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Clinical Studies Conducted Over The Total Product Life Cycle Of High-Risk Therapeutic Medical Devices Receiving Us Food And Drug Administration Premarket Approval In 2010 And 2011

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by

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Abstract

CLINICAL STUDIES CONDUCTED OVER THE TOTAL PRODUCT LIFE CYCLE OF HIGH-RISK THERAPEUTIC MEDICAL DEVICES RECEIVING US FOOD AND DRUG ADMINISTRATION PREMARKET APPROVAL IN 2010 AND 2011.

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The US Food and Drug Administration (FDA) approves high-risk medical devices, those that support or sustain human life or present potential unreasonable risk to patients, via the Premarket Approval (PMA) pathway. In recent years, the FDA has begun shifting premarket evidentiary requirements to the postmarket period as part of a broader effort to continually evaluate device safety and effectiveness throughout the total product life cycle. We therefore sought to characterize the clinical evidence generated for high-risk therapeutic devices over the total product life cycle. In October 2014, we identified all clinical studies of high-risk therapeutic devices receiving initial market approval via the PMA pathway in 2010 and 2011 through ClinicalTrials.gov and publicly available FDA documents. Studies were characterized by type (pivotal, studies that served as the basis of FDA approval; FDA-required postapproval studies [PAS]; or manufacturer/investigator-initiated); premarket or postmarket; status (completed, ongoing, or terminated/unknown); and design features,

including enrollment, comparator, and longest duration of primary effectiveness end point follow-up. We identified 286 clinical studies of the 28 high-risk therapeutic devices which received initial marketing approval via the PMA pathway in 2010 and 2011: 82 (28.7%) premarket and 204 (71.3%) postmarket, among which there were 52 (18.2%) nonpivotal premarket studies, 30 (10.5%) pivotal premarket studies, 33 (11.5%) FDA-required PAS, and 171 (59.8%) manufacturer/investigator-initiated postmarket studies. Six of 33 (18.2%) PAS and 20 of 171 (11.7%) manufacturer/investigator-initiated postmarket studies were reported as completed. No postmarket studies were identified for 5 (17.9%) devices; 3 or fewer were identified for 13 (46.4%) devices overall. Median enrollment was 65 patients (interquartile range [IQR], 25-111), 241 patients (IQR, 147-415), 222 patients (IQR, 119-640), and 250 patients (IQR, 60-800) for nonpivotal premarket, pivotal, FDA-required PAS, and manufacturer/investigator-initiated postmarket studies, respectively. Approximately half of all studies used no comparator (pivotal: 13/30 [43.3%]; completed postmarket: 16/26 [61.5%]; ongoing postmarket: 70/153 [45.8%]). Median duration of primary effectiveness end point follow-up was 3.0 months (IQR, 3.0-12.0), 9.0 months (IQR, 0.3-12.0), and 12.0 months (IQR, 7.0-24.0) for pivotal, completed postmarket, and ongoing postmarket studies, respectively. In conclusion, among high-risk therapeutic devices approved via the FDA PMA pathway, total product life cycle evidence generation varied in both the number and quality of premarket and postmarket studies, with approximately 13% of initiated postmarket studies completed between 3 and 5 years after FDA approval.

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Introduction

Medical Device Risk Classification & Regulatory Pathways

The United States Food and Drug Administration (FDA) primarily regulates medical devices through 1 of 3 pathways – the 510(k) Premarket Notification (510[k]), Humanitarian Device Exemption (HDE), and Premarket Approval (PMA) pathways.[1-3] The pathway through which each device is regulated depends on the risk associated with use, the intended patient population, and the presence of similar previously marketed devices. First established under the 1976 Medical Device Amendments Act, the FDA risk classification system for devices categorizes products into 1 of 3 tiers based on the level of regulatory control necessary to assure device safety and effectiveness (Class I – low risk, Class II – moderate risk, and Class III – high-risk; *Table 1*).[4] Roughly two-thirds of all devices regulated by the FDA are classified as low-risk; these devices (e.g., dental floss and walking canes) are subject to general regulatory controls such as good manufacturing practices and largely exempt from FDA premarket review.[5] Approximately 30% of devices are classified as moderate-risk; these devices (e.g., electrocardiographs and tympanostomy tubes) are regulated via the 510(k) pathway and require both general and special (e.g., performance standards) regulatory controls for marketing. High-risk devices – those that support or sustain human life, are of substantial importance in preventing illness, or present potential, unreasonable risk to patients – comprise a small fraction of all devices. These devices (e.g., coronary stents and hip implants) are regulated either via the PMA or HDE pathways, the latter of which is reserved for devices used in the diagnosis or treatment of uncommon illnesses affecting fewer than 4,000 patients in the United States each year.

Table 1. FDA Risk Classification System for Medical Devices

Device Class	**Risk Classification**	**Regulatory Controls**[a]	**FDA Review Pathway**[b]	**Premarket Evidence Requirements**	**Examples**
Class I	Low-risk	General Controls (e.g., good manufacturing practices and manufacturer registration with FDA)	None	None	Walking cane and nasal oxygen cannula
Class II	Moderate-risk	General Controls and Special Controls (e.g., performance standards and special labeling requirements)	510 (k) Premarket Notification	Substantial equivalence to predicate 510 (k) device; rarely requires clinical evidence	Electrocardiograph and diagnostic intravascular catheter
Class III	High-risk	General Controls and Premarket Approval or Humanitarian Device Exemption	Premarket Approval or Humanitarian Device Exemption	Clinical evidence providing reasonable assurance of device safety and effectiveness (Premarket	Replacement heart valve and implantable cardiac defibrillator

				Approval) or safety and probable benefit (Humanitarian Device Exemption)	

[a] Exceptions include select Class I devices exempt from good manufacturing practices and Class III devices subject to Special Controls

[b] Exceptions include select Class I and Class III devices reviewed via the 510 (k) pathway

Premarket Clinical Evidence Requirements & Generation

Device manufacturers must satisfy FDA premarket evidence requirements prior to marketing moderate- and high-risk devices. To obtain marketing clearance for a new device via the 510(k) pathway, manufacturers must demonstrate that the device is "substantially equivalent" in materials, purpose, and mechanism of action to a previously marketed "predicate" device (or components thereof);[3,6] fewer than 10% of 510(k) submissions to the FDA require clinical evidence for clearance.[3] In recent years, the 510(k) pathway has come under increased scrutiny in the wake of high-profile device recalls (e.g., the Depuy ASR metal-on-metal hip implant, which was withdrawn from the market in 2010 after the National Joint Registry for England and Wales reported a 5-year revision rate of 13%);[7-9] in 2011, the Institute of Medicine issued a report recommending that the 510(k) pathway be replaced by an entirely new regulatory framework for moderate-risk devices.[5,10] Criticism of the 510(k) pathway centers around 5 major issues. First, certain high-risk devices are still permitted to enter the market via the less stringent 510(k) pathway as a result of temporary exemptions dating back to the 1976 Medical Device Amendments Act.[11-14] Second, manufacturers may obtain marketing clearance on the basis of substantial equivalence to unsafe predicates, including permanently recalled devices.[15] Third, manufacturers may claim unproven new devices to be substantially equivalent to predicates with different technological

characteristics and indications for use.[11,16,17] Fourth, manufacturers may market poorly understood technologies through the process of "predicate creep," whereby multiple cycles of substantial equivalence determinations result in a new device that is quite dissimilar from the original predicate.[15,16] Fifth, the FDA has permitted manufacturers to market chimeric new devices on the basis of substantial equivalence to the individual characteristics of several distinctly different predicates (i.e., "split" predicates).[7] In response to these criticisms, the FDA has committed to transitioning all high-risk devices away from the 510(k) pathway,[11,12] improving the quality of publicly available summaries of scientific data supporting each device,[18] and adopting less permissive standards of substantial equivalence (e.g., prohibiting split predicates).[3]

In contrast to the 510(k) pathway, the PMA pathway is intended to regulate high-risk devices and requires premarket clinical evidence providing reasonable assurance of device safety and effectiveness as a condition of approval;[1] in addition, manufacturers must submit supplemental PMA applications prior to implementing any post-approval changes affecting device safety or effectiveness (e.g., design modifications or labeling changes expanding indications for use).[19] By statute, the FDA may only require manufacturers to generate the "least burdensome" clinical data necessary to establish device safety and effectiveness.[20] Though these data requirements are more stringent than those of European regulators,[21,22] recent studies have criticized the strength of clinical evidence supporting FDA approval of high-risk devices.[23-25] Whereas most novel pharmaceuticals are approved on the basis of 2 large double-blind randomized controlled trials demonstrating independent evidence of efficacy,[26] FDA premarket evaluation of device safety and effectiveness typically focuses on a single clinical study without blinding, comparators, or clinical (i.e., non-surrogate) primary

endpoints.[23,24,27] In addition, the external validity of these studies is often limited by small enrollment numbers and inadequate representation of important subpopulations, including women, racial minorities, and children.[24,25]

