

FDA Executive Summary

Circulatory System Devices Panel Meeting

November 3, 2021

General Issues Panel

Real World Surveillance of AAA Endovascular Stent Grafts

Table of Contents

1	Introduction.....	5
2	Overview of Abdominal Aortic Aneurysms	5
2.1	Abdominal Aortic Aneurysms	5
2.2	Current Therapies for Abdominal Aortic Aneurysms.....	5
3	History and Current Status of Endovascular AAA Repair ^s	7
3.1	History.....	7
3.2	EVAR Market in US	7
3.3	Currently FDA Approved AAA Endovascular Grafts	8
3.4	EVAR Guidelines	11
3.5	EVAR Longitudinal Outcomes Reported in the Medical Literature.....	11
3.6	EVAR Longitudinal Outcomes from Pivotal Studies	14
4	Regulatory Framework	16
4.1	Pre-market Evaluation of New and Iterative Endovascular Stent Grafts.....	16
4.2	Post-Market Evaluation of New and Iterative Endovascular Stent Grafts.....	18
5	Real World Evidence	20
5.1	Need for Real-World Surveillance in EVAR Patients	20
5.2	Outcomes of Interest for Real-World Surveillance in EVAR Patients	21
5.3	Potential Resources for Real-World Surveillance in EVAR Patients	22
5.4	Mechanisms for Real-World Surveillance in EVAR Patients	22
6	Conclusion	23

Tables

Table 1: AAA endovascular grafts currently marketed in the US	9
Table 2: Pivotal study clinical endpoint results	15
Table 3: AAA Endovascular Graft Study Primary Endpoints	16
Table 4: AAA Endovascular Graft Study Secondary Endpoints	17
Table 5: EVAR Outcomes of Interest.....	21

Figures

Figure 1: Open and Endovascular Abdominal Aortic Aneurysm (AAA) Repair	6
Figure 2: Comparison of open repair vs EVAR by year	8
Figure 3: Commercially available devices.....	10
Figure 4: Number of MDR events occurring at timepoints after implant procedure.....	30

INDEX: For the purposes of this document, the following terms and definitions apply. These definitions are based on current Society for Vascular Surgery guidelines¹ and ISO 25539-1:2017². Note that other documents and studies may use slightly modified definitions.

Term	Definition
Adverse Event	Adverse change in health that occurs in a subject who participates in a study to receive treatment or within a specified time after receiving treatment
Aortic Neck	Section of healthy aortic tissue from the bottom of the lowest renal artery to the top of the aneurysm sac (defined as where the vessel diameter is 10% greater than the vessel diameter at the bottom of the lowest renal artery)
Aneurysm Enlargement	Increase in aneurysm sac diameter greater than 5 mm relative to the diameter at a specified baseline timepoint (e.g., 1-month post-implantation)
Device Migration	Movement of the endovascular device (either in a cranial or caudal direction) greater than 10 mm from the device location at a specified baseline timepoint (e.g., 1-month post-implantation)
Device Occlusion	Full or partial blockage of the endovascular lumen due to thrombo-embolism, device kink, or compression
Endoleak	<p>Persistent blood flow outside the lumen of the endovascular prosthesis but within the aneurysm sac after EVAR.</p> <ul style="list-style-type: none"> ○ Type I: leak arising from inadequate sealing between the endovascular prosthesis and the aortic tissue, occurring at the proximal (Type Ia) or distal (Type Ib) attachment zone ○ Type II: filling of the aneurysm sac by retrograde flow from patent branch arteries (e.g., lumbar and intercostal arteries) ○ Type III: leak arising from inadequate seal between modular graft components (Type IIIa) or from a defect in the graft material (Type IIIb) ○ Type IV: leak through stent graft due to graft porosity

¹ Chaikof EL, Dalman RL, Eskandari MK, et al. “The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm”. J Vasc Surg. 2018.

² ANSI/AAMI/ISO 25539-1:2017 Cardiovascular implants – Endovascular devices – Part 1: Endovascular prostheses.

	<ul style="list-style-type: none">○ Type V: sac enlargement without a discernable source of endoleak, also known as Endotension
Reintervention	Surgical or endovascular procedures performed to address adverse events associated with the endovascular device or initial endovascular aneurysm repair (EVAR) procedure
Stent Fracture	Breakage of any metallic component of the stent graft (e.g., stent ring, barb, strut)

1 Introduction

This is FDA’s Executive Summary for the General Issues Circulatory System Devices Advisory Committee Meeting on Real-World Surveillance of Endovascular Stent Grafts Approved for Treatment of Abdominal Aortic Aneurysms (AAA). This meeting is being held for the Committee to discuss and make recommendations on the need for strengthening long-term post-market real-world assessment of endovascular stent graft device performance. Specifically, the Committee will be asked to make recommendations on long-term endovascular graft safety and effectiveness, relevant clinical events that are feasible to capture in a real-world setting, potential real-world data collection infrastructures, and ways to improve patient compliance with real-world data collection efforts.

The Executive Summary discusses the AAA disease condition, general history and durability of endovascular repair, existing regulatory framework, and current thinking from the Food and Drug Administration (FDA or “the Agency”) on the need for real-world device and patient outcome surveillance. The Advisory Committee’s review and discussion will inform the Agency’s recommendations for future engagement with stakeholders to implement enhanced surveillance of AAA endovascular grafts.

2 Overview of Abdominal Aortic Aneurysms

2.1 Abdominal Aortic Aneurysms

Aneurysmal disease is characterized by structural deterioration of the aortic wall and gradual expansion of the aneurysm sac. As the sac enlarges, the risk of rupture increases, making detection and treatment of aneurysms essential to minimize the risk of mortality.³

Aortic aneurysms are most commonly located in the abdomen, with more than 90% occurring inferior to the renal arteries (infrarenal AAAs, Figure 1).⁴ Risk factors for AAA include obesity, coronary artery disease, hypertension, previous myocardial infarction, and a family history of AAA.³

AAAs result in an estimated 10,000 deaths each year in the US, most of which occur in people over the age of 65.^{5,6} AAAs are four to six-fold more common in males than females.⁷ The risk of AAA rupture is proportional to aneurysm size.¹ Once rupture occurs, death may occur rapidly, with mortality rates as high as 80% to 90%.³

2.2 Current Therapies for Abdominal Aortic Aneurysms

³ Kent, CK. "Abdominal Aortic Aneurysms". *New England Journal of Medicine*. 2014; 371:2101-2108.

⁴ Clouse WD, Cambria, R. P. Complex Aortic Aneurysm: Pararenal, Suprarenal, and Thoracoabdominal. In: Hallett JR, JW. *Comprehensive Vascular and Endovascular Surgery: Expert Consult*. 2 ed. Philadelphia: Mosby; 2009.

⁵ Gillum, Richard F. "Epidemiology of aortic aneurysm in the United States". *Journal of Clinical Epidemiology*. 1995, Vol 48(11).

⁶ Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2019 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2019, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at <http://wonder.cdc.gov/ucd-icd10.html>.

⁷ Villard C, Hultgren R. "Abdominal aortic aneurysm: Sex differences." *Maturitas*. 2018, Vol 109: 63-69.

