positive samples) from other newborn screening laboratories. | **Performance:**<br>Invalid test rate<br>Presumed positive rate<br>Normal rate | Clinical assessment of DNSB samples from patient medical records to confirm that the newborn had not died from SCID-related complications (or had been associated with SCID) at one-year. | Dried-blood spot samples linked to medical records. |

**Narrative:**

The clinical cut-off values for the IVD were determined in a clinical trial using retrospective dried blood spot specimens (DBSS) from the Danish Newborn Screening Biobank (DNSB). IVD performance was then evaluated in a pivotal trial using retrospective DBSS from DNSB and confirmed positive samples from other laboratories. Clinical assessment of the DNSB samples was determined using data from Danish medical records to confirm that the newborn had not died from SCID-related complications (or had been associated with SCID) at one-year.

## Example 87. De Novo - Classification of an IVD Using Peer-Reviewed Real-World Literature [189]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN160026 | 23andMe | 23andMe Personal Genome Service (PGS) | Please see De Novo Decision Summary for indications for use. | Meta-analysis, real-world literature | **Premarket:** Sole source of clinical evidence |

## Premarket Use – Real-World Literature

| Population | Key Elements or Endpoints from RWE Sources |
|---|---|
| Individual real-world literature evaluations were conducted for each of the 10 analytes claimed to calculate likelihood ratios. Relevant patient descent represented in these studies were delineated in the intended use. In each case, a lower bound of 95% confidence interval for LR greater than 1 indicates that the test result is associated with the disease. | **Primary Elements:**<br>Likelihood ratios to estimate how the test result affects the chances of a condition. |

**Narrative:**

Authorization of the 23andMe GHR tests was supported by data from peer-reviewed literature that demonstrated a link between specific genetic variants and each of the 10 health conditions. The published data originated from studies that compared genetic variants present in people with a specific condition to those without that condition. The FDA also reviewed studies, which demonstrated that 23andMe GHR tests correctly and consistently identified variants associated with the 10 indicated conditions or diseases from a saliva sample.

## Example 88. De Novo - Classification of a Next Generation Sequencing Based Tumor Profiling Test Using an Analysis of Medical Records [190, 191, 192]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| DEN170058 | Memorial Sloan-Kettering Cancer Center | MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) | The MSK-IMPACT assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center. | Medical records<br><br>Genomic sequencing data | **Premarket:** Evaluation of a claim, validation of a cut-off and to provide additional clinical data on somatic mutation prevalence and cancer type |

## Premarket Use – Analysis of Patient Medical Records and Genomic Sequencing Data to Support a De Novo Classification Request

**Narrative:**

In DEN170058, the sponsor submitted a De Novo classification request for a next generation sequencing based tumor profiling test. Clinical data for this submission came from an electronic medical record database of advanced cancer patients with associated pathological and clinical data generated as part of routine workflow at Memorial Sloan Kettering Cancer Center. This database includes patient-matched normal controls as well, to create a comprehensive catalog of tumor-specific mutations. A retrospective analysis of the electronic medical records provided evidence to support a pan-cancer claim, to validate a test cut-off, and to provide data on somatic mutation prevalence.

# Example 89. PMA - Additional Postmarket RWE Data Collection Through Sponsor Database for Condition-of-Approval [193]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P140020 | Myriad Genetic Laboratories, Inc. | BRACAnalysis CDx | BRACAnalysis CDx is an in vitro diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in BRCA1 and BRCA2 are detected using multiplex PCR. Results of the test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108. | Sponsor database | **Postmarket:** Postmarket data collection of IVD results during commercial use |

## Postmarket Use – Sponsor Database

**Narrative:**
As part of the condition-of-approval, the sponsor will be required to monitor and assess all variants detected by the assay during commercial use, summarize and report the results annually. Additionally, the sponsor is to track and report results from samples provided in both K2EDTA and K3EDTA tubes submitted for testing. In this case, data collected in the postmarket setting during real-world / commercial use will be analyzed to evaluate the robustness of the classification process and the impact of K2EDTA and K3EDTA tubes on performance.

# Example 90. PMA - Approval for a Placental Alpha Microglobulin-1 Immunoassay using Observational Study with Follow-up Data Collection from Medical Records [194, 195, 196, 197]

| File | Sponsor | Device | Approved/Cleared/Granted Indication | RWE Source | Use of RWE |
|---|---|---|---|---|---|
| P160052 | QIAGEN, Inc. | PartoSure Test | The PartoSure test is a rapid, qualitative test for detecting the presence of placental alpha microglobulin 1 (PAMG-1) in cervicovaginal secretions. The device is indicated as an aid to rapidly assess the risk of spontaneous preterm delivery in ≤ 7 days from the time of cervicovaginal sample collection in pregnant women with signs and symptoms of early preterm labor, intact amniotic membranes and minimal cervical dilatation (<3 cm), sampled between 24 weeks, 0 days and 34 weeks, 6 days gestation in women with a singleton gestation. | **Premarket:** Patient medical records | **Premarket:** Primary source of clinical evidence |