Calls for more robust premarket clinical evidence have grown louder following recent device failures, such as fractures (Medtronic Sprint Fidelis) and insulation breakdowns (St. Jude Riata) of widely-used cardioverter-defibrillator leads.[28,29] Unlike pharmaceuticals, many high-risk devices are implantable and cannot simply be discontinued when concerns arise, leaving patients and physicians to weigh the risks of re-operation against leaving potentially harmful foreign bodies in place.[27,30] Furthermore, high-risk devices often undergo extensive postmarket changes via supplemental PMA applications,[31-33] which are typically approved without supporting clinical evidence[19] and may be subject to less stringent review than intended by the FDA (e.g., labeling changes expanding indications for use approved via review tracks requiring only pre-clinical data).[32] In a recent study, implantable cardiac electronic devices were found to have accumulated nearly 30 labeling or design changes over their market life, with approximately one-fifth of major design changes supported by new clinical data.[33] These incremental changes may nonetheless pose unanticipated danger to patients (e.g., otogenic meningitis caused by the addition of an electrode positioner to Advanced Bionics CII cochlear implant),[34] reduce therapeutic benefit (e.g., spontaneous shutdown of the best-selling and recently recalled Cochlear Nucleus CI500),[35] and ultimately lead devices used in practice to differ substantially from those originally described in published studies.[31]

Premarket evidentiary standards are lower for high-risk devices approved via the HDE pathway, which does not require reasonable assurance of device effectiveness for

marketing; instead, manufacturers must provide clinical evidence of safety and "probable benefit" to obtain FDA approval.[2] Prior work has accordingly found HDE approvals to be supported by less rigorous clinical studies,[36] leading patients to be implanted with devices that were subsequently proven dangerous (e.g. the Wingspan neurovascular stent, which was found to cause an increased risk of stroke and death in implanted patients).[37] Nonetheless, the FDA and Congress have recently proposed regulatory reforms that would lower premarket evidence requirements for high-risk devices in an effort to expedite patient access to new therapies and promote technological innovation.[38,39]

Postmarket Clinical Evidence Requirements & Generation

To complement premarket understanding of safety and effectiveness, the FDA has become increasingly committed to devices throughout their "total product life cycle,"[40] an approach that involves ongoing study and reevaluation for as long as devices remain in use.[41] As part of this approach, the FDA conducts both passive and active postmarket data collection following device approval. The FDA conducts passive data collection through 3 distinct reporting programs, known as Mandatory Medical Device Reporting, MedWatch, and the Medical Product Safety Network.[42] Mandatory Medical Device Reporting requires manufacturers, importers, and user facilities (i.e., hospitals, nursing homes, and outpatient treatment and diagnostic centers) to report all deaths and serious adverse events for which a device is suspected or known to have caused or contributed to patient harm.[43] MedWatch is a voluntary reporting program enabling consumers and healthcare professionals to alert the FDA about all manner of safety issues, ranging from product quality problems and potential harms to serious adverse events and death.[44] The Medical Product Safety Network consists of approximately 250 clinical sites, which have partnered with the FDA to identify safety

concerns beyond the scope of Mandatory Medical Device Reporting (e.g., product use errors and close calls).[45]

While these passive surveillance measures may help detect safety signals and assess real-world device performance (e.g., hydrocephalus shunt valve failures due to rough handling),[46] their utility is greatly limited by the variable quality and inadequate number of reports,[47-49] which are often delayed in their submission by manufacturers and review by the FDA (e.g., deaths caused by vagus nerve stimulators reported several years later).[47,48] These unstandardized reports often lack critical information necessary to identify devices, understand adverse events, and exclude unrelated factors (e.g., procedural errors) as the cause of harm.[48] This critical information is altogether unavailable for reports never submitted as a result of poor end-user engagement; only 6% of adverse event reports originate from consumers and healthcare professionals[48] who may be impeded by fear of litigation, failure to connect devices to outcomes, and insufficient knowledge or support to fulfill reporting obligations.[47,48,50] The pervasive problem of underreporting is compounded by the fact that manufacturers determine whether adverse events are linked to devices and need not report unrelated incidents, which may incentivize mischaracterization of negative outcomes.[47,48,51] Both underreporting and lack of information on the number of devices in use prevent calculation of product-specific adverse event rates through passive surveillance, thereby decreasing the strength of safety signals relative to noise and precluding direct comparison between devices.[48,49]

In addition to monitoring passively collected reports, the FDA can actively address clinical questions by requiring manufacturers to complete postmarket studies. The FDA is authorized to order 2 types of postmarket studies, known as 522 Postmarket Surveillance

Studies and Post-Approval Studies (PAS).[52,53] 522 Postmarket Surveillance Studies (522 studies) may be ordered at any point during the market life of a device, and are most often initiated in response to safety concerns emerging in the course of real-world clinical practice (e.g., infection transmission via reprocessed duodenoscopes).[54] The FDA may order 522 studies up to 3 years in duration for both 510(k) and PMA-regulated devices, provided that the device meets any of the following 4 criteria: (1) failure would be reasonably likely to have adverse health consequences, (2) expected to have significant use in pediatric populations, (3) intended to be implanted in the body for more than 1 year, or (4) intended to be a life-sustaining or life-supporting device operated outside a user facility.[55] In practice, nearly 95% these studies have examined devices cleared via the 510(k) pathway (i.e., on the basis of substantial equivalence), with more than three-quarters of these studies ordered for metal-on-metal hip implants (cited above) and surgical mesh used in urogynecological procedures (linked to adverse events such as dyspareunia and vaginal erosion and pain).[56,57] Although the FDA has ordered roughly 400 postmarket surveillance studies to date,[56] there are concerns that these studies may have limited potential to inform regulatory and clinical decision making as a result of delays by manufacturers avoiding unfavorable findings, lack of harmonization to allow cross-product comparison, and inadequate follow-up to assess long-term outcomes.[58]

In contrast to 522 studies, the FDA may order PAS as a condition of approval for devices regulated via the PMA (including supplemental applications) and HDE pathways.[53] These studies are not subject to statutory limits on duration and typically designed to complement premarket understanding of device safety and effectiveness with information unavailable at the time of approval, such as evidence on long-term outcomes, expanded

indications for use, and subgroup safety.[56] These FDA-required studies serve as important opportunities to assess device performance, and approximately half of PMA and HDE devices approved since 1995 have been subject to PAS,[59] three quarters of which involved prospective clinical data collection (as opposed to laboratory or retrospective studies).[56] However, PAS may often be small,[60] delayed,[37,60] or not generalizable to real-world populations of use (including women and children).[25,59] Moreover, only one-quarter of PAS required by the FDA between 2005 and 2011 were completed.[60] Nonetheless, PAS may have significant implications for clinical practice, as study findings have prompted manufacturers to remove unsafe devices from the market and update device labeling with critical information (e.g., no dose-response for a depression treatment), though the effect of such labeling changes on treatment decisions is unknown.[60]

Beyond FDA-required postmarket studies, complementary sources of evidence may be generated through studies initiated by manufacturers or independent investigators. A recent survey suggests that manufacturers may primarily conduct postmarket clinical studies to comply with regulatory requirements.[61] Alternatively, these companies may also choose to invest in postmarket studies as a means to broaden applications of use and clinical acceptance of a product.[62] As the FDA adopts more flexible premarket evidence standards to expedite patient access to new technologies,[38,63,64] the information generated from both FDA-required and manufacturer/investigator-initiated postmarket studies will become increasingly important in guiding regulatory and clinical decisions.

Statement of Purpose

Our objective was to characterize the clinical studies of high-risk therapeutic devices initially approved via the FDA PMA pathway between 2010 and 2011 to better understand the amount and quality of evidence generated over the total product life cycle. Prior to conducting this study, we put forth the following specific hypotheses:

1. The FDA will have approved virtually all high-risk therapeutic devices receiving initial Premarket Approval in 2010 and 2011 on the basis of a single pivotal clinical study; additional premarket clinical evidence generated through feasibility studies of these devices will be of limited strength due to small enrollment numbers.
2. The number of postmarket studies per device will vary widely; little postmarket evidence will have been generated for a significant proportion of devices.
3. Manufacturers and independent investigators will initiate a significant proportion of postmarket studies without FDA requirement; many of these studies will assess devices in clinical contexts beyond those specified by FDA-approved indications.
4. Postmarket device studies will be of higher quality compared to premarket studies, particularly with respect to enrollment number, comparator, and duration of primary endpoint follow-up.