There are three treatment options for AAAs: medical management, open surgical repair, and endovascular repair. Selection of the appropriate treatment depends on several factors including aneurysm size, location, and patient risk factors.⁸

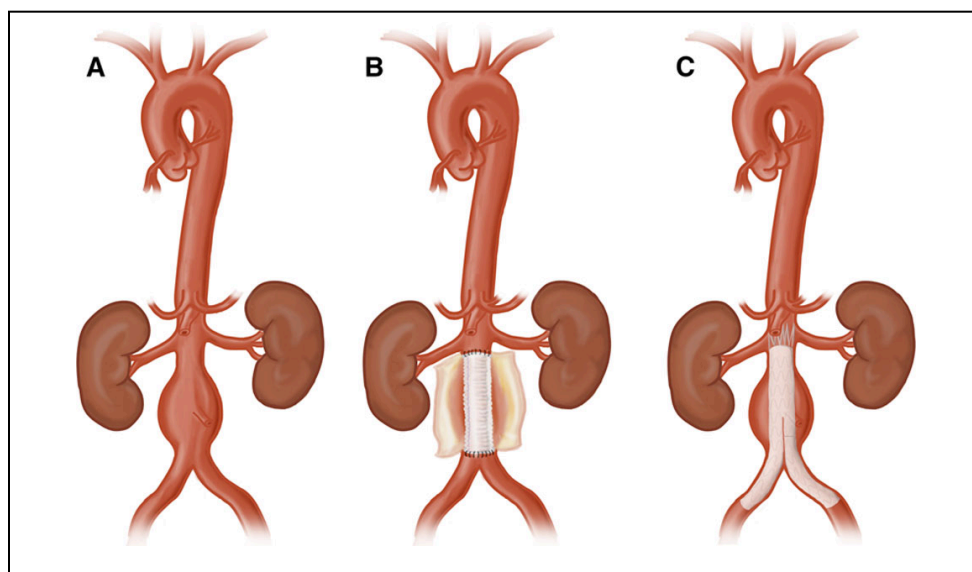


Figure 1: Open and Endovascular Abdominal Aortic Aneurysm (AAA) Repair. A, Unrepai red Infrarenal AAA. B, Open Repair with Tube Graft. C, Endovascular Repair⁸

Medical management is preferred for patients who are not at high risk of rupture.¹ Patients are treated to normalize blood pressure and address other cardiovascular risk factors, such as smoking and hypertension. Patients with small, asymptomatic aneurysms are monitored for symptoms and with periodic imaging studies (most often ultrasound exams) to determine whether sac expansion has progressed to a stage where intervention is indicated.¹

Open surgical repair may be offered to patients who are at increased risk of aneurysm rupture. The surgical procedure involves aortic exposure via laparotomy or a left retroperitoneal exposure and replacing the aneurysmal section of the aorta with a prosthetic vascular graft, which is usually made of a durable synthetic polymer (Figure 1B). The vascular graft is sutured to the native aorta.

Endovascular aneurysm repair (EVAR) is a less invasive alternative to open surgical repair, which may be offered to patients with adequate anatomic characteristics, such as an adequate landing zone proximally in the aorta and distally in the iliac arteries. During the procedure, a catheter delivers a stent-graft system to the desired location. The stent-graft typically consists of a tubular metal frame covered by synthetic graft material that is expanded to provide a conduit to exclude the aneurysm from blood flow (Figure 1C). With cessation of blood flow into the aneurysm, pressure in the aneurysm is reduced. Decreased pressure may slow or arrest aneurysm expansion or can lead to reduction in sac size over time.⁸

⁸ Swerdlow NJ, Wu WW, Schermerhorn ML. "Open and Endovascular Management of Aortic Aneurysms." *Circulation Research*. Vol 124 Issue 4. 2019.

3 History and Current Status of Endovascular AAA Repair[§]

3.1 History

Regulatory approval for the first abdominal aortic stent-graft occurred in 1996 in Europe and in the US in 1999. Today in the US, approximately 80% of AAAs repairs are performed endovascularly. During the early years of EVAR, randomized trials vs. open surgical repair were completed. A Cochrane meta-analysis of the pooled data from 2790 subjects enrolled in the four largest randomized trials demonstrated that the in-hospital or 30-day mortality rate with EVAR was 1.4% vs. 4.2% for open surgery (odds ratio 0.3, 95% confidence interval 0.22-0.50; $P<0001$).⁹ Although the periprocedural complication rate (including mortality) associated with EVAR is lower than with open surgery, longer-term outcomes analyses of randomized trials and in the Medicare database show that lower mortality rates post-EVAR vs. open surgery is not sustained beyond the intermediate term (e.g., 2-3 years). Additional details comparing EVAR to open surgical repair are in Appendix 1, and Appendix 2 contains a comparison of EVAR to Medical Management in high surgical risk patients.

3.2 EVAR Market in US

Over the past three decades, the refinement of EVAR technology and the availability of various commercial endograft systems, many now in their 3rd or 4th generation, have led to a transition of clinical practice from open surgical repair to EVAR in the elective management of AAAs. An analysis of data from the National Inpatient Sample showed that in 2005, the number of EVARs performed for unruptured AAAs in the US exceeded the number of open surgical aneurysm repairs.¹⁰ As show in Figure 2, EVAR is the current primary treatment approach for AAA repair in the US despite reports of late events post-EVAR including late aneurysm-related death, re-intervention, aneurysm sac expansion, and endoleaks.

⁹ Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD004178.

[§]Information in this section is used with permission from this article was published in Rutherford's Vascular Surgery and Endovascular Therapy, 72, Sidawy and Perler, Aortoiliac aneurysms Endovascular Therapy, 910-928, Copyright Elsevier (2018).

¹⁰ Epidemiology of endovascular and open repair for abdominal aortic aneurysms in the United States from 2004 to 2015 and implications for screening. Dansing KD, Varkevisser RRB, et al. J Vasc Surg 2021;74:414-24.

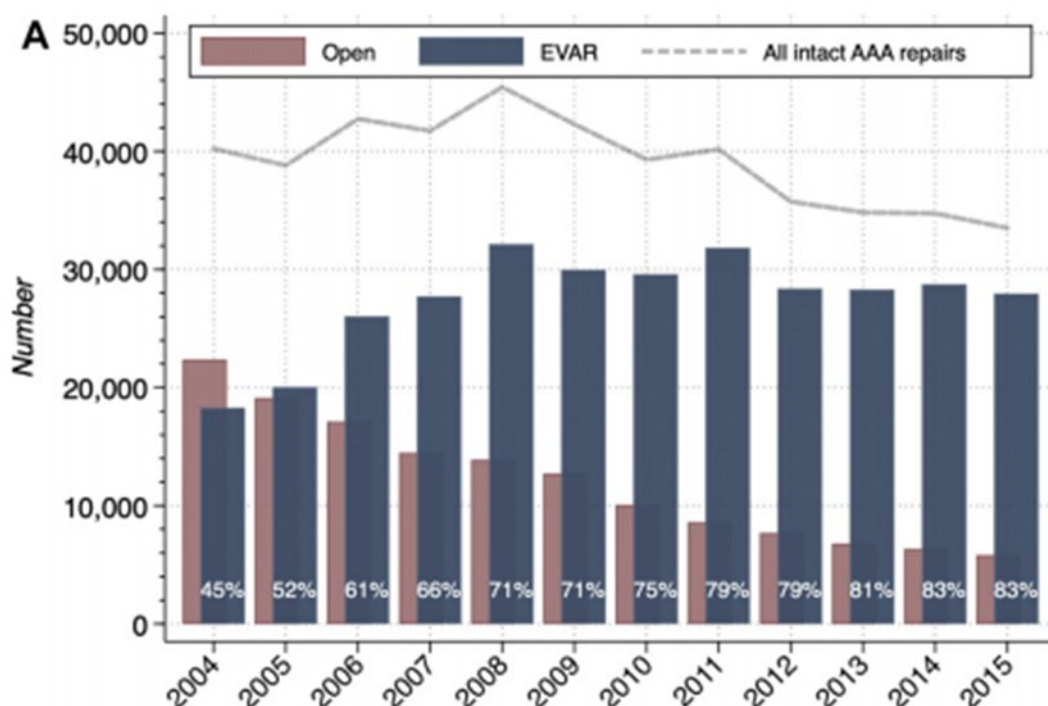


Figure 2: Comparison of open repair vs EVAR by year¹⁰

In 2020, the UK National Institute for Health and Care Excellence (NICE) guidelines for AAA management¹¹ recommended EVAR in unruptured AAA patients who meet the repair criteria and who have abdominal co-pathology, such as a hostile abdomen, horseshoe kidney or a stoma, or other considerations. Additionally, EVAR or conservative management is suggested for patients with unruptured AAAs meeting the repair criteria who have anesthetic risks and/or medical comorbidities that would contraindicate open surgical repair. The NICE document emphasizes the importance of following the device's instructions for use to reduce re-intervention rates.