## Premarket Use – Observational, Clinical Study with Follow-Up Data Collected from Patient Medical Records

| Population | Key Elements or Endpoints from RWE Source |
|---|---|
| **Multi-Center Clinical Study**: Observational study performed in the United States (15 sites) with 839 enrolled pregnant patients who were symptomatic for pre-term labor | Pregnancy outcomes<br>Delivery within seven days or less of testing<br>Spontaneous or medically indicated preterm labor<br>Adverse events<br>Please see Summary of Safety and Effectiveness Data for full list. |

**Narrative:**

For this original premarket approval application, the sponsor provided clinical evidence from an observational, clinical study that enrolled 839 pregnant patients who were symptomatic for pre-term labor. To evaluate the performance of the subject device, samples were obtained from consented patients and then tested with the subject device. Follow-up pregnancy and delivery outcomes were also collected from the patient's (and infant's) medical records. These data were used to evaluate the effectiveness of the test (e.g. positive predictive value, negative predictive value, test sensitivity and test specificity) as well as the safety (e.g. adverse events). Clinical evidence from this study was considered to be the basis for the PMA. The sponsor also submitted additional, supplemental data from an Outside-the-US retrospective study performed at single site. This submission illustrates an example of a clinical study used to support a PMA that leverages follow-up data collection from patient medical records.

## Postmarket Use – Post-Approval Study

| Population | Key Elements or Endpoints from RWE Source | Follow-up |
|---|---|---|
| **PartoSure PAS (PAS001):** Pregnant women presenting with signs and symptoms of preterm labor with clinically intact membranes, a cervical dilation <3 cm, a singleton gestation between 240/7 and 346/7 weeks of gestation and tested with the Partosure Test in routine clinical care.<br><br>Please see the Partosure PAS page for additional details and complete list of inclusion and exclusion criteria. | PartoSure Test result (positive or negative)<br>Patient's delivery status, defined as whether a spontaneous preterm delivery occurred within 7 days of test with subject device | Until subject reaches 39 weeks of gestation, sponsor will attempt to collect missing delivery data via follow-up telephone calls |

**Narrative:**

As a conditional-of-approval, the sponsor has agreed to conduct a confirmatory study to collect additional safety and effectiveness data from medical records of pregnant women presenting with signs and symptoms of preterm labor. 4800 patients will be enrolled in the study to obtain data from 168 spontaneous preterm deliveries within 7 days of testing with the subject device, based on a prevalence of 3.5%. The key endpoints are the subject device test results and the patients' delivery status, and the sponsor will follow-up with study participants up to 39 weeks of gestation in order to collect any missing delivery data.

## References


[1] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K170411 510(k) Letter and Summary," 4 April 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K170411.pdf. [Accessed 29 November 2019].

[2] Endovascular Skills in Trauma and Resuscitative Surgery (ESTARS) Working Group, "Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA): A prospective observational study of the Endovascular Skills in Trauma and Resuscitative Surgery (ESTARS) Working Group," [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/27050883/. [Accessed 19 February 2021].

[3] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K173032 510(k) Letter and Summary," 7 June 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173032.pdf. [Accessed 28 February 2020].

[4] National Library of Medicine, "ClinicalTrials.gov. Scalp Cooling to Prevent Chemo-induced Hair Loss (SCALP). Identifier: NCT01986140," [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT01986140?term=NCT01986140&draw=2&rank=1. [Accessed 12 May 2020].

[5] C. J. van den Hurk, M. Peerbooms, L. V. van de Poll-Franse, J. W. Nortier, J. W. W. Coebergh and W. P. Breed, "Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients-results of the Dutch Scalp Cooling Registry," Acta oncologica, vol. 51, no. 4, pp. 497-504, 2012.

[6] J. Nangia, T. Wang, C. Osbrone, P. Niravath, K. Otte, S. Papish, F. Holmes, J. Abraham, M. Lacouture, J. Courtright, R. Paxman, M. Rude, S. Hilsenbeck, C. K. Osborne and M. Rimawi, "Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial," JAMA, vol. 317, no. 6, pp. 596-605, 2017.

[7] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K173585 510(k) Letter and Summary," 19 July 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173585.pdf. [Accessed 3 December 2019].

[8] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K173860 510(k) Letter and Summary," 11 April 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173860.pdf. [Accessed 5 March 2020].

[9] Matthias Götberg, M.D., Ph.D., Evald H. Christiansen, M.D., Ph.D., Ingibjörg J. Gudmundsdottir, M.D., D.M., Lennart Sandhall, M.D., Mikael Danielewicz, M.D., et al., "Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI," New England Journal of Medicine, vol. 376, no. 19, pp. 1813-23, 2017.

[10] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "H170001 Approval Letter," 23 August 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/H170001a.pdf. [Accessed 3 December 2019].