The specific aim of the thesis was twofold: (1) to promote critical evaluation of the clinical evidence available to inform medical decision-making about high-risk medical devices by patients and physicians and (2) to inform ongoing legislative and regulatory efforts seeking to balance pre- and postmarket evidentiary requirements for high-risk medical devices and develop robust methods of postmarket surveillance.

Methods

Sample Construction

We constructed a sample of high-risk therapeutic devices initially receiving US marketing approval via the FDA PMA pathway between January 1, 2010 and December 31, 2011 using the publicly accessible PMA database (*Figure 1*).[65] We selected this sample period in order to ensure that the majority of relevant trials were registered on ClinicalTrials.gov – an online public clinical trials registry maintained by the National Library of Medicine – in compliance with the 2007 FDA Amendments Act.[66] We used information on device type listed within the FDA database to exclude all nontherapeutic (i.e., diagnostic) devices,[67] including detection kits, molecular assays, and imaging machines. Based on information within the publicly available FDA Summary of Safety and Effectiveness Data (SSED, hereafter referred to as the FDA Summary) linked to each original PMA application,[68] we further excluded therapeutic devices that were previously marketed in the United States for another indication.

Device Characteristics

Using information within the PMA database, we classified each device in our sample by the following characteristics: approval year, medical specialty area,[67] review type (normal/expedited), implantable designation (yes/no), and life-saving designation (yes/no). We also characterized their recall history by searching the FDA's online Medical Device Recalls Database using PMA application numbers and recording the highest recall class for each affected device (Class I-III).[69]

Identification of Clinical Studies

We primarily identified clinical studies using ClinicalTrials.gov (*Figure 2*); with the exception of small feasibility studies, the 2007 FDA Amendments Act required that all device studies ongoing as of December 2007 be registered on ClinicalTrials.gov.[66] For each device in our cohort, we initially searched ClinicalTrials.gov for the device trade name specified at the time of PMA application, any previously marketed trade names appearing in the FDA Summary, and any newly marketed trade names appearing in the PMA database. We included all resulting studies describing use of the device under these trade names, excluding duplicates. Using the FDA Summary for each device, we then searched for any trade names of its component devices as applicable. If the component was originally approved as part of the PMA application, we included all newly identified studies describing its use. If the component was not approved as part of the PMA application, we included any newly identified studies describing its use as adjunctive to a comparable device that we could not exclude as being the device of interest within our sample.

After searching for clinical studies of interest based on trade names, we then screened further using combinations of manufacturer names and device descriptors as our search terms. We first used information provided in the FDA Summary, the FDA website,[70,71] and manufacturer website to determine relevant device descriptors and abbreviations thereof for each device (e.g., "bronchial radiofrequency" and "bronchial RF"), leveraging descriptors in the generic technology name to differentiate our device of interest within the manufacturer's product line when necessary (e.g., "everolimus platinum stent" as opposed to "everolimus stent" for Boston Scientific). We also searched the PMA database to identify all manufacturers listed as applicants for each device in order to account for manufacturer

mergers, acquisitions, and rebranding. For each device, we then searched ClinicalTrials.gov for combinations of manufacturer name(s) and device descriptors. We included newly identified resulting studies that mentioned relevant combinations of manufacturer name(s) and device descriptors, provided that the study examined a technologically equivalent, unnamed device that was both attributable to the correct manufacturer by study description or sponsorship and conducted in a setting consistent with the marketing history outlined in the FDA Summary. For devices produced by smaller manufacturers or with device descriptors either highly specific in name or unique to a single manufacturer, we additionally searched ClinicalTrials.gov for these manufacturer names and device descriptors alone. We included newly identified studies resulting from these searches that described use of a comparable device that we could not exclude as being the device of interest within our sample.

All searches were performed by VKR in October 2014. The principal investigator (J.S.R.) reviewed all potentially relevant studies derived from this multi-step search algorithm along with another investigator (V.K.R.) to determine appropriateness for inclusion. We excluded studies with an enrollment status of "Not yet recruiting," "Suspended," or "Withdrawn." If an identified study compared two or more devices in our sample, the study was counted once for each device.

Following our search of ClinicalTrials.gov, we then reviewed all feasibility and pivotal studies described in FDA Summaries and PAS listed within the FDA PAS database;[72] no 522 postmarket surveillance studies were ordered for devices in our sample.[55] Pivotal studies are those which serve as the primary basis for the FDA's premarket evaluation of device safety and effectiveness.[73] Studies described solely within FDA documents were included, even if not registered on ClinicalTrials.gov (*Figure 2*). For devices with sub-studies

conducted in support of the PMA application, we considered each named sub-study with FDA-required follow-up of the premarket cohort as a separate PAS.

Clinical Study Features

For all identified studies, we abstracted the following information from ClinicalTrials.gov and/or FDA documents (*Box 1*): enrollment number, study status (completed, ongoing, terminated/unknown), primary completion date (i.e., final data collection for primary outcomes), and study type (pivotal study, FDA-required PAS, or manufacturer/investigator-initiated study).

Box 1. Coding of Premarket & Postmarket Clinical Study Enrollment, Status, and Type

Enrollment: Study enrollment size was recorded as specified in the "Enrollment" field on ClinicalTrials.gov or described in FDA approval letters mandating post-approval studies. Study enrollment size for pivotal studies identified through FDA Summaries was recorded as the number of randomized patients. For feasibility studies identified through FDA Summaries, the number of patients receiving the study intervention was recorded as the enrollment size.

Study status: For studies identified through ClinicalTrials.gov, study status was recorded as most recently specified on the study page; studies listed as "Completed" were categorized as completed, studies listed as "Recruiting," "Enrolling by invitation," or "Active, not enrolling" were categorized as ongoing, and studies listed as "Terminated" or "Unknown" were categorized as terminated/unknown. We considered all pivotal and feasibility studies identified through FDA Summaries to be completed. We determined the study status of FDA-required post-approval studies using the "Study Progress" field within the FDA Post-Approval Studies database; studies were categorized as "Ongoing" if study progress was reported as "Progress Adequate" or "Progress Inadequate," "Unknown" if progress was reported as "Study Pending," and "Completed" if reported as such.

Primary completion date: For studies identified through ClinicalTrials.gov, primary completion date was recorded as specified in the "(Estimated) Primary Completion Date" field. In rare instances, no primary completion date was reported on ClinicalTrials.gov, and we used information reported in the "Completion Date" field instead. If neither field was populated, we estimated the primary completion date by adding the duration of longest follow-up for the primary outcome measure to the date of last verification by the study sponsor. For pivotal studies identified through FDA Summaries, we used the date of last data collection as reported. For feasibility studies identified through FDA Summaries, we performed a search of the literature to identify the completion date of the study as reported or

estimate the primary completion date by adding the duration of longest follow-up to the date of final patient enrollment. In rare instances, we were unable to locate a published report of the feasibility study within the literature, and instead used a search of the Web to identify the dates of news items reporting on the results of these studies. Studies with a primary completion date prior to initial FDA marketing approval were categorized as premarket; all other studies were categorized as postmarket.

Study type: Studies identified through ClinicalTrials.gov were determined to be pivotal or post-approval studies if described as such within the "Official Title," "Brief Description," or "Detailed Description" fields. We further identified pivotal and post-approval studies among those identified through ClinicalTrials.gov by comparing reported enrollment size, setting, and design features to study descriptions provided within FDA resources. All other studies were considered to be manufacturer/investigator-initiated.

We then abstracted additional information on study features for all pivotal premarket, completed postmarket, and ongoing postmarket studies; non-pivotal premarket and terminated/unknown studies were excluded from further analysis because the information available was often insufficient for characterization. We collected the following additional study features (*Box 2*): funder, centers, location, registry design, blinding, study groups, comparator, and randomization.

Box 2. Coding of Pivotal Premarket & Completed/Ongoing Postmarket Clinical Study Features

Funder: Coded as "Industry," "Other," or "Mixed" (i.e., both industry and outside funding sources) based on ClinicalTrials.gov downloadable output. Pivotal and post-approval studies identified through FDA resources were considered to be "Industry" funded.

Centers: Coded as "Single-center" or "Multi-center." Studies explicitly described as single-center or with only one study center listed were considered to be "Single-center." All other studies were considered to be "Multi-center."

Locations: Coded as "All US," "Some US," or "No US" based on the description and/or listing of study center locations. All multi-center studies with at least one US location listed were considered to be "Some US." Studies with no stated location were considered to be "Some US."

Registry: Coded as "Registry" or "Non-registry." A clinical study was considered to be a "Registry" if the term "registry" was used explicitly either in the study name or description.