3.3 Currently FDA Approved AAA Endovascular Grafts

Current generation stent-graft design consists of a fully supported bifurcated graft, most commonly using a modular system. Several FDA-approved AAA endovascular grafts (with varying infrarenal neck length requirements) are commercially available in the US (Table 1, Figure 2). There are some common and some unique design features among approved devices. Most stent-graft designs have suprarenal stents. Several designs have barbs to provide active fixation. One stent graft design has unique polymer-filled sealing rings intended to create enhanced seal. One device has passive fixation, whereby the flow divider of the stent-graft sits directly on the aortic bifurcation. One device with suprarenal fixation is approved for use with adjunctive endoanchor fixation, and another device allows for a proximal seal zone extension into the visceral segment (i.e., suprarenal aortic portion) by incorporating fenestrations into the design.

¹¹ National Institute for Health and Care Excellence (NICE). Abdominal Aortic Aneurysm: Diagnosis and Management, NICE guideline NG156. <https://www.nice.org.uk/guidance/ng156> [accessed 23 March 2020].

*Table 1: AAA endovascular grafts currently marketed in the US**

Sponsor	Device Name	Year of Original PMA Approval	Currently Marketed Iteration¹²
W. L. Gore and Associates, Inc	Excluder AAA Endoprosthesis	2002	Excluder AAA Endoprosthesis
Cook, Inc	Zenith AAA Endovascular Graft	2003	Zenith Flex AAA Endovascular Graft & Zenith Fenestrated AAA Endovascular Graft**
Endologix, LLC	Powerlink System	2004	AFX2 Endovascular AAA System
Medtronic Vascular	Endurant Stent Graft System	2010	Endurant II & IIs Stent Graft System**
Trivascular, Inc / Endologix, LLC	Ovation Abdominal Stent Graft System**	2013	Alto Abdominal Stent Graft System**
W. L. Gore and Associates, Inc	Excluder Conformable AAA Endoprosthesis	2020	Excluder Conformable AAA Endoprosthesis
Bolton Medical Inc (a Terumo Aortic Company)	TREO Abdominal Stent Graft System	2020	TREO Abdominal Stent Graft System

*The Cordis US Corporation Incraft AAA Stent Graft System is PMA approved (2018) but is not yet marketed in the US.

** These devices have unique device designs and approved indications to treat more challenging proximal anatomies.

¹² Endovascular Device Guide: US version 2021

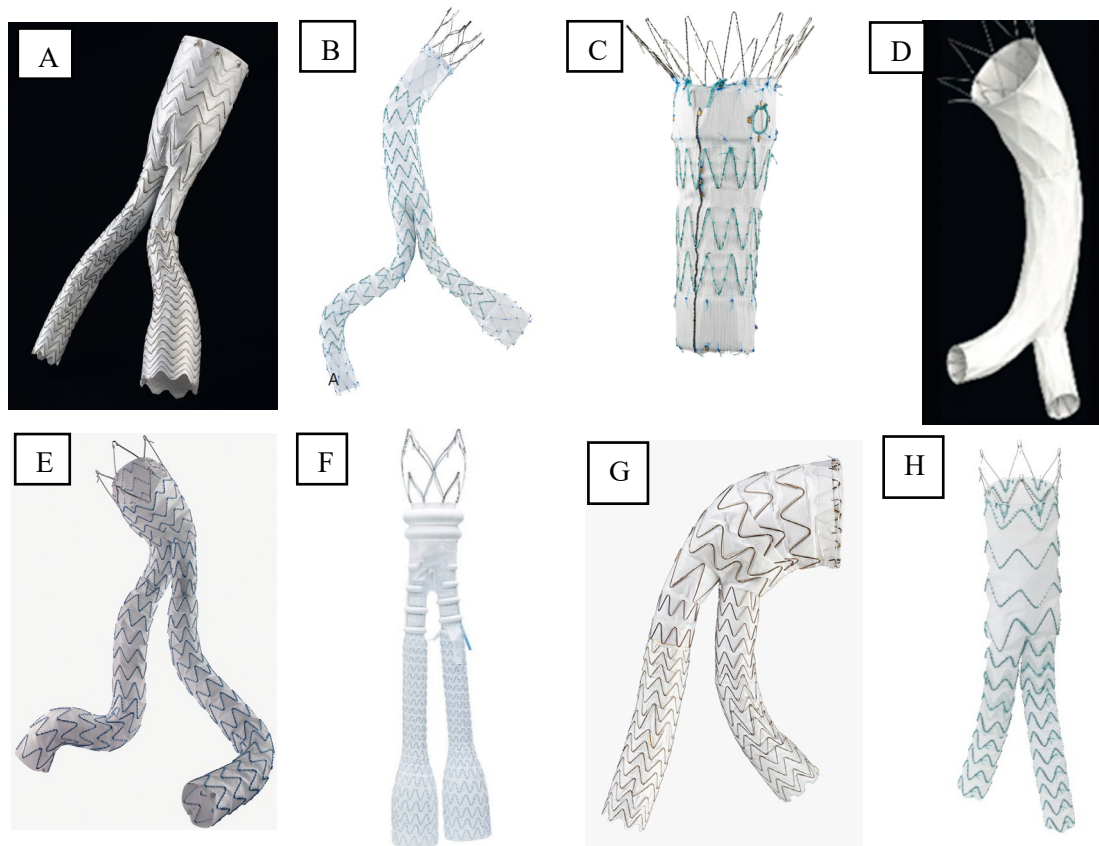


Figure 3: Commercially available devices: A, Gore Excluder. B, Cook Zenith Flex. C, Cook Zenith Fenestrated. D Endologix AFX2. E, Medtronic Endurant II. F, Endologix Alto. G, Gore Excluder Conformable. H, Bolton TREO.

EVAR technology has advanced via applying acute and longer-term device performance experience and physician feedback on device usability into stent graft design changes. New device designs have been associated with improvements in periprocedural and long-term clinical outcomes and expansion of the patient populations that are EVAR candidates. Recent technologic advances have focused on new anatomic subsets such as challenging infrarenal necks and access vessels. With the advent of smaller delivery systems, percutaneous techniques are commonly used, decreasing the morbidity of the procedure and leading to shorter hospital stays. However, novel device designs and iterative changes have been associated with new failure modes. Examples of investigational and commercial EVAR device failure modes include: delivery system failures, iliac limb stenoses/occlusions, stent graft migrations, fabric tears, excessive fabric porosity, stent or barb fractures, loss of proximal or distal seal, and modular stent graft separation. These failure modes are associated with different clinical sequelae (e.g., vascular injury, tissue ischemia, branch vessel coverage/thrombosis, dissection creation or extension, endoleaks) and may require additional interventions or, if not treated, risk AAA repressurization associated with an increased rupture risk. In summary, device developments have helped address known problems but have also introduced new risks.

Aortic endovascular grafts are tracked devices¹³, which means that EVAR device manufacturers are required to track devices from their manufacture through the distribution chain. The purpose of device tracking is to ensure that manufacturers can locate devices in commercial distribution. Tracking information may be used to facilitate notifications and recalls ordered by FDA in the case of serious risks to health associated with device use.¹⁴

3.4 EVAR Guidelines

In 2003, a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery published guidelines for AAA treatment.¹⁵ These guidelines reported that the risk of rupture of small AAA (<5 cm) is quite low and that a policy of careful surveillance up to a diameter of 5.5 cm is safe, unless rapid expansion (>1 cm/year) or symptoms develop.

The Society for Vascular Surgery updated their practice guidelines for repair of AAA in 2018.¹ This article reported that the benefits of EVAR vs. open repair include a high degree of patient acceptance, shorter operative times, reduced operative blood loss, lower major operative complications, elimination of intensive care unit stays, reduced hospital length of stay, rapid recovery, selective use of local anesthesia, and reduced 30-day mortality. The update also acknowledged EVAR disadvantages compared with open repair including higher re-intervention rates related to patency, aneurysm sac expansion, endoleaks, the need for long-term imaging surveillance (requiring radiation and intravenous contrast), and a higher risk of late aneurysm-related death.