[11] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "HDE H170001 FDA Summary of Safety and Probable Benefit," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/H170001b.pdf. [Accessed 3 December 2019].

[12] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "H170001/PAS001 MID-C System Registry PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=5615&t_id=615082. [Accessed 2 January 2020].

[13] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160035 Approval letter (Revised)," 7 June 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160035A.pdf. [Accessed 23 February 2018].

[14] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P160035: FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160035B.pdf. [Accessed 23 February 2018].

[15] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P100047 Approval letter," 20 November 2012. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047a.pdf. [Accessed 23 February 2018].

[16] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Premarket Approval (PMA) Database: P100047," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=P100047. [Accessed 26 February 2018].

[17] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P100047 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047b.pdf. [Accessed 23 February 2018].

[18] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P100047/ PAS001 OSB Lead-Newly Enrolled (HW-PAS-01)," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=461797&c_id=789. [Accessed 23 February 2018].

[19] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P150036 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150036B.pdf. [Accessed 23 February 2018].

[20] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P180001 Approval Letter," 31 December 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180001a.pdf. [Accessed 4 December 2019].

[21] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P180001 / PAS002 SVS VQI Postmarket Surveillance Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=634171&c_id=5132. [Accessed 11 December 2019].

[22] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160013/S002 Approval Letter," 31 May 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160013S002A.pdf. [Accessed 4 December 2019].

[23] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P160013/S002 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160013S002B.pdf. [Accessed 2 January 2020].

[24] U.S. Food and Drug Administration, Center for Devices and Radiological Health , "P160013 S002/ PAS001 EXPAND Continuation PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=648930&c_id=5427. [Accessed 4 December 2019].

[25] U.S. Food and Drug Administration, Center for Devices and Radiological Health , "P160013 S002/ PAS002 OCS-LUN-PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=648930&c_id=5428. [Accessed 4 December 2019].

[26] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P070026/S004 Approval letter," 2 April 2013. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf7/P070026S004A.pdf. [Accessed 23 February 2018].

[27] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P070026 S004/PAS003 OSB Lead-COC36 PAS: UK & Australian Natl Joint Reg," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=479992&c_id=858. [Accessed 23 February 2018].

[28] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P970003/S207 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf/P970003S207B.pdf. [Accessed 25 February 2018].

[29] T. Yamamato, "Vagus Nerve Stimulation Therapy: Indications, Programing, and Outcomes," Neurologia Medico-Chirurgica, vol. 55, no. 5, p. 407–415, 2015.

[30] K. Kawai, T. Tanak, H. Baba, M. Bunker, A. Ikeda, Y. Inoue, S. Kameyama, S. Kaneko, A. Kato, T. Nozawa, E. Maruoka, M. Osawa, T. Otsuki, S. Tsuji, E. Watanabe and T. Yamamoto, "Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry," Epileptic Disord, vol. 1, no. 19, pp. 327-338, 2017.

[31] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P070015/S128 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015S128B.pdf. [Accessed 23 February 2018].

[32] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P110019/S075 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110019S075B.pdf. [Accessed 25 February 2018].

[33] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140010/S015 Approval letter," 7 September 2016. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140010S015A.pdf. [Accessed 23 February 2018].

[34] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140010/S015 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140010S015b.pdf. [Accessed 23 February 2018].

[35] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140010 S015/ PAS001 OSB Lead-Surveillance Post Market Registry," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=590766&c_id=4107. [Accessed 23 February 2018].

[36] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P070014/S037 Approval letter," 31 May 2016. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf7/P070014S037A.pdf. [Accessed 23 February 2018].

[37] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P070014 S037/ PAS001 OSB Lead-Popliteal Indication PAS Surv Project," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=504881&c_id=3981. [Accessed 23 February 2018].

[38] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P040043/S051 Approval letter," 23 June 2014. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040043S051A.pdf. [Accessed 25 February 2018].

[39] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P040043 S051/ PAS002 OSB Lead-Comprehensive/Linked-Registry Based Surv," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=508665&c_id=2909. [Accessed 25 February 2018].

[40] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P100040/S012 Approval letter," 23 June 2014. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100040S012A.pdf. [Accessed 25 February 2018].

[41] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P100040 S012/ PAS002 OSB Lead-Comprehensive/Linked-Registry Based Surv.," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=517294&c_id=2698. [Accessed 25 February 2018].

[42] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P010031/S232 Approval Letter," 4 April 2012. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf/P010031S232A.pdf. [Accessed 4 December 2019].

[43] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P010031 S232/ PAS001 REVERSE NCDR ICD Registry Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=732&t_id=463105. [Accessed 4 December 2019].

[44] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P010031 S232/ PAS002 REVERSE Product Surveillance Registry," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=463105&c_id=733. [Accessed 4 December 2019].

[45] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K163244 510(k) Letter and Summary," 24 May 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/K163244.pdf. [Accessed 25 February 2018].