Blinding: Coded as "Open label", "Single-blind", or "Double-blind." Studies described as being blinded to an objective outcomes assessor or without explicit mention of blinding were considered to be "Double-blind." Studies described as being blinded to either patient or investigator without mention of the other were considered to be "Single-blind." Observational, single-group, and registry studies were considered to be "Open label." All other studies were classified as reported.

Study Groups: Coded as "Single-group" or "Multi-group." Studies explicitly described as single-group, with only one group listed, or in which all groups received the same treatment were considered to be "Single-group." All other studies were considered to be "Multi-group."

Comparators: Coded as "None", "Active comparator," or "Placebo/Sham." Clinical studies with standard of care as the control group were considered to have an "Active Comparator." Single-group studies were considered to have "None." All other studies were classified as reported.

Randomization: Coded as "Randomized", "Non-randomized", or "N/A." Single-group studies were classified as "N/A" because randomization is not possible in such a design. Studies not explicitly described as being randomized were considered to be "Non-randomized." All other studies were classified as reported.

Using clinical experience and judgment, members of the study team (V.K.R. and J.S.R.) additionally determined whether the indications for device use in each ongoing and completed postmarket study (both FDA-required PAS and manufacturer/investigator-initiated studies) differed from the original FDA-approved indication as explicitly described in the corresponding FDA Summary. This determination (original or different) was made based on information within the postmarket study description and inclusion/exclusion criteria, which outlined the conditions and population for which the device was used. If there was insufficient information to make a determination, we categorized the indication as not differing by default. Of note, we did not consider studies using the Edwards Sapien transcatheter heart valve in high-risk surgical patients to have a differing indication; although the device was originally cleared for the treatment of inoperable patients, the same pivotal study was used as the basis for approval in treating high-risk surgical patients as well. All

data pertaining to clinical study features was abstracted by VKR; all characterizations of indications were confirmed by JSR, with conflicts resolved by consensus. Several representative examples of differing and non-differing indications are provided with supporting rationale (*Box 3*).

Box 3. Characterization of Indications for Device Use in Postmarket Studies

Indications Differing from Original FDA-Approved Indication

Different Example #1

Original FDA indication: "The Arctic Front Cardiac CryoAblation Catheter and CryoConsole (Arctic Front® Cryocatheter System) are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation."

ClinicalTrials.gov study description: "The purpose of this study is to evaluate the effectiveness of Pulmonary Vein Isolation (PVI) performed with the Arctic Front™ Advance Cardiac CryoAblation Catheter System as first-line therapy in comparison with antiarrhythmic drugs (AAD) in patients with paroxysmal atrial fibrillation (AF)."

Supporting rationale: Cryoballoon ablation was originally FDA-approved for the indication of treating drug-refractory patients, but here is studied as first-line treatment.

Different Example #2

Original FDA indication: "The Edwards SAPIEN Transcatheter Heart Valve (THV), model 9000TFX, sizes 23mm and 26mm, is indicated for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis."

ClinicalTrials.gov study description: "The purpose of this registry is to retrospectively and prospectively obtain clinical data in consecutively treated patients, in order to demonstrate that the commercially available Edwards SAPIEN Valve with the RF3 delivery system is a safe and effective treatment for patients with pulmonary regurgitation or stenosis."

Supporting rationale: Study assesses artificial heart valve implantation in the pulmonic position, whereas device is originally FDA-approved for the indication of implantation in the aortic position.

Different Example #3

Original FDA indication: "Belotero® Balance is indicated for injection into the mid-to-deep dermis for correction of moderate- to-severe facial wrinkles and folds such as nasolabial folds."

ClinicalTrials.gov study description: "Inclusion criteria: (1) Active stage TO [thyroid opthalmopathy] as determined by symptom onset of under 9 months AND (2) Upper eyelid retraction of 1 mm or greater in one or both eyes AND (3) Complaints of either significant ocular symptoms (despite appropriate use of ocular lubricants), or cosmetic deformity associated with the eyelid retraction"

Supporting rationale: Study assesses dermal filler for treatment of thyroid eye disease, whereas the filler is originally FDA-approved for the indication of treating facial wrinkles.

Different Example #4

Original FDA indication: "The PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients with symptomatic heart disease due to *de novo* lesions in native coronary arteries >2.25 mm to <4.00 mm in diameter in lesions <28 mm in - length."

ClinicalTrials.gov study description: "Inclusion criteria: long lesion (lesion length >30mm by visual estimation) or in stent restenosis of bare metal stent or everolimus-eluting stent."

Supporting rationale: Study includes patients with stent restenosis and patients with lesion length ≥ 28 mm, but the stent was originally FDA approved for the indication of treating symptomatic heart disease caused by *de novo* lesions < 28 mm in length. Lesions 28-34 mm in length were approved as an indication for treatment via supplemental pre-market application based on clinical evidence supporting a different size of the stent.

<u>Indications Consistent with Original FDA-Approved Indication</u>

Original Example #1

Original FDA indication: "The Alair ® Bronchial Thermoplasty System is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long acting beta agonists."

ClinicalTrials.gov study description: "Inclusion Criteria: (1) Patient with severe persistent asthma uncontrolled found in stable [condition] for at least 3 weeks AND (2) Patient receiving regular treatment with inhaled corticosteroids (beclomethason[e] > 1000 mcg or equivalent) and LABA (salmeterol >= 100 mcg or equivalent) AND (3) AQLQ score < 6.25 AND (4) FEV1 >= 60% predicted AND (5) Patients not smoking for at least one year "

Supporting rationale: Patients eligible for inclusion must have uncontrolled asthma despite receiving inhaled corticosteroid and long acting beta agonist treatment.

Original Example #2

Original FDA indication: "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."

ClinicalTrials.gov study description: "Inclusion Criteria: (1) Post-operative clinical evaluation judged successful using Harris Hip Scoring system (HHS > 90) AND (2) Body weight less than 270 lbs AND (3) No evidence of post-operative hip subluxation or dislocation AND (4) Do not walk with detectable limp AND (5) Be able to actively abduct their operated hip against gravity without falling AND (6) Must be willing to sign Informed Consent and Health Insurance Portability and Accountability (HIPAA) forms. Exclusion Criteria: (1) Pregnant, lactating females or females not using reliable form of birth control AND (2) Patients that do not meet study requirements AND (3) Patients unwilling to sign Informed Consent or HIPAA forms"

Supporting rationale: Insufficient information is provided to determine the indications for hip prosthesis implantation (i.e., inflammatory vs. non-inflammatory joint disease) among study patients.

Original Example #3

Original FDA indication: "The Pipeline Embolization Device is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments."

ClinicalTrials.gov study description: "Inclusion Criteria: (1) Subjects who are age 22 or higher AND (2) IA of at least 10 mm in maximum distension along the internal carotid artery between the petrous and superior hypophyseal segments"

Supporting rationale: Inclusion criteria specify use of the device in the same patient population (age 22 years or older) and disease state (large IA within specific anterior circulation anatomical bounds) as the original FDA indication.

Original Example #4

Original FDA indication: "Gel-One ® is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics, e.g., acetaminophen."

ClinicalTrials.gov study description: "Inclusion Criteria: (1) Have knee pain AND (2) Grade 1 to 3 on the Kellgren-Lawrence grading scale [for radiographic evaluation of osteoarthritis].

Exclusion Criteria: (1) BMI greater than 35 kg/m2 AND (2) Received an intra-articular hyaluronic acid injection for the treatment of OA of the knee within 6 months prior to screening AND (3) Had a joint replacement of the target knee"

Supporting rationale: Inclusion criteria specify device use for the indication of knee pain secondary to osteoarthritis. Insufficient information is provided to definitively determine whether the device is to be used as first- or second-line treatment (i.e., whether patients have failed non-pharmacologic and pharmacologic therapies prior to enrollment).

Clinical Study Primary Effectiveness Endpoints

We identified and characterized all primary effectiveness endpoints assessed in pivotal premarket, completed postmarket, and ongoing postmarket studies. Primary endpoints of pivotal and postmarket studies identified through ClinicalTrials.gov were recorded as reported in the "Current Primary Outcome Measures" field on each study page. Additionally, we searched the FDA Summary for each pivotal study registered on ClinicalTrials.gov to identify any additional primary endpoints discussed in the study description. We classified endpoints describing adverse events or other sequelae related to previous treatment with the study device (e.g., blood metal ion level measurement following metal-on-ceramic hip implantation) as safety endpoints. We classified endpoints describing the state of the medical condition for which the patient received treatment with the study device (e.g., number of severe respiratory exacerbations observed in asthma patients undergoing bronchial thermoplasty) as effectiveness endpoints. In the event that a composite endpoint described elements of both, we classified the endpoint as an effectiveness endpoint. Mortality was considered an effectiveness endpoint unless specifically designated otherwise; whenever an endpoint was explicitly classified on ClinicalTrials.gov, we considered it to be as such.