The goal of postoperative surveillance is to reduce the risk of late rupture and aneurysm-related death by identifying sac growth, endoleak, device migration, or other device failure. The Society for Vascular Surgery guidelines¹ also provide the following recommendations for post-EVAR patient follow-up:

- CT scan at 1 month: Concerning findings should prompt surveillance at 6 months
- Annual duplex ultrasound: Evidence of new endoleak or sac enlargement should prompt additional CT imaging
- Abdominal and pelvic CT imaging every 5 years

The guidelines report that despite the risks of late device-related complications and aneurysm rupture, there is uncertainty whether annual surveillance decreases aneurysm-related mortality because not all ruptures are preceded by endoleak or sac enlargement. The panel will be asked to comment on elements of patient follow-up relevant to real-world data collection, including follow-up frequency, duration, and compliance.

3.5 EVAR Longitudinal Outcomes Reported in the Medical Literature

A few large clinical studies have reported longitudinal results associated with EVAR for AAAs.

¹³ 21 CFR 821 Medical Device Tracking Requirements

¹⁴ Center for Devices and Radiological Health. Medical Device Tracking. U.S. Food and Drug Administration. <https://www.fda.gov/medical-devices/postmarket-requirements-devices/medical-device-tracking>.

¹⁵ Brewster D.C. et al., Guidelines for the treatment of abdominal aortic aneurysms. J Vasc Surg. 2003; 37: 1106-1117

Long-term Mortality

Large, randomized trials such as EVAR-1¹⁶^{Error! Bookmark not defined.}, DREAM¹⁷ and OVER¹⁸ have reported peri-operative or 30-day mortality rates after EVAR to be in the 0.5-1.7% range. In the latest update (2016)¹⁹, the EVAR 1 study group noted a 23.8% survival rate at 15 years in EVAR patients. The DREAM trial updated outcomes in all 233 patients surviving at the time of the last analysis in February 2009 and reported a 38.5% survival rate at 12 years.

Endoleaks and Reintervention

In a retrospective review of a 16-year EVAR experience (1,835 EVARs performed between 2000-2016) from the University of Pennsylvania,²⁰ the overall re-intervention rate was 7.5%, and reinterventions were performed to 8 years following EVAR. In patients who required re-intervention, 80% underwent two or fewer procedures, 13.0% underwent three, and 7.0% underwent four or more reinterventions. The mean time to first re-intervention was 2.3 ± 2.5 years. The most common causes of reintervention were as follows:

- type II endoleak 52.5%
- type I endoleak 18.2%
- type III endoleak 9.5%
- limb kink 7.3%
- iliac occlusive disease 5.8%
- endotension 1.5%

Although re-intervention was not predictive of mortality, type II endoleak and progressive sac expansion were the most common cause of open conversion and explant of the stent graft. The number of reinterventions was significantly associated with the need for device explantation.

Another retrospective analysis²¹ demonstrated that at 1 year after EVAR in 14,817 patients enrolled in the Vascular Quality Initiative (VQI) between 2003-2017:

- 40% of abdominal aortic aneurysm sacs regressed
- 35% remained stable
- 25% expanded

¹⁶ Greenhalgh RM, et al. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. *Lancet*. 2004;364(9437):843–848.

¹⁷ Prinssen M, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med*. 2004;351(16):1607–1618.

¹⁸ Lederle FA, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. *N Engl J Med*. 2012;367(21):1988–1997

¹⁹ Patel et al., Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial, *The Lancet*, Volume 388, Issue 10058, p2366-2374, November 12, 2016

²⁰ Fairman AS et al., Characterization and outcomes of reinterventions in Food and Drug Administration-approved versus trial endovascular aneurysm repair devices. *J Vasc Surg*. 2017 67(4): 1082-1090.

²¹ T.F.X. O'Donnell et al., Aneurysm sac failure to regress after endovascular aneurysm repair is associated with lower long-term survival, *J Vasc Surg*, 69 (2019), pp. 414-422

This analysis used multivariable, multilevel logistic regression clustering by hospitals to determine which factors are associated with sac expansion compared with stable size or regression, and to assess the association between sac dimensions and the development of new endoleaks. In this study, in patients without interventions before their 1-year surveillance imaging, compared with sac regression patients, both sac expansion and a stable sac diameter were associated with the presence of an endoleak. Sac dimension was similarly associated with the development of new endoleaks either at the time of implantation or during follow-up. In unadjusted analysis, patients with sac regression experienced significantly higher long-term survival than patients with AAA sac diameters that remained stable or expanded. Most importantly, this manuscript suggested sac stability following EVAR may not predict long-term survival.

Columbo et al.²² compared the rate of reintervention in a combined data set of Vascular Quality Initiative (VQI) registry data linked to Medicare claims (VQI-Medicare) against the rate found on retrospective chart review at Dartmouth Hitchcock Medical Center. This analysis involved 547 patients who underwent EVAR between 2003-2013 and had follow-up information available from each of the three data sources. The Kaplan-Meier estimated 1-year rate of reintervention after EVAR from each source was as follows:

- VQI registry alone: 3%
- Chart review: 6%
- VQI-Medicare: 6% at 1 year and 18% at 3 years

Overall, VQI data linked to Medicare claims closely mirrored chart review in evaluating reintervention after EVAR, and the authors noted that the rates of reintervention were similar to those published in randomized clinical trials.

Although these moderate-to-large studies do not provide device specific information, they help demonstrate clinical outcomes of interest in EVAR patients including short- and long-term mortality, aneurysm sac expansion and the need for reinterventions. There are limited data reported in the medical literature on imaging-based outcomes of interest (e.g., device integrity issues or migration). Of note, device-specific studies are typically small-to-moderate in size and include early and mid-term clinical and imaging outcomes without long-term results (see Section 4).

The panel will be asked to comment on the overall safety and effectiveness of endovascular stent grafts in treatment of AAA.

²² Jesse A. Columbo et al., A comparison of reintervention rates after endovascular aneurysm repair between the Vascular Quality Initiative registry, Medicare claims, and chart review, *Journal of Vascular Surgery*, Volume 69, Issue 1, 2019, Pages 74-79.

Key Messages:

- Continuous evolution of EVAR technology has been noted over the last 3 decades. Technological refinements have resulted in iterative changes and unique device designs. The intent of the device evolution has been expansion of EVAR to a wider range of patients, improving outcomes, and implementing features to improve usability. Although improved device designs have resulted in treatment advancements, new early, mid, and late-term failure modes have emerged.
- The Society of Vascular Surgery guidelines for the care of AAA patients includes important recommendations on patient selection, choice of treatment (open surgery vs. EVAR), intraoperative strategies, perioperative care, and long-term follow-up. The guidelines and individual device instructions for use recommend annual follow-up imaging surveillance.
- Several largescale studies have analyzed outcomes of interest in EVAR patients. The studies provide insights into the longitudinal rates of aneurysm sac expansion, endoleaks, and need for reintervention after EVAR.
- Largescale real-world studies of EVAR patients have not historically captured imaging outcomes of interest, such as device integrity failures and device migration.
- Although there is variation among approved EVAR device designs, FDA believes that as a device class there is limited long-term outcomes data.

3.6 EVAR Longitudinal Outcomes from Pivotal Studies

Following approval of new AAA EVAR devices, FDA typically requires post-market follow-up of pivotal study subjects through a minimum of 5 years. Table 2 shows 5-year publicly available follow-up results for three EVAR devices currently marketed in the US. Of note, some manufacturing and design changes may have implemented since marketing which are not reflected in the study device.

Table 2: Pivotal study clinical endpoint results

Device and Follow-up Period	Aneurysm-Related Mortality Rate (KM estimate)	Aortic Ruptures	Conversion to Open Repair	Aneurysm Expansion >5 mm	Reintervention Rate
Medtronic Endurant ²³					
1 year	0.994	0.3% (1/314)	0%	0.4% (1/283)	5.1% (16/314)
5 year	0.990	0.9% (2/220)	0%	5.8% (10/173)	12.7% (35/220)
Cook Zenith Fenestrated ^{24,25}					
1 year	1.00	0%	0%	1.4% (1/71)	9.2 ± 3.6%*
5 year	0.975	2.3% (1/44)	0%	5.3% (2/38)	36.5 ± 7.2%*
Cook Zenith AAA ^{26,27}					
1 year	0.995	0%	1.0% (2/198)	1.2% (2/168)	9.4%
5 year	0.989	0%	3.8% (4/105)	4.3% (3/70)	19.0%

*The higher rate of secondary intervention for the fenestrated EVAR device may be the result of the increased complexity of this device compared to standard infra-renal endografts. In the ZFEN pivotal trial, the most frequent indication for secondary intervention was for in-stent stenosis of bare metal renal stents.