[46] National Library of Medicine, "ClinicalTrials.gov. truFreeze Spray Cryotherapy Patient Registry. Identifier: NCT01802203," 1 March 2013. [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT01802203. [Accessed 25 February 2018].

[47] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K171626 510(k) Letter and Summary," 30 August 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171626.pdf. [Accessed 25 February 2018].

[48] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K171257 510(k) Letter and Summary," 20 October 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171257.pdf. [Accessed 4 December 2019].

[49] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K190779 510(k) Letter and Summary," 25 June 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K190779.pdf. [Accessed 5 March 2020].

[50] National Library of Medicine, "ClinicalTrials.gov. Trevo® Retriever Registry Post Market Surveillance. Identifier: NCT02040259," [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT02040259. [Accessed 21 May 2020].

[51] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "H190005 Approval Letter," 16 August 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf19/H190005a.pdf. [Accessed 8 December 2019].

[52] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "HDE H190005 FDA Summary of Safety and Probable Benefit," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf19/H190005b.pdf. [Accessed 8 December 2019].

[53] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Humanitarian Device Exemption (HDE) Database: H190005," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H190005. [Accessed 8 December 2019].

[54] National Library of Medicine, "ClinicalTrials.gov. Safety and Efficacy Study of Spinal Tethering. Identifier: NCT02897453," [Online]. Available: https://www.clinicaltrials.gov/ct2/show/NCT02897453. [Accessed 8 December 2019].

[55] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "FDA NEWS RELEASE: FDA approves first of its kind device to treat pediatric patients with progressive idiopathic scoliosis," [Online]. Available: https://www.fda.gov/news-events/press-announcements/fda-approves-first-its-kind-device-treat-pediatric-patients-progressive-idiopathic-scoliosis. [Accessed 8 December 2019].

[56] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "H190005/PAS001 The Tether Vertebral Tethering System Registry PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=5609&t_id=668478. [Accessed 2 January 2020].

[57] U.S. Food and Drug Administration, Center for Drugs and Radiological Health, "DEN160062 Decision Summary," 19 December 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160062.pdf. [Accessed 3 March 2020].

[58] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P120017 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120017b.pdf. [Accessed 25 February 2018].

[59] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140003 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003B.pdf. [Accessed 25 February 2018].

[60] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P150033 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150033B.pdf. [Accessed 25 February 2018].

[61] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P150033 / PAS002 OSB Lead-Micra Transcatheter Pacing System PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=579631&c_id=3924. [Accessed 25 February 2018].

[62] Centers for Medicare & Medicaid Services, "Coverage with Evidence Development: Leadless Pacemakers," [Online]. Available: https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Leadless-Pacemakers.html. [Accessed 25 February 2018].

[63] National Library of Medicine, "ClinicalTrials.gov. Micra Transcatheter Pacing System Post-Approval Registry. Identifier: NCT02536118," [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT02536118. [Accessed 25 February 2018].

[64] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160036 Approval Letter," 4 June 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160036a.pdf. [Accessed 3 December 2019].

[65] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P160036 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160036b.pdf. [Accessed 3 December 2019].

[66] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160036 / PAS001 Hinternmann Series H3 TAR Long Term Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=601967&c_id=5490. [Accessed 3 December 2019].

[67] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P160043 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160043B.pdf. [Accessed 25 February 2018].

[68] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Premarket Approval (PMA) Database: P110013," [Online]. Available: https://www.accessdata.fda.gov/scrIpts/cdrh/cfdocs/cfpma/pma.cfm?id=P110013. [Accessed 25 February 2018].

[69] National Library of Medicine, "ClinicalTrials.gov. RESOLUTE International Registry: Evaluation of the Resolute Zotarolimus-Eluting Stent System in a 'Real-World' Patient Population (R-Int) Identifier: NCT00752128," [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT00752128.

[70] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P110013 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110013B.pdf. [Accessed 25 February 2018].

[71] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P170011 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170011B.pdf. [Accessed 25 February 2018].

[72] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140003/S004 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003S004B.pdf. [Accessed 25 February 2018].

[73] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140003 S004/ PAS001 OSB Lead-Impella AMI CS PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=577423&c_id=3925. [Accessed 25 February 2018].

[74] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140003/S005 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003S005b.pdf. [Accessed 25 February 2018].

[75] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140003 S005/ PAS001 OSB Lead-Impella PCCS PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=577479&c_id=3926. [Accessed 25 February 2018].

[76] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P130024/S009 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130024S009B.pdf. [Accessed 25 February 2018].

[77] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130024 S009/ PAS001 ODE Lead-ISR and LL Cohorts of the Global SFA Reg," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=586385&c_id=4275. [Accessed 25 February 2018].

[78] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P100021/S063 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100021S063b.pdf. [Accessed 25 February 2018].

[79] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P100047/S090 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047S090b.pdf. [Accessed 25 February 2018].

[80] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P960043/S097 Summary of Safety and Effectiveness," 16 February 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf/P960043S097B.pdf. [Accessed 3 March 2020].