For pivotal studies identified through FDA Summaries, we classified endpoints as explicitly named. If only one primary endpoint was named for a pivotal study, we considered

it to be an effectiveness endpoint. If no primary endpoint was explicitly named, we designated the endpoints discussed within the "Effectiveness Endpoints" and "Safety Endpoints" sections as primary endpoints; in these select instances, a maximum of 3 endpoints were named in per section. We considered the primary endpoints of PAS providing follow-up of previously enrolled cohorts to be the same as the original study, unless explicitly specified otherwise by information within the Post-Approval Studies database.

For each primary effectiveness endpoint, we recorded the duration of longest follow-up (using the pre-specified duration for ongoing studies). Primary effectiveness endpoints were then classified as "clinical outcomes," "clinical scales," or "surrogate markers of disease" based on an established framework and a recent Institute of Medicine report.[26,74] "Clinical outcomes" measure patient survival or function (e.g., overall survival, 50-foot walk test, or freedom from reoperation). "Clinical scales" represent rubrics for the quantification of subjective patient-reported symptoms (e.g., Harris Hip Score, best-corrected visual acuity, or New York Heart Association Functional Classification Status). "Surrogate markers of disease" represent biomarkers expected to predict clinical status (e.g., aortic insufficiency as measured by echocardiogram, maximum observed everolimus blood concentration, or reduction in smooth muscle surface area as objectified on bronchial biopsies). Endpoints classified as "Clinical outcomes" and "Clinical scales" were grouped together and classified as "Clinical outcomes" for purposes of analysis. Composite endpoints with both clinical and surrogate components were considered to be "Clinical outcomes." All data pertaining to primary endpoints was abstracted by VKR; all characterizations of endpoints were confirmed by JSR, with conflicts resolved by consensus.

Statistical Analysis

We used descriptive statistics to characterize our high-risk therapeutic device sample. We calculated median enrollment numbers for non-pivotal premarket, pivotal premarket, FDA-required PAS, and manufacturer/investigator-initiated postmarket studies, and used the Kruskal-Wallis test to assess for a difference between these 4 study types. We then used descriptive statistics to characterize all other features of pivotal premarket, completed postmarket, and ongoing postmarket clinical studies; FDA-required PAS and manufacturer/investigator-initiated postmarket studies were categorized together to provide a holistic perspective of completed and ongoing postmarket evidence generation. Analyses of primary effectiveness endpoints were conducted at the endpoint-level because some studies had multiple primary effectiveness endpoints and some studies had only safety endpoints. We then used χ^2 and Kruskal-Wallis tests as appropriate to examine for differences in features and primary effectiveness endpoints between these 3 study types. Analyses were performed using Microsoft Excel 2011 and JMP version 10.0 (SAS Institute Inc.). All statistical tests were 2-tailed, and we used a type 1 error rate of 0.05 in testing enrollment number. To account for multiple comparisons, we used type I error rates of 0.006 and 0.0125 in testing all other study features (9 comparisons) and endpoint characteristics (4 comparisons), respectively.

Results

Study Sample

Between 2010 and 2011, the FDA granted initial marketing approval for 28 high-risk therapeutic devices via the PMA pathway: 21 (75.0%) were implantable and 9 (32.1%) were life-sustaining (*Table 1*). About half (n=15; 53.6%) were for cardiovascular conditions. Ten (35.7%) were recalled at least once, with one (3.6%) undergoing a Class I recall (highest-risk: reasonable probability of serious health problems or death) and one (3.6%) voluntarily withdrawn from market.

Table 2. High-Risk Therapeutic Devices Receiving Initial Marketing Approval via the FDA Premarket Approval Pathway in 2010 and 2011

	No. (%)
Approval Year	
2010	12 (42.9)
2011	16 (57.1)
Medical Specialty Area	
Anesthesiology	2 (7.1)
Cardiovascular	
Coronary stent	3 (10.7)
Non-coronary stent	12 (42.9)
Ear, Nose, and Throat	2 (7.1)
General and Plastic Surgery	1 (3.6)
Neurology	2 (7.1)

Ophthalmology	3 (10.7)
Orthopedics	3 (10.7)
Priority Review	
Yes	6 (21.4)
No	22 (78.6)
Implantable[A]	
Yes	21 (75.0)
No	7 (25.0)
Life-Sustaining[A]	
Yes	9 (32.1)
No	19 (67.9)
Highest Recall Class[B]	
Class I	1 (3.6)
Class II	8 (28.6)
Class III	1 (3.6)
Withdrawn	1 (3.6)
No Recall	17 (60.7)

Notes: FDA=Food and Drug Administration.
[A] Determined based on the product code given for each device.
[B] The FDA classifies recalls into 3 categories based on the relative degree of health hazard presented by the device being recalled: Class I – reasonable probability of serious adverse health consequences or death; Class II – reasonable probability of temporary or medically reversible adverse health consequences, or remote probability of serious adverse health consequences or death; and Class III – low probability of adverse health consequences.

Premarket & Postmarket Clinical Study Enrollment, Status, and Type

We identified 286 clinical studies of these 28 high-risk therapeutic medical devices (*Figure 3*): 52 (18.2%) non-pivotal premarket studies, 30 (10.5%) pivotal premarket studies, 33 (11.5%) FDA-required PAS, and 171 (59.8%) manufacturer/investigator-initiated postmarket studies. A total of 44 (84.6%) non-pivotal premarket studies were reported as completed, as were all 30 (100.0%) pivotal premarket studies (*Table 2*). In contrast, 6 (18.2%) FDA-required PAS and 20 (11.7%) manufacturer/investigator-initiated postmarket studies were reported as completed, with 23 (69.7%) and 130 (76.0%) reported as ongoing, respectively; 2 (6.1%) FDA-required PAS were pending.

The median number of non-pivotal premarket studies per device was 1 (Interquartile Range [IQR], 0-2), and 26 (92.9%) devices received FDA approval on the basis of a single pivotal premarket study. At least 1 PAS was required by the FDA for 19 (67.9%) devices; nearly all (n=29; 87.9%) were ordered as a condition of approval for the original PMA application, while the remainder (n=4; 12.1%) were ordered following market introduction as a condition of approval for a supplemental PMA application. The median number of manufacturer/investigator-initiated postmarket studies was 3 (IQR, 1-6). We were unable to identify any postmarket studies (including completed, ongoing, or terminated/unknown studies) for 5 (17.9%) devices; 3 or fewer studies were identified for 13 (46.4%) devices overall.

Median enrollment was 65 (Interquartile Range [IQR], 25-111), 241 (IQR, 147-415), 222 (IQR, 119-640), and 250 (IQR, 60-800) patients for non-pivotal premarket, pivotal, FDA-required PAS, and manufacturer/investigator-initiated postmarket studies, respectively. Median enrollment was lower among completed FDA-required PAS and manufacturer/investigator-initiated postmarket studies (202 [IQR, 126-694] and 100 [IQR,

43-252], respectively) than among ongoing postmarket studies (300 [IQR, 120-1115] and 300 [IQR, 60-1011], respectively).

Although only 3 of 28 (10.7%) devices in our sample were coronary stents, 75 of 179 (41.8%) completed and ongoing postmarket studies (including FDA-required PAS) examined these devices. Among these coronary stent studies, median enrollment was 572 patients (IQR, 237-2000), whereas median enrollment was 135 patients (IQR, 50-326) for the 104 studies of all other devices. Focusing on the 10 devices in our sample that were recalled at least once, 67 of 104 (64.4%) 'non-coronary stent' completed and ongoing postmarket studies examined these devices; median study enrollment was 130 patients (IQR, 50-318) for recalled devices, 165 patients (IQR, 40-346) for non-recalled devices.