Key Messages:

- 5-year outcomes from pivotal AAA EVAR device studies (from Table 2):
 - Aneurysm-related mortality at 5 years: 1% - 2.5%
 - Aneurysm rupture: 0 - 2.3%
 - Conversion to open surgery: 0 - 3.8%
 - Aneurysm sac expansion at 5 years: 4.3% - 5.8%
- Longer term follow-up in pivotal studies show that clinical events continue to occur after 1-year, which is the typical follow-up duration necessary to support FDA approval of a new AAA EVAR device.
- The panel will be asked to comment on the overall safety and effectiveness of endovascular stent grafts in treatment of AAA.

²³ Medtronic Endurant Instructions for Use:

https://manuals.medtronic.com/content/dam/emanuals/cardio/M052195T001DOC1_RevAA_view.pdf

²⁴ Cook Zenith Fenestrated Annual Clinical Update: https://www.cookmedical.com/data/resources/2019_Clinical-Update-for-Zenith-Fenestrated_Final_1600874994758.pdf

²⁵ Oderich et al. Final 5-year results of the United States Zenith Fenestrated prospective multicenter study for juxtarenal abdominal aortic aneurysms. J Vasc Surg. 2020 Vol 73(4).

²⁶ Cook Zenith AAA Endovascular Stent Graft annual clinical update:

https://www.cookmedical.com/data/resources/2019_Zenith-AAA-Clinical-Update_1600876734713.pdf

²⁷ Sternbergh et al. Redefining postoperative surveillance after endovascular aneurysm repair: Recommendations based on 5-year follow-up in the US Zenith multicenter trial. S Assoc Vasc Surg. 2008 Vol 48 (2).

4 Regulatory Framework

FDA considers benefits and risks and applies least burdensome principles when making regulatory decisions. This means that FDA balances pre- and post-market data to make safe and effective treatments available to U.S. patients in an efficient manner.²⁸ Balancing pre-market and post-market data collection facilitates timely patient access to new medical products without undermining patient safety.

4.1 Pre-market Evaluation of New and Iterative Endovascular Stent Grafts

For investigational medical devices, FDA and device manufacturers typically work together to determine a reasonable and least burdensome pre-market evaluation plan by focusing on the variables that affect device performance and factors that determine the device's benefit/risk, including the availability of alternative treatment options.

New AAA Endovascular Stent Grafts

Evidence to support a pre-market application for a new endovascular stent graft is comprised of nonclinical and clinical studies. Nonclinical device testing typically includes mechanical engineering performance testing, computational modeling, biocompatibility evaluation, magnetic resonance compatibility assessment, and sterilization validation. Animal studies focus on *in vivo* device safety (i.e., acute and chronic biologic responses). Finally, valid scientific evidence from one or more clinical studies provide data on whether “the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device.”²⁹ Recent pre-market pivotal studies^{30,31,32} supporting marketing applications for novel AAA endovascular grafts (Original PMAs) have had the following key characteristics:

- A multi-center, prospective, single-arm, non-randomized, non-blinded clinical study design.
- A sample size ranging from 150 to 200 patients and 25 to 40 investigational sites.
- A 30-day primary safety endpoint and a 12-month primary effectiveness endpoint (see Table 3).
- Study follow-up duration is a minimum of 5 years. Typical secondary endpoints reported through 5 years are shown in Table 4.

Table 3: AAA Endovascular Graft Study Primary Endpoints

Primary Safety Endpoint	Composite of major adverse events (CMAE) at 30 days defined as: <ul style="list-style-type: none"> • AAA related mortality • Myocardial infarction • Stroke • Renal failure
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²⁸ FDA Executive Summary, Circulatory System Devices Panel Meeting, General Issues Panel - Clinical Evaluation of Anti-Hypertensive Devices, December 5, 2018

²⁹ Section 513(a)(3)(A) of the FD&C Act

³⁰ PMA P190015: FDA Summary of Safety and Effectiveness Data

³¹ PMA P150002: FDA Summary of Safety and Effectiveness Data

³² PMA P120006 Summary of Safety and Effectiveness Data

	<ul style="list-style-type: none"> • Respiratory failure • Paraplegia • Bowel ischemia • Procedural blood loss of 1000 cc or greater
Primary Effectiveness Endpoint	<p>Successful aneurysm treatment at 1 year defined as:</p> <ul style="list-style-type: none"> • Technical Success at the conclusion of the procedure; and • Absence of the following through 12 months <ul style="list-style-type: none"> ○ Aneurysm enlargement ○ Device migration ○ Device integrity issues ○ Conversion to open surgical repair ○ Aneurysm rupture ○ Type I and III endoleaks ○ Device occlusion

Table 4: AAA Endovascular Graft Study Secondary Endpoints

Secondary Safety Endpoints	<ul style="list-style-type: none"> • The rate of individual component of the CMAE at 30 days, 6 months, and 12 months • The composite MAE rate at 12 months and annually to 5 years • Procedure-related complications through 30 days, 6 months, 12 months, and annually to 5 years
Secondary Effectiveness Endpoints	<ul style="list-style-type: none"> • Aneurysm-related mortality at 30 days, 180 days, 360 days, and annually through 5 years • Incidence of secondary interventions (or the need for secondary interventions) to repair vascular events or malfunctions related to device or peri-graft complications at 1 month, 6 months, 1 year and annually to 5 years. Secondary intervention is defined as any vascular event which requires intervention to repair the AAA or device. Indications for secondary intervention include endoleaks, stent graft migration, occlusion, or aneurysm sac rupture. • The rate of secondary interventions within 1-year post-procedure needed to prevent the occurrence of a significant event (defined as aneurysm enlargement, device migration >10 mm compared to the 1-month size, type I or III endoleak, device occlusion, and aneurysm rupture).

	<ul style="list-style-type: none"> • Device-related events at 1 month, 6 months, 1 year, and annually to 5 years. Device-related events include: <ul style="list-style-type: none"> • Aneurysm enlargement • Endoleaks • Aneurysm sac rupture • Device integrity issues • Delivery system malfunction • Device migration • Device occlusion • Conversion to open surgery
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In typical pivotal trials, the primary safety and effectiveness endpoints tested against performance goals. FDA reviews the totality of information and considers the overall benefit-risk profile of the device for the proposed indication. A study that meets the predefined performance goals may not be adequate to support marketing approval if there are outstanding concerns that do not support the reasonable assurance of safety and effectiveness (e.g., the performance goal is met, yet there are higher than expected rates of specific safety events in which risk mitigation efforts have not been identified). Conversely, if the 95% confidence interval around the observed event rate narrowly misses the pre-specified performance goal, but the totality of the data demonstrates a favorable benefit-risk profile of the device in the intended population, the totality of the data may still support marketing approval.

Iterative Changes to Approved AAA Endovascular Stent Grafts

Evidence to support approval of an iterative change to an approved endovascular stent graft is based on the specific changes to the device design or proposed indication for use.

It is common for EVAR devices to undergo design and manufacturing changes over time. Some iterative changes may be supported by non-clinical evaluations alone (e.g., extension of device size matrix to incorporate new intermediate device sizes, modifications to the delivery system). Conversely, significant device design changes or an important expansion in the indication for use often requires both nonclinical and clinical evaluation.

Examples of recent regulatory approvals for iterative design changes and/or an indication expansion of previously approved EVAR devices that were supported by both nonclinical and clinical data are summarized in Appendix 3. Data requirements to support approval of iterated devices are calibrated to address the potential impact of the changes on device performance. For many modified devices, there is less long-term clinical data compared to the data available to support approval of the original version of the device.