[81] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160043/S012 Summary of Safety and Effectiveness," 14 December 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160043S012B.pdf. [Accessed 5 March 2020].

[82] Food and Drug Administration, Center for Devices and Radiological Health, "P110013/S088 Summary of Safety and Effectiveness Data," December 14 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110013S088B.pdf. [Accessed 15 May 2020].

[83] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160043 S012/ PAS001 RESOLUTE ONYX CTO Post-Approval Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=634844&c_id=5105. [Accessed 15 May 2020].

[84] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P110013 S088/ PAS001 RESOLUTE ONYX CTO Post-Approval Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=634847&c_id=5106. [Accessed 15 May 2020].

[85] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P180035 Approval letter," 15 November 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180035A.pdf. [Accessed 8 December 2019].

[86] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P180035 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180035B.pdf. [Accessed 8 December 2019].

[87] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P180035 / PAS002 MiSight 1 Day Safety PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=650185&c_id=5794. [Accessed 2 January 2020].

[88] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P040020/S049 Approval letter," 22 December 2016. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040020S049A.pdf. [Accessed 23 February 2018].

[89] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130013 Approval letter," 13 March 2015. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013A.pdf. [Accessed 23 February 2018].

[90] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130013 / PAS003 OSB Lead-WATCHMAN Comprehensive/Linked-Registry," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=512509&c_id=3358. [Accessed 23 February 2018].

[91] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031 Approval letter," 17 June 2015. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031a.pdf.

[92] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140031 Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031b.pdf. [Accessed 23 February 2018].

[93] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031 / PAS002 OSB Lead-Comprehensive/Linked-Registry," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=562750&c_id=3511. [Accessed 23 February 2018].

[94] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Transcatheter Valve Therapy (TVT) Registry," 2017. [Online]. Available: http://mdepinet.org/wp-content/uploads/TVT-CRN.pdf. [Accessed 25 February 2018].

[95] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Premarket Approval (PMA) Database: P110042/S077," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P110042S077. [Accessed 23 February 2018].

[96] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P110042 Approval letter," 28 September 2012. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110042a.pdf. [Accessed 23 February 2018].

[97] Boston Scientific, "User's Manual EMBLEM S-ICD Subcutaneous Electrode Model 3501," [Online]. Available: https://www.bostonscientific.com/content/dam/elabeling/crm/92346951-001_EMBLEM_UM_en-USA_S.pdf. [Accessed 19 February 2021].

[98] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P110042 S077/ PAS001 OSB Lead-EMBLEM S-ICD Electrode Model 3501 PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=612348&c_id=4601. [Accessed 23 February 2018].

[99] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031/S028 Approval letter," 5 June 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S028a.pdf. [Accessed 23 February 2018].

[100] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140031/S028: FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S028b.pdf. [Accessed 23 February 2018].

[101] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031 S028/ PAS001 OSB Lead-SAPIEN 3 Aortic Valve-in-Valve Comp Surv," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=608841&c_id=4424. [Accessed 23 February 2018].

[102] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031 S028/ PAS002. OSB Lead-SAPIEN 3 Mitral Valve-in-Valve Comp Surv," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=608841&c_id=4425. [Accessed 23 February 2018].

[103] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN160062 Decision Summary," 19 December 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160062.pdf. [Accessed 3 March 2020].

[104] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130009/S034 Approval letter," 9 October 2015. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009S034a.pdf. [Accessed 23 February 2018].

[105] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P130009/S034 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009S034b.pdf. [Accessed 23 February 2018].

[106] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130009 S034/PAS002 OSB Lead-Comprehensive Linked Registry-Based Surv," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=569657&c_id=3710. [Accessed 23 February 2018].

[107] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130021/S010 Approval letter," 30 March 2015. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/p130021S010a.pdf. [Accessed 23 February 2018].

[108] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130021 S010/PAS002 OSB Lead-Comprehensive/Linked-Registry," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=562366&c_id=3399. [Accessed 23 February 2018].

[109] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130009/S057 Approval letter," 18 August 2016. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009S057A.pdf. [Accessed 23 February 2018].

[110] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130009 S057/PAS002 OSB Lead-Comprehensive/Linked-Registry Based Surv," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=594156&c_id=4106. [Accessed 23 February 2018].

[111] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130021/S033 Approval letter," 10 July 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S033A.pdf. [Accessed 23 February 2018].

[112] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031/S010," 18 August 2016. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010a.pdf. [Accessed 23 February 2018].

[113] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031 S010/PAS002 OSB Lead-Comprehensive/Linked-Registry Based Surv," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=590125&c_id=4104. [Accessed 23 February 2018].

[114] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P100009/S028 Approval Letter," 14 March 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100009S028A.pdf. [Accessed 4 December 2019].

[115] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P100009 S028/ PAS002 Registry-Based CAP Cohort and RWU Surveillances," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=654507&c_id=5314. [Accessed 4 December 2019].

[116] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P130021/S058 Approval Letter," 16 August 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S058A.pdf. [Accessed 4 December 2019].