Table 3. Number of and Enrollment in Clinical Studies Examining High-Risk Therapeutic Devices Receiving Initial Marketing Approval via the FDA Premarket Approval Pathway in 2010 and 2011, by Study Status and Type

	Non-Pivotal Premarket (n=52)	**Pivotal Premarket (n=30)**	**FDA-Required Post-Approval (n=33)**	**Manufacturer/ Investigator Postmarket (n=171)**
Overall, No. (%)	52 (18.2)	30 (10.5)	33 (11.5)	171 (59.8)
No. (%) by Study Status				
Completed	44 (84.6)	30 (100.0)	6 (18.2)	20 (11.7)
Ongoing	3 (6.8)	0 (0)	23 (69.7)	130 (76.0)
Terminated/Unknown	5 (11.4)	0 (0)	4 (12.1)	21 (12.3)

Median No. Studies per Device (IQR)	1 (0-2)	1 (1-1)	1 (0-2)	3 (1-6)
Median No. Studies per Device (IQR) by Study Status				
Completed	1 (0-2)	1 (1-1)	0 (0-0)	0 (0-1)
Ongoing	0 (0-0)	0 (0-0)	1 (0-1)	2 (0-5)
Terminated/Unknown	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)
Median Enrollment (IQR)	65 (25-111)	241 (147-415)	222 (119-640)	250 (60-800)
Median Enrollment (IQR) by Study Status				
Completed	50 (21-114)	241 (147-415)	202 (126-694)	100 (43-252)
Ongoing	65 (60-291)	N/A	300 (120-1115)	300 (60-1011)
Terminated/Unknown	78 (57-104)	N/A	136 (69-210)	156 (55-1150)

Notes: FDA=Food and Drug Administration; IQR=Interquartile Range.

Pivotal Premarket & Completed/Ongoing Postmarket Clinical Study Features

Study features were characterized for 209 studies: 30 (14.4%) pivotal premarket studies, 26 (12.4%) completed postmarket studies, and 153 (73.2%) ongoing postmarket studies (*Figure 2*). Whereas all pivotal studies were solely funded by industry (30 of 30 [100.0%)] and virtually all were multi-center (28 of 30 [93.3%]) and enrolled U.S. patients (29 of 30 [96.7%]), fewer postmarket studies were supported by industry (completed: 17 of

26 [65.4%]; ongoing: 91 of 153 [59.5%]), were multi-center (completed: 18 of 26 [69.2%], ongoing: 92 of 153 [60.1%]), and enrolled U.S. patients (completed: 15 of 26 [57.7%], ongoing: 63 of 153 [41.2%]) (p values ≤ 0.002; *Table 3*). Pivotal and postmarket study design features were otherwise broadly similar, as approximately 10% were designated registries, roughly three-quarters were unblinded, and nearly half were single-group and thus had no comparator. Among multi-group studies, more than three-quarters used active comparators and were randomized. Finally, nearly half of all postmarket studies (83 of 179 [46.4%]) explicitly described examining devices for different indications than those originally approved by the FDA (completed: 9 of 26 [34.6%], ongoing: 74 of 153 [48.4%]).

Table 4. Characteristics of Clinical Studies Examining High-Risk Therapeutic Devices Receiving Initial Marketing Approval via the FDA Premarket Approval Pathway in 2010 and 2011, by Study Status and Type

Clinical Study Characteristic	**Study Type and Status**			***P* value**
	Pivotal Premarket (n = 30)	**Completed Postmarket (n = 26)**	**Ongoing Postmarket (n = 153)**	
Funder, No. (%)				< 0.001
Industry	30 (100.0)	16 (61.5)	57 (37.3)	
Mixed	0 (0.0)	1 (3.8)	34 (22.2)	
Other	0 (0.0)	9 (34.6)	62 (40.5)	
Centers, No. (%)				0.002
Multi-center	28 (93.3)	18 (69.2)	92 (60.1)	
Single-center	2 (6.7)	8 (30.8)	61 (39.9)	

Locations, No. (%)				< 0.001
All US	15 (50.0)	9 (34.6)	38 (24.8)	
Some US	14 (46.7)	6 (23.1)	25 (16.3)	
No US	1 (3.3)	11 (42.3)	90 (58.8)	
Registry, No. (%)				0.75
No	28 (93.3)	23 (88.5)	136 (88.9)	
Yes	2 (6.7)	3 (11.5)	17 (11.1)	
Blinding, No. (%)				0.06
Double-blind	6 (20.0)	2 (7.7)	8 (5.2)	
Single-blind	5 (16.7)	2 (7.7)	25 (16.3)	
Open label	19 (63.3)	22 (84.6)	120 (78.4)	
Study Groups, No. (%)				0.29
Multiple-groups	17 (56.7)	10 (38.5)	83 (54.2)	
Single-group	13 (43.3)	16 (61.5)	70 (45.8)	
Comparator, No. (%)				0.01[A]
Active comparator	13 (43.3)	9 (34.6)	80 (52.3)	
Placebo/Sham	4 (13.3)	1 (3.8)	3 (2.0)	
None	13 (43.3)	16 (61.5)	70 (45.8)	
Randomization, No. (%)				0.19[A]
N/A (Single-group)	13 (43.3)	16 (61.5)	70 (45.8)	
Non-randomized	0 (0.0)	2 (7.7)	13 (8.5)	
Randomized	17 (56.7)	8 (30.8)	70 (45.8)	
Indication, No. (%)				0.19 [B]

Original	N/A	17 (65.4)	79 (51.6)	
Different	N/A	9 (34.6)	74 (48.4)	

Notes: FDA= Food and Drug Administration; IQR=Interquartile Range. P values represent statistical comparisons across study type and status for each clinical study characteristic.
[A] Excluding single-group studies.
[B] Excluding pivotal studies.

Pivotal Premarket & Completed/Ongoing Postmarket Clinical Study Primary Effectiveness Endpoints

We identified 226 primary effectiveness endpoints among these 209 studies: 44 (19.5%) endpoints among 30 pivotal studies, 27 (11.9%) endpoints among 26 completed postmarket studies, and 155 (68.6%) endpoints among 153 ongoing postmarket studies (*Figure 2*). Nearly 80% (35 of 44) of pivotal study endpoints were clinical outcomes, in contrast to 57.1% of postmarket study endpoints (completed: 14 of 27 [51.9%], ongoing: 90 of 155 [58.1%]; p=0.02) (*Table 4*). Median duration of endpoint follow-up was 3.0 months (IQR, 3.0-12.0) for pivotal studies, 9.0 months (IQR, 0.3-12.0) for completed postmarket studies, and 12.0 months (IQR, 7.0-24.0) for ongoing postmarket studies (p=0.002). However, we found no difference in median duration of endpoint follow-up for implantable device studies (pivotal: 12.0 months [IQR, 4.0-12.0], completed postmarket: 10.5 months [IQR, 0.3-21.0], ongoing postmarket: 12.0 months [IQR, 8.0-24.0]; p=0.07).

Table 5. Primary Effectiveness Endpoints of Clinical Studies Examining High-Risk Therapeutic Devices Receiving Initial Marketing Approval via the FDA Premarket Approval Pathway in 2010 and 2011, by Study Status and Type

	Study Type and Status			
	Pivotal Premarket	**Completed Postmarket**	**Ongoing Postmarket**	**P value**

	Endpoints (n = 44)	**Endpoints (n = 27)**	**Endpoints (n = 155)**	
Endpoint Type, No. (%)				
Clinical Outcome	35 (79.5)	14 (51.9)	90 (58.1)	0.02
Surrogate Marker	9 (20.5)	13 (48.1)	65 (41.9)	
Median Duration of Longest Follow-Up (months) (IQR)				
Overall	3.0 (3.0 - 12.0)	9.0 (0.3 - 12.0)	12.0 (7.0 - 24.0)	0.002
Non-Implantable[A]	1.5 (0.0 - 12.0)	6.0 (0.0 - 12.0)	12.0 (6.0 - 24.0)	0.01
Implantable[A]	12.0 (4.0 - 12.0)	10.5 (0.3 - 21.0)	12.0 (8.0 - 24.0)	0.07

Notes: FDA=Food and Drug Administration; IQR=Interquartile Range. P values represent statistical comparisons across study type and status for endpoint type and median duration of longest follow-up.

[A] Determined based on the product code given for each device.

Discussion

Study Findings & Prior Literature

Our characterization of the clinical studies examining high-risk therapeutic medical devices initially approved via the FDA PMA pathway between 2010 and 2011 demonstrates that the amount and quality of evidence generated over the total product life cycle varies widely. Some devices are currently being evaluated through ongoing studies that, if completed, will provide evidence on clinical outcomes for large numbers of patients with planned follow-up of a year or longer. However, most devices have been or will be evaluated through only a few studies, which often focus on surrogate markers of disease in small numbers of patients followed over short time periods of time, and study indications that differ from the original FDA-approved indication.