4.2 Post-Market Evaluation of New and Iterative Endovascular Stent Grafts

Approval of new and iterated endovascular stent grafts requires continued follow-up of all eligible subjects enrolled in the pre-market clinical study through at least 5 years. In some cases, annual descriptive analyses of the primary and secondary endpoints are sufficient. In other

situations, new enrollment post-market studies have been required as a condition of PMA approval to collect confirmatory safety and effectiveness data on the device. These include:

- Real-world data collection on a novel device design or treatment approach. A benefit of such post-market evaluation is that it can also allow an assessment of the manufacturer's training program by comparing the incidence of adverse events as a function of physician experience.
- Additional clinical data on specific events in a larger patient population.
- Additional information on the translation of the pivotal clinical study results to real-world use.

Manufacturers and FDA work together to develop an acceptable protocol, including endpoints and event definitions appropriate for the post-market evaluations warranting new enrollment. Upon completion of the post-market evaluations, manufacturers update their device labeling with the final study results.

A condition of approval for all endovascular stent grafts is an annual clinical update to physician users to inform them of the latest available device data. For pre-market and post-market studies, clinical updates include the number of patients for whom data are available and rates of major adverse events, aneurysm-related mortality, aneurysm rupture, secondary endovascular procedures, conversions to surgical repair, endoleaks, aneurysm enlargement, prosthesis migration, occlusions, stenoses, loss of device integrity, and other procedure or device-related events. Reasons for secondary interventions and conversion to open surgery as well as causes of aneurysm-related death and rupture are also described. Additional relevant information from US and non-US commercial experience, explant analysis findings, and literature reviews are included. Clinical updates also describe worldwide recalls, safety communications and field safety notices sent by the device manufacturer to physician users.

Key Messages:

- FDA balances pre- and post-market data requirements to make safe and effective devices available in the US in a timely manner.
- The pre-market nonclinical and clinical data requirements to support approval of an EVAR device depend on the novelty of device design and proposed indication. Typically, clinical studies intended to evaluate safety and effectiveness of new EVAR devices have the following characteristics:
 - Multi-center, prospective, single-arm, non-randomized, non-blinded clinical study design
 - A sample size ranging from 150 to 200 patients and 25 to 40 investigational sites.
 - A 30-day primary safety endpoint, 12-month primary effectiveness endpoint, and secondary endpoints evaluated through 5-years.
- A condition of PMA approval of new EVAR devices typically includes continued follow-up of all eligible subjects enrolled in the pre-market clinical study through at least 5 years.
 - De novo enrollment may also be required in some situations to collect confirmatory safety and effectiveness data. Study designs vary.
- Pre-market or post-market clinical study data may not be required for some iterative device changes.

5 Real World Evidence

Real-world evidence is the clinical evidence regarding the usage and potential benefits and risks of a medical product derived from analysis of real-world data (RWD). RWD is data that is routinely collected from a variety of sources, such as product and disease registries, medical claims data, and electronic health records. It may potentially be used as some or all of the evidence necessary for understanding medical device performance at different points in the total product life cycle.³³

The following sections describe the potential use of RWE for public health surveillance efforts in EVAR patients.

5.1 Need for Real-World Surveillance in EVAR Patients

Improvements in medical care have resulted in an increase in life expectancy of EVAR patients. EVAR is associated with good early and intermediate-term outcomes, but there are less available long-term data.

Pivotal studies are critical in supporting reasonable assurance of safety and effectiveness and informing clinical decision making. However, there is often valuable clinical experience gained after regulatory approval and marketing. For example, outcomes reported from surveillance sources during commercial use may differ from those reported in a controlled clinical study.

³³ Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and Food and Drug Administration Staff

More favorable pre-market results are attributable selected patient enrollment criteria, highly experienced investigational centers and physicians, and high compliance with patient follow-up; these characteristics are not assured during commercial use.³⁴ In contrast, longer-term device surveillance in a large sample size reflective of the real-world device use may provide greater precision around observed event rates.

Physicians can use real world long-term information to target patient selection and refine procedural and post-procedural decision-making. Device manufacturers may use this information to inform future device design development and manufacturing process improvements. Regulators may use this information to change product labels to include updated safety and effectiveness EVAR data, make informed recommendations to sponsors regarding pre-and post-market study designs, and identify safety signals in a timely manner to communicate with the public.

A recent example of the benefits of longer-term study data collection and surveillance was reported by Verzini et al.,³⁵ in which late structural graft failures were reported for an endovascular stent graft intended for non-AAA lesions in the descending thoracic aorta. Although short-term outcomes provided to support device approval were positive, longer-term follow-up of IDE study subjects post-approval and commercial complaint reports indicated significant device integrity events (stent fractures, stent ring enlargement, and type IIIb endoleaks). The manufacturer issued a recall, which included a request that all devices not yet implanted be returned to the manufacturer and provided guidelines for following patients implanted with the device. The manufacturer also initiated a commercial surveillance program to gather information regarding additional events and imaging to help identify the root cause of the device integrity issues and more precisely define the event rate.

5.2 Outcomes of Interest for Real-World Surveillance in EVAR Patients

Sections 3 and 4 describe the clinical events that are typically captured in endovascular stent graft pre-market and post-market evaluations. These events may be categorized as imaging-based assessments and clinical assessments (Table 5).

Table 5: EVAR Outcomes of Interest

Imaging-based Assessments	Clinical Assessments
Loss of Device Integrity	All-cause mortality
Aneurysm Size	AAA-related mortality
Endoleak	EVAR Reintervention
Device Occlusion/Stenosis	Aneurysm rupture
Device Migration	Conversion to open repair

Although all the events listed in Table 5 are of interest in assessing long-term EVAR safety and effectiveness outcomes, FDA acknowledges the limitations of the current database

³⁴ Kim et al. Real-world Evidence versus Randomized Controlled Trial: Clinical Research Based on Electronic Medical Records. J Korean Med Sci. 2018;33(34).

³⁵ Verzini et al., A preliminary analysis of late structural failures of the Navion stent graft in the treatment of descending thoracic aortic aneurysms, Journal of Vascular Surgery, April 2021.

infrastructures in capturing all of these outcomes. The panel will be asked to comment on the key outcomes that are clinically meaningful and feasible to capture in real-world data to help provide more information on long-term EVAR benefits and risks.

5.3 Potential Resources for Real-World Surveillance in EVAR Patients

Whether the RWD resides within paper or electronic medical records, is collected by administrative databases, is abstracted, aggregated and stored in disease- or treatment-specific databases (i.e., registries), or collected and aggregated through other means, data relevance and reliability are important considerations.³³

Examples of post-market EVAR patient surveillance include:

- Stakeholder collaboration (e.g., professional societies, manufacturers, regulators, academia) to identify and improve existing infrastructures or develop new patient registries that would collect data to address long term benefits and risks of EVAR.
- Use of medical claims or billing data that may involve assessment of International Classification of Diseases (ICD) codes for data collection.
- Combination approaches that allow linkage of medical claims data to an already existing or new registry network.
- Individual collaborations between manufacturer and clinical sites or health systems to collect long term data on device performance using electronic health records.

5.4 Mechanisms for Real-World Surveillance in EVAR Patients

The agency requests panel input on ways to implement real-world data collection for approved EVAR devices.

From a regulatory perspective, options for real-world surveillance include:

- A condition of EVAR device PMA approval that requires collecting and reporting of RWD on the device. If a registry infrastructure is available to collect RWD, this condition may supplement or even obviate the need for a new enrollment post-approval study.
- A post-market surveillance order, related to investigating patient safety issues, under the authority of section 522 of the FD&C Act.³⁶ 522 orders can cover multiple devices from different manufacturers that are similar in intended use, design, and other characteristics, if the surveillance questions are identical.³⁷ A similar approach may be utilized for EVAR devices to address outstanding questions on long-term device performance associated with real-world use.

A known challenge in collecting long-term data is high rates of missing follow up clinical status checks and imaging data. The panel will be asked for input on the role of stakeholders such as physician users, device manufacturers, and professional societies in addressing this issue to increase long-term real world data quality.