[117] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140031/S085 Approval Letter," 16 August 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S085A.pdf. [Accessed 4 December 2019].

[118] National Library of Medicine, "ClinicalTrials.gov. The PARTNER II Trial: S3iCAP (The PARTNER II) Identifier: NCT02687035," [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT02687035. [Accessed 8 March 2018].

[119] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K171120 510(k) Letter and Summary," 13 October 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171120.pdf. [Accessed 3 December 2019].

[120] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K172959 510(k) Letter and Summary," 1 May 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172959.pdf. [Accessed 4 March 2020].

[121] M. J. Rothman, J. J. Tepas III, A. J. Nowalk, J. E. Levin, J. M. Rimar, A. Marchetti and A. L. Hsiao, "Development and validation of a continuously age-adjusted measure of patient condition for hospitalized children using the electronic medical record," Journal of Biomedical Informatics, vol. 66, pp. 180-193, 2017.

[122] M. J. Rothman, S. I. Rothman and J. Beals IV, "Development and validation of a continuous measure of patient condition using the Electronic Medical Record," Journal of Biomedical Informatics, vol. 46 , no. 5, pp. 837-848, 2013.

[123] G. D. Finlay, M. J. Rothman and R. A. Smith, "Measuring the modified early warning score and the Rothman Index: Advantages of utilizing the electronic medical record in an early warning system," Journal of Hospital Medicine, vol. 9, no. 2, pp. 116-119, 2014.

[124] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K180111 510(k) Letter and Summary," 25 May 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180111.pdf. [Accessed 3 December 2019].

[125] Brunelli SM, Van Wyck DB, Njord L, Ziebol RJ, Lynch LE, and Killion DP, "Cluster-Randomized Trial of Devices to Prevent Catheter-Related Bloodstream Infection," Journal of the American Society of Nephrology, vol. 29, no. 4, pp. 1336-1343, 2018.

[126] National Library of Medicine, "ClinicalTrials.gov. Product Evaluation for the Effectiveness of the ClearGuard® HD End Cap. Identifier: NCT02593149," [Online]. Available: https://www.clinicaltrials.gov/ct2/show/NCT02593149. [Accessed 8 December 2019].

[127] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "510(k) Database: K180111," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K180111. [Accessed 3 December 2019].

[128] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K180163 510(k) Letter and Summary," 25 May 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180163.pdf. [Accessed 28 February 2020].

[129] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K180894 510(k) Letter and Summary," 19 September 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180894.pdf. [Accessed 3 December 2019].

[130] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K180986 510(k) Letter and Summary," 15 May 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180986.pdf. [Accessed 28 February 2020].

[131] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K181323 510(k) Letter and Summary," 3 August 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181323.pdf. [Accessed 3 December 2019].

[132] Shammas NW, Shammas GA, Jones-Miller S, Radaideh Q, "Safety of the ATLAS® GOLD Balloon in Treating Iliofemoral Veins: Experience From a Single Center," J Invasive Cardiol, vol. 30, no. 11, pp. 401-405, 2018.

[133] C.R. Bard, Inc., "ATLAS® Gold Vein Brochure," [Online]. Available: https://www.crbard.com/CRBard/media/ProductAssets/BardPeripheralVascularInc/PF10008/en-US/BD_BARD_Atlas-Gold-Vein_BR_EN.pdf. [Accessed 3 December 2019].

[134] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K191173 510(k) Letter and Summary," 25 July 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K191173.pdf. [Accessed 3 December 2019].

[135] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170001 Decision Summary," 10 April 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170001.pdf. [Accessed 28 February 2020].

[136] M. McQueen, J. Rojas, S. C. Sun, R. Tero, K. Ives, F. Bednarek, L. Owens, K. Dysart, G. Dungan, T. H. Shaffer and T. L. Miller, "Safety and Long Term Outcomes with High Flow Nasal Cannula Therapy in Neonatology: A Large Retrospective Cohort Study," Journal of Pulmonary & Respiratory Medicine, vol. 4, no. 6, p. 216, 2014.

[137] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170015 Decision Summary," 7 May 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170015.pdf. [Accessed 28 February 2020].

[138] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170064 Decision Summary," 24 April 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170064.pdf. [Accessed 12 March 2020].

[139] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170073 De Novo Classification Request for ContaCT," 13 February 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170073.pdf. [Accessed 3 December 2019].

[140] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170073: Evaluation of Automatic Class III Designation for ContaCT," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170073.pdf. [Accessed 3 December 2019].

[141] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160022 Approval Letter," 5 December 2019. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160022A.pdf. [Accessed 2 January 2020].

[142] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P160022 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160022B.pdf. [Accessed 3 December 2019].

[143] Hess EP, Agarwal D, Myers LA, et. al., "Performance of a rectilinear biphasic waveform in defibrillation of presenting and recurrent ventricular fibrillation: a prospective multicenter study.," Resuscitation, vol. 82, no. 6, pp. 685-9, 2011.