Premarket clinical studies of high-risk therapeutic devices were limited in number and quality. Nearly all devices were cleared on the basis of 2 studies: 1 non-pivotal and 1 pivotal study. Non-pivotal studies are typically conducted to assess device feasibility, enrolling a limited number of patients to examine device performance and guide premarket development (e.g., design modifications) and clinical use (e.g., anatomical restrictions).[75] Non-pivotal studies may also include internationally-based studies initiated prior to FDA approval; in our study, all incomplete non-pivotal premarket studies were internationally-based. In addition, to support market approval, the FDA requires at least one pivotal study providing substantial evidence of device safety and effectiveness. We found that pivotal studies generally enrolled fewer than 300 patients and were often designed without blinding, comparators, or primary endpoint follow-up exceeding 1 year. Our results are consistent with previous studies of premarket evidentiary standards focused on devices used for

cardiovascular diseases, rare conditions, and patients who are children or have unmet medical needs,[24,25,36,63] with the exception of primary endpoint selection; whereas prior work found the majority of primary endpoints in pivotal studies to be surrogate markers of disease,[24,25] we identified nearly 80% as clinical outcomes for devices in our sample. Nonetheless, our findings confirm that premarket studies provide limited data to address important clinical questions that often arise after approval, including those related to long-term device performance, new indications or iterations, and safety and effectiveness in real-world populations.[32,33,36,76]

Prior studies have not examined total product life cycle evidence generation for high-risk therapeutic devices, instead focusing solely on the FDA PAS program or orthopedic prostheses, which often receive market clearance via the 510(k) regulatory pathway intended for moderate-risk devices.[60,77] We found that postmarket studies, like premarket studies, were often small, un-blinded, and without comparators. In addition, postmarket studies – including those examining implantable devices – were also generally limited to 1 year of primary endpoint follow-up, and nearly half focused on surrogate markers of disease. However, approximately 13% of identified postmarket studies were completed between 3 and 5 years after FDA approval; three-quarters of postmarket studies remained ongoing. Postmarket evidence may be generated from ongoing observational studies and registries before completing primary effectiveness endpoint follow-up, as well as afterwards from longer-term follow-up of safety endpoints. However, the potential for this postmarket evidence to inform practice remains unclear, even under the presumption that all ongoing studies will be completed, given that clinicians often rapidly adopt new devices after market introduction[31,78] and short-comings of the medical device literature related to selective publication and

selective outcome reporting.[79-81] Furthermore, it is unclear how this evidence will inform regulatory decisions, if at all, such as whether to recall a product. Interestingly, completed and ongoing postmarket studies examining recalled and non-recalled devices were similar in size.

Clinical & Policy Implications

The FDA has adopted a total product life cycle approach to device evaluation with the understanding that, "[a]t the time of device approval, certain safety and effectiveness questions may not be fully resolved [...] because controlled clinical studies do not fully represent the benefit-risk profile of a device when used in real-world clinical practice."[64] Although the FDA may not require a PAS for every newly approved device, the agency often requires a postmarket study to complement premarket understanding of device safety and effectiveness. However, by law, the FDA may only require the "least burdensome" postmarket data necessary to address unresolved clinical questions about devices,[38] limiting its capacity to mandate additional studies for the purpose of generating evidence to inform regulatory and clinical decision-making. Furthermore, the FDA has not imposed penalties against manufacturers failing to comply with postmarket study requirements mandated through its PAS program.[60] Our findings of limited premarket evidence generation and few FDA-required postmarket studies highlight the need for continued study, either through manufacturer-initiated or investigator-initiated studies, to advance postmarket understanding of device safety and effectiveness. Approximately 85% of the postmarket studies we identified were not initiated in response to FDA requirements, and 40% were conducted without manufacturer support. To ensure generation of additional robust, objective evidence to inform the use of high-risk devices in clinical practice, government agencies may consider

taking on a more principal role in supporting postmarket research, as they have done for several commonly used pharmaceutical products. For instance, the Patient-Centered Outcomes Research Institute – newly established under the 2010 Patient Protection and Affordable Care Act – could further prioritize funding of large, pragmatic comparative effectiveness studies designed to empower patients and physicians with real-world data on high-risk devices and their therapeutic alternatives.[82]

The "right" number and "appropriate" design of premarket and postmarket studies for high-risk therapeutic devices should vary based on expected benefit and risk, therapeutic alternatives, and anticipated challenges of widespread use, including physician learning curves and facility expertise. For any given device, conducting numerous large studies with long periods of follow-up may not be a feasible or efficient use of resources. However, pending legislative efforts will only further reduce premarket evidence requirements for medical devices in order to expedite patient access to new technologies.[83] Although the FDA has begun developing postmarket safety surveillance methods, used primarily for pharmaceuticals and biologics, that leverage routinely collected electronic health information through a distributed data model under its Mini-Sentinel initiative,[84] the validity of these methods remains uncertain and this approach cannot be used for surveillance of medical devices until there is widespread adoption of unique device identifiers.[85] Moreover, safety surveillance efforts have uncertain applications for generation of comparative effectiveness evidence or insights into long-term effectiveness of medical devices. Postmarket assessments of both medical device safety and effectiveness in real-world practice through clinical trials, registries, and analysis of health systems data will continue to provide complimentary evidence to guide regulatory and clinical decision-making. With this framework in mind, the

FDA has actively engaged in efforts to strengthen our national network of device registries and develop powerful accompanying analytical tools through the Medical Device Epidemiology Network and High-Performance Integrated Visual Environment initiatives,[86-88] though much work remains to realize the promise of big data in analyzing health outcomes across disparate sources.

Limitations

Our study has several limitations that deserve consideration. First, we may not have identified all clinical studies of devices in our sample despite the inclusive nature of our search algorithm, and our findings may thus under-represent the clinical evidence generated. This is more likely true of non-pivotal premarket clinical studies, as these could have taken place prior to the ClinicalTrials.gov registration requirements that took effect in late 2007. Nevertheless, all pivotal studies were identified, and these studies represent the most robust evidence available during premarket evaluation. Conversely, by including all studies registered on ClinicalTrials.gov, our study may over-represent the clinical evidence generated, particularly in the postmarket period; approximately one-third of clinical trials remain unpublished even years after study completion and only one-fifth of completed trials registered on ClinicalTrials.gov report their results,[89,90] such that the results of many studies we identified may never be disseminated to inform clinical practice. Second, we cannot account for postmarket studies not registered on ClinicalTrials.gov, such as chart reviews or case-studies, though the strength of evidence derived from these studies is often limited. In addition, internationally-based studies may also be less likely to be registered on ClinicalTrials.gov, although more than half of the postmarket studies we identified were conducted entirely outside of the U.S. Similarly, observational studies and patient registries

of medical devices are required to be registered on ClinicalTrials.gov under FDAAA and comprised nearly half of the postmarket studies we identified. However, non-product-specific registries (i.e., disease registries) were unlikely to have been identified, and may importantly contribute to device evaluation over the total product life cycle.[7,91,92] Third, our analysis was cross-sectional and our search was completed in October 2014, allowing between 3 and 5 years for studies to be initiated and completed after FDA approval. It is likely that there will be additional clinical studies examining these devices, and some of the studies we identified as ongoing will be completed or already have been completed. However, we expect that most major postmarket clinical studies of devices are likely to be initiated within 5 years of approval given their relatively short market life, and our findings therefore likely reflect the best evidence available and anticipated to inform clinical practice. Finally, our study was focused on evidence generated for high-risk therapeutic devices receiving PMA approval. Our findings do not apply to devices receiving market clearance via the 510(k) or Humanitarian Device Exemption regulatory pathways, which are used less frequently for high-risk devices and subject to lower evidentiary standards, nor to diagnostic devices receiving PMA approval; of note, the FDA will no longer allow manufacturers to obtain marketing clearance for high-risk devices via the 510(k) pathway in the near future,[11,12] further enhancing the generalizability of our findings.

Conclusions

Among high-risk therapeutic devices approved via the FDA PMA pathway between 2010 and 2011, total product life cycle evidence generation varied in both the number and quality of premarket and postmarket studies, with approximately 13% of initiated postmarket studies completed between 3 and 5 years after FDA approval.