³⁶ 21 CFR 822.3(i)

³⁷ [Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act](#); Draft Guidance for Industry and Food and Drug Administration Staff

6 Conclusion

Post-market surveillance can contribute critical information about real world device performance. However, this resource has remained underutilized for EVAR devices. EVAR technology and treatment practices are continually evolving with novel device designs coming to market, iterative design and indications being approved, and updates to procedural practices and follow-up guidelines. Typically, one-year data from clinical studies are required to show a reasonable assurance of safety and effectiveness and support PMA approval. However, robust longer term post-market confirmatory data are needed to confirm continued device safety and effectiveness. IDE studies are designed to reflect the patient population to be treated in clinical practice, and the device instructions for use is crafted to reflect the specific patient populations treated in pre-market clinical studies. However, once a device is approved, there is often important knowledge gained from real world use. For example, patients included in pre-market studies are often highly selected, but following approval, there is significant EVAR device use in patients with anatomic features in which safety and effectiveness have not been established. In a study of 10,228 US patients who underwent EVAR from 1999 to 2008, only 42% of patients met the most stringent instructions for use criteria.³⁸ Additionally, clinical data is not always available for current device design, which has undergone iterative changes from the original version.

A better understanding the real-world safety and effectiveness profile of these devices through improved surveillance aligns with FDA's mission of protecting and promoting public health. FDA believes that improved systems of long-term data collection and analysis are in the best interest of physician users, device manufacturers, hospital systems and patients. Input from the panel and subsequent collaboration among relevant stakeholders can allow development of frameworks that provide additional information on safety and effectiveness and supplement information collected in current pre-market and post-market studies. From FDA's perspective, an ideal surveillance platform would include a validated infrastructure wherein high-quality clinical data can be entered and analyzed in a timely and efficient manner. It would include the key clinical outcomes of interest over an appropriate duration with a high level of follow-up compliance (i.e., a low proportion of missing data). Such an effort may provide relevant stakeholders, including the Agency, the ability to analyze device specific outcomes and collect event rates over time. This approach would also allow detection of safety signals to allow for timely communication to the public and implementation of appropriate risk mitigation measures for patient safety.

The Agency asks the panel to consider the totality of information on the overall safety and effectiveness of endovascular stent grafts in treatment of Abdominal Aortic Aneurysms, the need for additional reliable long-term data on EVAR outcomes, and the critical outcomes and duration of follow-up to capture via real-world surveillance. In the deliberations, the Agency encourages the panel to consider how limitations of current real-world data collection efforts may challenge

³⁸ Schanzer A. Predictors of Abdominal Aortic Aneurysm Sac Enlargement After Endovascular Repair. *Circulation*. 2011 123(24):2848-2855.

the success of your recommended surveillance efforts and how stakeholders can work together to overcome these challenges.

Appendix 1: EVAR vs Open Surgical Repair

Acknowledging the outcomes of randomized trials of endovascular aneurysm repair (EVAR) versus traditional open repair is relevant to understanding why today in the United States, 80% of AAAs are repaired endovascularly.

Short Term Outcomes

EVAR-1 was a randomized prospective U.K. study including 1082 patients that compared EVAR with open AAA repair in patients who were fit enough to undergo open surgical repair from 1999 to 2003¹⁶. The 30-day mortality rate was reduced in the EVAR group (1.7% vs. 4.7%), although secondary interventions were more common in the EVAR group (9.8% vs. 5.8%).

The DREAM trial was a multicenter randomized trial (enrolling from 2000 to 2003) that compared open repair with EVAR in 345 patients³⁹, with a reduction in operative mortality in EVAR patients (1.2% vs. 4.6%) and a combined rate of operative mortality and severe complications (4.7% vs. 9.8%), with the majority of complications accounted for by pulmonary issues.

The Open Versus Endovascular Repair (OVER) trial (2002 -2011) including 881 patients from 42 Veterans Affairs centers randomized to either EVAR or open repair⁴⁰ demonstrated that perioperative mortality was improved in the EVAR group (0.5% vs. 3.0%). The Aneurisme de l'aorte abdominal: Chirurgie versus Endoprothese trial compared EVAR with open surgical repair in low-to moderate-risk patients. In-hospital mortality and the incidence of postoperative complications were not statistically different⁴¹.

Longer Term Outcomes

Survival analysis from EVAR-1 demonstrated no difference in all-cause mortality at 6 years, although only 24% of patients survived until the end of the study period. The initial survival benefit of EVAR was lost within 2 years of repair, secondary to a higher death rate from cardiovascular causes among those patients who had undergone EVAR⁴². The rate of graft-related complications and need for re-interventions was significant at 4 years, likely accounting for the higher aneurysm-related death rate in the EVAR group. The rates of aneurysm-related death converged at 6 years in these two groups.

³⁹ Prinssen M, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med*. 2004;351(16):1607–1618.

⁴⁰ Lederle FA, et al. Outcomes following endovascular versus open repair of abdominal aortic aneurysm: a randomized trial. *JAMA*. 2009;302(14):1535–1542.

⁴¹ Becquemin JP, et al. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. *J Vasc Surg*. 2011;53(5):1167–1173 e1

⁴² Greenhalgh RM, et al. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med*. 2004;362(20):1863–1871.

The 2-year follow-up study from the DREAM trial showed similar results with a reduction in aneurysm-related mortality in the EVAR group compared with the open surgery group (2.1% vs. 5.7%), which was not reflected in overall mortality.⁴³ Mortality from cardiovascular causes in the EVAR group again contributed to the equalization of survival between groups at 2 years. As expected, the need for re-intervention was higher in the EVAR group and was 3 times that of the open group in the first 9 months after randomization. At 6-years follow-up, secondary interventions were again higher in the EVAR group: 30% versus 19.1%. The cumulative 6-year survival in the two groups was similar, at 69.9% for the open group and 68.9% for the EVAR group.⁴⁴

The OVER trial 2-year results revealed that, although the perioperative advantage of EVAR was still realized at 3 years, survival was similar between groups beyond this time.⁴⁵ In the Aneurysme de l'aorte abdominal: Chirurgie versus Endoprothese trial⁴¹, with a median follow up of 3 years, no difference was observed in survival or the incidence of major events.

Discussion

Although the results from the EVAR-1, DREAM, and OVER trials demonstrate improved perioperative morbidity and mortality profile of EVAR compared with open aortic aneurysm repair, concerns remain over the longer-term outcomes and survival benefit of EVAR.⁴⁶

Studies based on administrative claims data have also confirmed the short-term advantages of EVAR over open AAA repair^{47,48}. In an analysis of Medicare data from 2001 to 2004, in which one can assume that most of the repairs in this study were performed with AneuRx stent grafts (a “first generation stent graft” no longer commercially available) because little else was available until 2003, the overall perioperative mortality rate was 1.2% for EVAR and 4.8% for propensity score-matched open surgical controls.⁴⁹ However, late survival was similar between the two groups, although the survival curves did not converge until after 3 years.

Although device modifications and improvements in design have led to a decrease in device failure, the 6-year follow-up data from the U.K. EVAR-1 trial indicated no differences in overall or aneurysm-related mortality compared with open repair in the long term. Furthermore, EVAR was associated with a higher rate of interventions and was costlier.⁴² Data from large registries

⁴³ Blankensteijn JD, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med*. 2005;352(23):2398–2405.

⁴⁴ De Bruin JL, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. *N Engl J Med*. 2010;362(20):1881–1889

⁴⁵ Lederle FA, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. *N Engl J Med*. 2012;367(21):1988–1997

⁴⁶ Ohki T, et al. Increasing incidence of midterm and long-term complications after endovascular graft repair of abdominal aortic aneurysms: a note of caution based on a 9-year experience. *Ann Surg*. 2001;234(3):323–334, discussion 334–335.

⁴⁷ Anderson PL, et al. A statewide experience with endovascular abdominal aortic aneurysm repair: rapid diffusion with excellent early results. *J Vasc Surg*. 2004;39(1):10–19.

⁴⁸ Lee WA, et al. Perioperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms in the United States during 2001. *J Vasc Surg*. 2004;39(3):491–496.

⁴⁹ Schermerhorn ML, et al. Endovascular versus open repair of abdominal aortic aneurysms in the Medicare population. *N Engl J Med*. 2008;358(5):464–474.

such as EUROSTAR have estimated a re-intervention rate of 5% per year and a continued rupture rate of 1% per year despite EVAR^{50, 51}.