[144] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160022 / PAS001 Reconfirmation Analysis Mode Algorithm PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=4649&t_id=598744. [Accessed 3 December 2019].

[145] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P140010/S037 Summary of Safety and Effectiveness," 26 April 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140010S037B.pdf. [Accessed 28 February 2020].

[146] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140017/S005 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/p140017s005b.pdf. [Accessed 25 February 2018].

[147] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN160014 Decision Summary," 22 December 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160014.pdf. [Accessed 17 August 2020].

[148] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN140018 De Novo Classification Request for Esophageal Cooling Device," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN140018.pdf. [Accessed 25 February 2018].

[149] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN150010 De Novo Classification Request for DigniCap Scalp Cooling System," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN150010.pdf. [Accessed 25 February 2018].

[150] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN160006 Decision Summary," 22 June 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160006.pdf. [Accessed 2020 28 February].

[151] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170052 De Novo Classification Request for Natural Cycles," 10 August 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170052.pdf. [Accessed 8 December 2019].

[152] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170052 Evaluation of De Novo Classification Request for Natural Cycles," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170052.pdf. [Accessed 8 December 2019].

[153] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P120024 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120024B.pdf. [Accessed 25 February 2018].

[154] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160012 Summary of Safety and Effectiveness," 21 December 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160012B.pdf. [Accessed 4 March 2020].

[155] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160012 Approval Order," 21 December 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160012A.pdf. [Accessed 15 May 2020].

[156] S. L. Higgins, J. M. Herre, A. E. Epstein, G. S. Greer, P. L. Friedman, M. L. Gleva, J. G. Porterfield, F. W. Chapman, E. S. Finkel, P. W. Schmitt, R. C. Nova and H. L. Greene, "A comparison of biphasic and monopahsic shocks for external defibrillation," Prehospital Emergency Care, vol. 4, no. 4, pp. 305-313, 2000.

[157] A. P. van Alem, F. W. Chapman, P. Lank, A. A. Hart and R. W. Koster, "A prospective, randomised and blinded comparison of first shock success of monophasic and biphasic waveforms in out-of-hospital cardiac arrest," Resuscitation, vol. 58, no. 1, pp. 17-24, 2003.

[158] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160032 Summary of Safety and Effectiveness," 1 February 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160032B.pdf. [Accessed 3 March 2020].

[159] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160032 Approval Order," 1 February 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160032A.pdf. [Accessed 14 May 2020].

[160] T. Schneider, P. R. Martens, H. Paschen, M. Kuisma, B. Wolcke, B. E. Gliner, J. K. Russell, W. D. Weaver, L. Bossaert and D. Chamberlain, "Multicenter, randomized, controlled trial of 150-J biphasic shocks compared with 200-to 360-J monophasic shocks in the resuscitation of out-of-hospital cardiac arrest victims," Circulation, vol. 102, no. 15, pp. 1780-1787, 2000.

[161] D. L. Atkins and D. B. Jorgenson, "Attenuated electrode pads for automated external defibrillator use in children," Resuscitation, vol. 66, no. 1, pp. 31-37, 2005.

[162] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160033 Approval Letter," 7 December 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160033A.pdf. [Accessed 3 December 2019].

[163] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P160033 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160033b.pdf. [Accessed 3 December 2019].

[164] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P100022/S020 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100022S020B.pdf. [Accessed 25 February 2018].

[165] E. Whatley and M. Malone, "Current Considerations on Real-World Evidence Use in FDA Regulatory Submissions: Examples and decision making from the Center for Devices and Radiological Health's Peripheral Interventional Devices Branch," Endovascular Today, vol. 16, no. 10, pp. 106-8, 2017.

[166] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P010030/S056 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf/P010030S056B.pdf. [Accessed 25 February 2018].

[167] K. Collins, J. Silva, E. Rhee and M. Schaffer, "Use of a Wearable Automated Defibrillator in Children Compared to Young Adults," Pacing Clin Electrophysiol, vol. 33, no. 9, pp. 1119-24, 2010.

[168] M. Everitt and E. Saarel, "Use of the wearable external cardiac defibrillator in children," Pacing Clin Electrophysiol, vol. 33, no. 6, pp. 742-6, 2010.

[169] M. LaPage, C. Canter and E. Rhee, "A fatal device-device interaction between a wearable automated defibrillator and a unipolar ventricular pacemaker," Pacing Clin Electrophysiol, vol. 31, no. 7, pp. 912-5, 2008.

[170] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P010030 S056/ PAS001 OSB Lead-PMA Post-Approval Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=540516&c_id=3799. [Accessed 25 February 2018].

[171] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Premarket Approval (PMA) Database P010030/S086," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P010030S086. [Accessed 25 February 2018].

[172] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Summary of PMA P050023/S087 Bundled with P950037/S151, P980023/S072, P070008/S063 AND P000009/S063," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050023S087M.pdf. [Accessed 25 February 2018].