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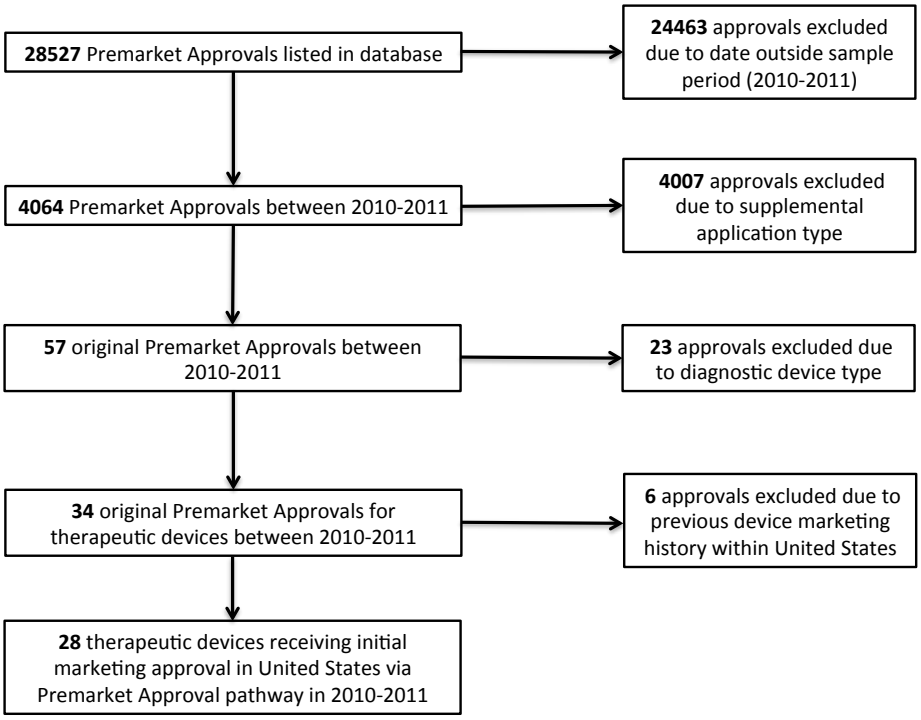
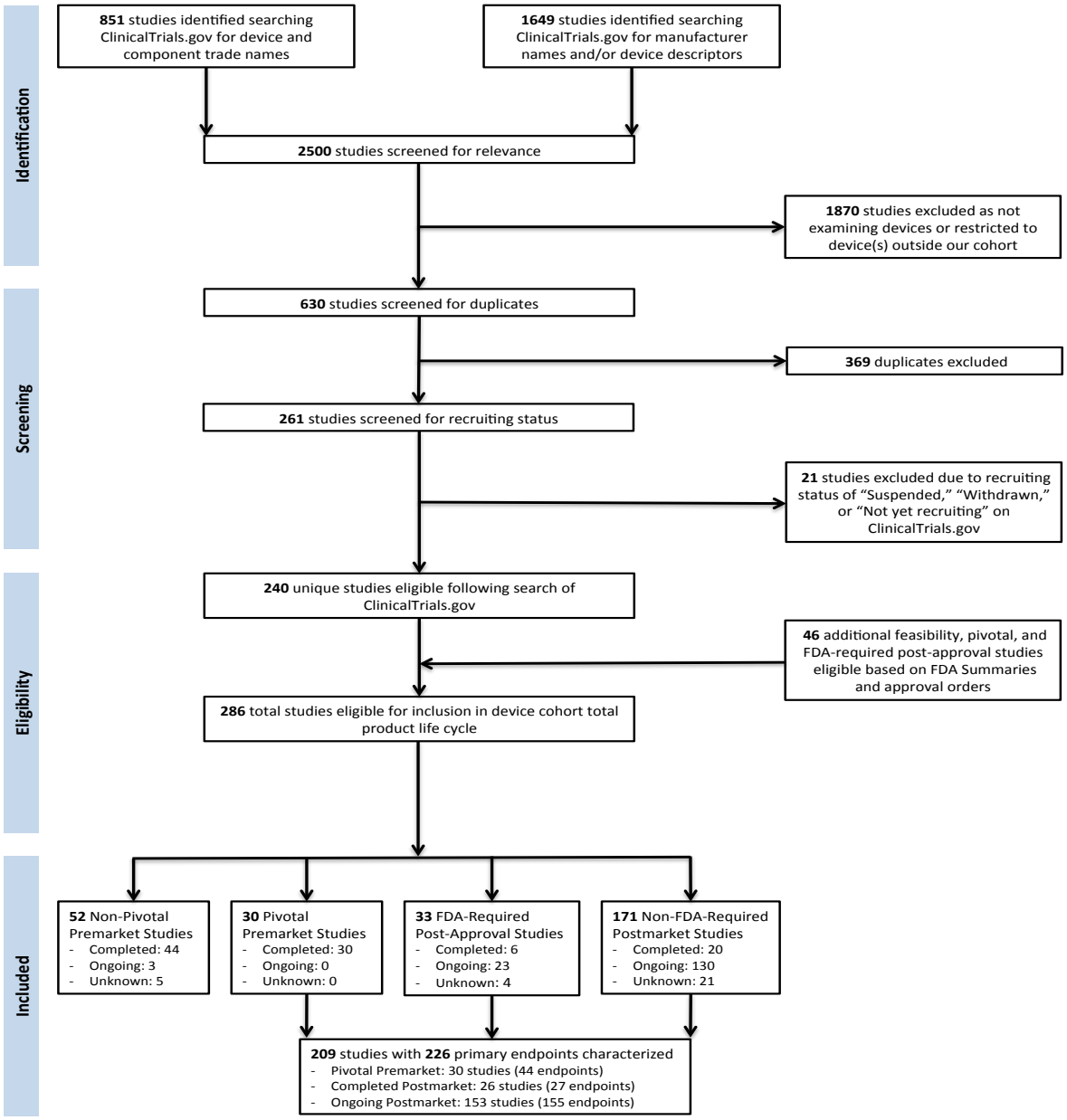
Figures, Titles, and Legends

Figure 1. Sample Construction of High-Risk Therapeutic Devices Receiving Initial Marketing Approval via the FDA Premarket Approval Pathway in 2010 and 2011



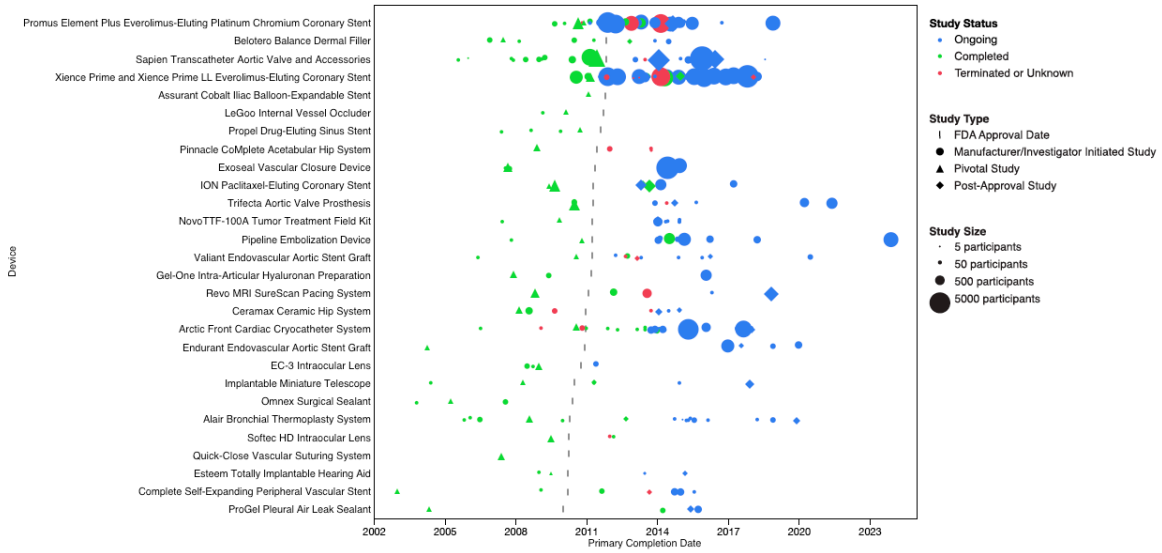
Legend: Abbreviation: FDA, Food and Drug Administration.

Figure 2. Identification of Clinical Studies Examining High-Risk Therapeutic Devices Receiving Initial Marketing Approval via the FDA Premarket Approval Pathway in 2010 and 2011



Legend: "Unknown" includes studies of both terminated and unknown status. The 26 "Completed Postmarket" studies were comprised of 6 completed FDA-required PAS and 20 completed manufacturer/investigator-initiated postmarket studies (i.e., "Non-FDA-Required Postmarket Studies"). Similarly, the 153 "Ongoing Postmarket" studies were comprised of 23 ongoing FDA-required PAS and 130 ongoing manufacturer/investigator-initiated postmarket studies. Abbreviation: FDA, Food and Drug Administration.

Figure 3. Evidence Generation for High-Risk Therapeutic Devices Receiving Initial Marketing Approval via the FDA Premarket Approval Pathway in 2010 and 2011, including premarket non-pivotal and pivotal studies and postmarket FDA-required Post-Approval studies and manufacturer/investigator-initiated studies.



Legend: Each vertical bar represents the device Premarket Approval approval date, organized from oldest (bottom) to newest (top). For each device, pre- and postmarket studies appear to the left and right of the vertical bar, respectively. A single large registry study involving two coronary stents in our cohort was excluded from the plot, as were the 3 premarket non-pivotal studies reported as "Ongoing." Abbreviation: FDA, Food and Drug Administration.