⁵⁰ Harris PL, et al. Incidence and risk factors of late rupture, conversion, and death after endovascular repair of infrarenal aortic aneurysms: the EUROSTAR experience. European Collaborators on Stent/graft techniques for aortic aneurysm repair. J Vasc Surg. 2000;32(4):739–749

⁵¹ Harris PL, Butth J. An update on the important findings from the EUROSTAR EVAR registry. Vascular. 2004;12(1):33–38

Appendix 2: EVAR vs Medical Management in High Surgical Risk Patients

The question of whether EVAR is better than medical management in high-risk patients was addressed by the EVAR-2 trial, in which 338 patients who were unfit for an open repair were randomized to either EVAR or medical management.⁵² The aneurysm-related mortality and all-cause mortality rates were no different between groups. The 30-day mortality rate for EVAR was 9%, although 3.6% of these deaths were from rupture while awaiting EVAR, because the median time to intervention was 57 days. Furthermore, 25% of patients assigned to medical management eventually underwent EVAR either because of patient preference or surgeon preference, with a strikingly low mortality rate. Given the number of AAA ruptures in the EVAR group while awaiting surgery, as well as crossover of the medically treated patients to the treatment group, it is perhaps not surprising that no difference was seen in aneurysm-related or overall mortality between groups at 4 years.

The Veterans Affairs large aneurysm study, which was an observational study of surgically unfit patients, showed a 1-year rupture rate of 9.4% for aneurysms measuring 5.5 to 5.9 cm, 10.2% for aneurysms 6.0 to 6.9 cm, and 32.5% for aneurysms measuring 7.0 cm or greater.⁵³

Although these studies indicate that EVAR performed by experienced surgeons in carefully selected high surgical risk patients may result in positive outcomes, considering that this sick population often has other major comorbidities, the risk of death due to aneurysm rupture remains low for this group. This leads one to question use of EVAR approach in high surgical risk patients.

⁵² Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet*. 2005;365(9478):2187–2192.

⁵³ Lederle FA, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *JAMA*. 2002;287(22):2968–2972.

Appendix 3: Examples of Iterative Changes to Approved Devices

Examples of recent regulatory approvals for iterative design changes and/or an indication expansion of previously approved EVAR devices that were supported by both nonclinical and clinical data are summarized below. In these examples, a pre-and post-market balance paradigm was implemented:

- Use of a prospective, consecutively enrolling, single-arm, nonrandomized multicenter clinical study design to support approval of a next generation device with modifications to its sealing mechanism and graft material under a Panel-Track Supplement⁵⁴. The study included 75 patients and 13 investigational sites, and a 12-month primary composite endpoint was evaluated to assess study success. This pre-market approval decision was also based on a condition that the manufacturer will conduct additional post-approval evaluation of the device on newly enrolled subjects. This is described further under Section 5.2.
- Use of real-world evidence to support expansion of the indication for a device under a Panel-Track Supplement to include treatment of infrarenal abdominal aortic aneurysms having short neck lengths when used in conjunction with the previously cleared device system⁵⁵. A total of 70 subjects with a core lab-verified infrarenal neck length of >4 mm and <10 mm were treated. Data was collected for each subject enrolled from baseline and up to 5 years after the index procedure. Follow-ups at 30 days and 12 months were included in the outcomes analyses to support the short neck indication. Continued follow up of the registry subjects was noted as a condition of pre-market approval.

⁵⁴ PMA P120006/S031: FDA Summary of Safety and Effectiveness Data

⁵⁵ PMA P100021/S063: FDA Summary of Safety and Effectiveness Data

Appendix 4: Additional Analyses

Findings from MDR Analyses

FDA receives hundreds of thousands of medical device reports (MDRs) each year of suspected device-associated deaths, serious injuries, and malfunctions. MDRs are submitted by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters (e.g., health care professionals, patients, and consumers). MDRs can be an informative surveillance tool to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of the products.

A review was performed of the MDRs for approved AAA Endovascular Grafts (Table 1) from data obtained from the MAUDE database on August 27, 2021 for the period of January 2016 through June 2021. MDRs were sorted based on reported implant date and associated event date (Figure 4). This analysis shows that even though the majority of event reports are from the acute follow up period, events continue to be reported in the longer term as well. The same MDR query was also sorted by device problem code and timepoint post-index procedure to provide an understanding of how failure modes of an implant device change over its lifetime. Somewhat intuitively, device failures occurring in the first 30 days following implantation are likely acute failures, while device failures occurring after 5 years are more likely due to wear of materials. Since mandatory and voluntary reporters continue to use the MDR system throughout the lifetime of a device, MDR has a potential to capture longer term device behavior.

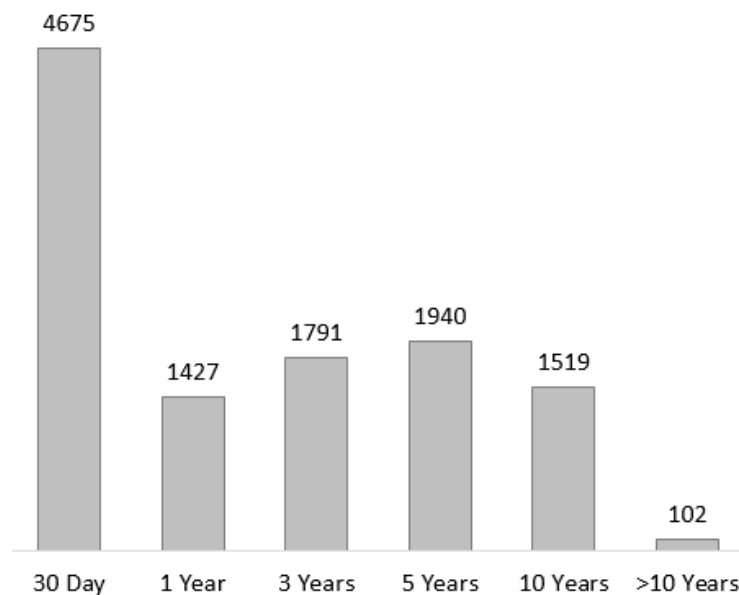


Figure 4: Number of MDR events occurring at timepoints after implant procedure

There are several limitations to the data sourced from MDRs which impede identification of patterns of device failures. Reports may be incomplete, inaccurate, untimely, unverified, or biased. In addition, the incidence or prevalence of an event cannot be determined from the reporting system due to under-reporting of events and inadequate information about frequency of device use. Device problem codes are imprecise; the commonly reported code “Leak” may refer

to an inconsequential delivery system valve leak or a life-threatening Type III endoleak, so it is impossible to quickly ascertain information about the more important device failures.

Although the MDR reporting system may be used as a supplemental means of informing real-world device performance, significant modifications to the system are warranted to derive meaningful information that would help with better understanding of long-term safety and effectiveness of EVAR technology, early identification of safety signals etc.

Findings from Systematic Literature Review (SLR)

A systematic literature review was conducted with the objective of identifying and examining the available evidence on the safety and long-term effectiveness of approved AAA endovascular grafts. The databases included in this literature search included PubMed/MEDLINE, Embase, CENTRAL, and Web of Science. The time period included articles published January 1, 2011 through March 12, 2021. Each eligible study was extracted independently by two experienced systematic reviewers. The extracted data were then reviewed and confirmed by, at minimum, a third reviewer to ensure accuracy of data entry. A total of 6,895 records were identified. After removal of duplicates, 5588 titles and abstracts were screened with 5,089 records excluded because they were either conducted in populations other than AAA patients or were not relevant to EVAR. A total of 499 full-text reports were retrieved and screened with 451 excluded for reasons such as geography, no specific outcome of interest or no device specific outcome. Data from 45 articles were finally extracted for analysis (see bibliography below). Although the articles did not provide Level 1 evidence and Grade A recommendations, the articles were generally in alignment that AAA endovascular grafts are an important treatment option for patients in the US. This analysis indicated that the reported rate of reinterventions after EVAR ranges from 1% to 32%. Type I, II and III endoleaks were the most cited reasons for reintervention. Other reasons were device migration, misalignment, and renal artery occlusion. Device-related major complications ranged from 4% to 11%; aneurysm related mortality ranged from 0% to 1.5%. Although this analysis did not allow assessment of outcomes longitudinally, it does indicate that there is a need for lifelong follow-up as mid- and late-term findings may warrant reinterventions.

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