[173] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P050023 S087/ PAS001 OSB Lead-ProMRI ICD Post-Approval Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=569760&c_id=3802. [Accessed 25 February 2018].

[174] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P120005/S041 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S041B.pdf. [Accessed 25 February 2018].

[175] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P120005 S041/ PAS001 OIR Lead-Post-Approval Study," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=580234&c_id=4223. [Accessed 25 February 2018].

[176] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P930016/S044 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf/P930016S044b.pdf. [Accessed 25 February 2018].

[177] S. Schallhorn, M. Brown, J. Venter, D. Teenan, K. Hettinger and H. Yamamoto, "Early clinical outcomes of wavefront-guided myopic LASIK treatments using a new-generation hartmann-shack aberrometer," J Refract Surg, vol. 30, no. 1, pp. 14-21, 2014.

[178] S. Schallhorn, J. Venter, S. Hannan and K. Hettinger, "Outcomes of wavefront-guided laser in situ keratomileusis using a new-generation Hartmann-Shack aberrometer in patients with high myopia," J Cataract Refract Surg, vol. 41, no. 9, pp. 1810-9, 2015.

[179] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P020050/S023 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf2/P020050S023B.pdf. [Accessed 25 February 2018].

[180] G. Kymionis, V. Diakonis, G. Kounis, D. Bouzoukis, E. Gkenos, H. Ginis, S. Yoo and I. Pallikaris, "Effect of excimer laser repetition rate on outcomes after photorefractive keratectomy," J Cataract Refract Surg, vol. 34, no. 6, pp. 916-9, 2008.

[181] E. Costa, N. Franqueira, A. Rosa, C. Tavares, M. Quadrado, C. Lobo and J. Murta, "Photorefractive keratectomy for myopia and myopic astigmatism correction using the WaveLight Allegretto Wave Eye-Q excimer laser system," Int Ophthalmol, vol. 34, no. 3, pp. 477-84, 2013.

[182] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K132750 510(k) Substantial Equivalence Determination Decision Summary," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/K132750.pdf. [Accessed 23 February 2018].

[183] "The Clinical and Functional Translation of CFTR (CFTR2)," [Online]. Available: https://cftr2.org/. [Accessed 23 February 2018].

[184] P. R. Sosnay, K. R. Siklosi, F. Van Goor, K. Kaniecki, H. Yu, N. Sharma, A. Ramalho, M. Amaral, R. Dorfman, J. Zielenski, D. Masica, R. Karchin, L. Millen, P. Thomas, G. Patrinos, M. Corey, M. Lewis , J. Rommens, C. Castellani, C. Penland and G. Cutting, "Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene.," Nature Genetics, vol. 45, no. 10, pp. 1160-1167, 2013.

[185] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K124006 510(k) Substantial Equivalence Determination Decision Summary," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/K124006.pdf. [Accessed 23 February 2018].

[186] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN150035 Evaluation of Automatic Class III Designation for SEEKER System Decision Summary," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN150035.pdf. [Accessed 23 February 2018].

[187] Baebies, Inc., "SEEKER DEN150035 Executive Summary: Prepared for the August 10, 2016 Meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee," [Online]. Available: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ClinicalChemistryandClinicalToxicologyDevicesPanel/UCM515324.pdf. [Accessed 23 February 2018].

[188] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN140010: Evaluation of Automatic Class III Designation for EnLite Neonatal TREC Kit Decision Summary," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN140010.pdf. [Accessed 23 February 2018].

[189] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN160026 Evaluation of Automatic Class III Designation for The 23andMe Personal Genome Service (PGS) Genetic Health Risk Test," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf. [Accessed 25 February 2018].

[190] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170058 De Novo Classification Request for MSK-IMPACT," 15 November 2017. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170058.pdf. [Accessed 4 December 2019].

[191] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "DEN170058: Evaluation of Automatic Class III Designation for MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170058.pdf. [Accessed 4 December 2019].

[192] Zehir, Ahmet et al., "Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients.," Nature Medicine, vol. 23, no. 6, pp. 703-713, 2017.

[193] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P140020 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140020B.pdf. [Accessed 25 February 2018].

[194] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160052 Approval Letter," 12 April 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160052a.pdf. [Accessed 5 March 2020].

[195] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "Premarket Approval (PMA) Database: P160052," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160052. [Accessed 5 March 2020].

[196] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "PMA P160052 FDA Summary of Safety and Effectiveness Data," [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160052b.pdf. [Accessed 5 March 2020].

[197] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "P160052/ PAS001 Partosure PAS," [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=4749&t_id=608315. [Accessed 17 May 2020].

[198] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K173585 510(k) Letter and Summary," 19 July 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173585.pdf. [Accessed 3 December 2019].

[199] U.S. Food and Drug Administration, Center for Devices and Radiological Health, "K172721 510(k) Letter and Summary," 7 June 2018. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172721.pdf. [Accessed 28 February 2020].