Obtaining an IDE for Physician-Modified or Off-Label Stent Grafts

A physician's perspective on applying for an IDE, interaction with the FDA, and practice under an IDE.

WITH PATRICK KELLY, MD

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IDENTIFYING NEED

How would you briefly describe the nature of a thoracoabdominal aortic aneurysm (TAAA) and how it differs from everyday cases? How does this affect the options that treating physicians have at their disposal?

The classic definition of a TAAA is an aneurysm that spans both the thoracic and abdominal cavities. I think with endovascular options evolving, this definition is coming into question and may be based more on limits of required aortic coverage. Patients who present with these aneurysms typically have other major comorbidities that increase the operative risk and complication rate. From both an open and endovascular repair standpoint, these cases are challenging because most require interruption of aortic flow above the visceral vessels. When placing an aortic clamp, we know that with each clamp position above a visceral vessel, the complication rate significantly increases; this can also be said for endovascular repairs.

INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS

What is a physician-sponsored investigational device exemption (PS-IDE)?

A PS-IDE is an IDE that allows a device that is not currently approved by the US Food and Drug Administration (FDA) to be studied in a clinical trial. In a PS-IDE, the physician is both the sponsor and the investigator and takes on a much greater responsibility than he or she would in an industry-sponsored IDE.

What made you seek alternative therapies, ultimately via an IDE, rather than what was available?

In March 2012, I was presented with a patient who had an extensive TAAA who was not eligible for open repair and had no other options. With the Zenith t-branch (Cook Medical) still being investigational in the United States and only available at select centers, I believed there had to be a better option.

Why is an IDE ideal in this instance, rather than doing the case without one? Is it required by the FDA?

An IDE is required any time you are evaluating the safety or efficacy of an unapproved device. If a new device (including physician-modified devices) is being studied or if an approved device is being used off-label to evaluate its safety and effectiveness, an IDE is required. A PS-IDE allows you to evaluate the safety and effectiveness of a device to determine if it should be used in a larger population. For vascular surgeons interested in complex aortic repair, this may be for a physician-modified endograft, or it may be for a phy-

sician-specified and industry-manufactured device. In either case, the PS-IDE is required.

How would you describe the process of applying for and obtaining the IDE?

Applying for and obtaining an IDE is a multistep process. Our first step was to finalize the device to be studied and then define our clinical protocol and device testing strategy. We submitted this information to the FDA through their presubmission process to see if our testing strategy was adequate and if there were any concerns with our proposed clinical protocol. We requested a face-to-face meeting with the FDA to discuss our presubmission, and we received written feedback from the FDA on our presubmission prior to our face-to-face meeting. Based on that feedback, we prepared a meeting agenda to address any remaining concerns and then traveled to Silver Spring, Maryland, for an in-person meeting. We met with FDA review staff, medical officers, and engineers, presenting slides detailing the device design, our history with the device, and our proposed testing and clinical strategies. This was followed by a question and answer session. It was a useful process, as it helped orient the FDA review team to our proposed approach and helped us to understand what types of concerns the FDA had. Once we were able to incorporate the FDA's feedback and recommendations, we submitted our formal application. Once we had approval of the application, we submitted the protocol to our local institutional review board (IRB) for approval. After IRB approval, we submitted the approval letters from the FDA and the IRB to the Centers for Medicare & Medicaid Services (CMS) for coverage and reimbursement review.

The process was not difficult once we understood the requirements, yet it was very time-consuming. Thankfully, I have a great team to support me, including people with experience in regulatory/quality, clinical research, and engineering. I am very fortunate, and not all surgeons will have that luxury. Hopefully, the new Society for Vascular Surgery (SVS) PS-IDE template will help people obtain an IDE and reduce the overall cost or resource burden. To request the current template, contact vascular@vascularsociety.org.

What was your specific role as the physician sponsor?

My specific role was to establish the device modifications and help define the clinical protocol. I also reviewed all materials once they were prepared and made all presentations to the FDA. As mentioned before, I have a regulatory and quality specialist who prepared materials and developed the strategies for responding to the FDA's questions. She also coordinated all submissions, including those that went to the IRB, CMS, and our conflict-of-interest committee. Finally, she coordinated the collection of test data from third-party contract research organizations and the component device manufacturers.

During the application process and during compassionate use approvals, we had several instances of interactive review.

How would you describe the exchange of ideas in your interactions with the FDA? How was communication handled?

Formal correspondence happened via the face-to face meeting and formal written feedback. When we needed informal feedback, we would email or arrange a phone call with our reviewer. The exchanges were surprisingly open and collaborative. During the application process and during compassionate use approvals, we had several instances of interactive review. These interactive reviews were either exchanged by phone or email and allowed for efficient, timely review of materials and the exchange of ideas during the review process.

What are the specifics of your IDE? Were there any limitations required by the FDA beyond what you proposed in your IDE?

Our IDE was for the endovascular repair of TAAAs using our two-piece visceral manifold stent graft system. We proposed to treat Crawford type I–V TAAAs. The FDA agreed to this proposed plan. One thing they didn't agree to was our requested number of patients. We asked to treat 20 patients, but they came back with a counterproposal where we could treat 15 patients with an interim review after every fifth patient.

How were devices and accessories selected for inclusion? Is each a part of the IDE?

I like to think of our IDE as studying an implant system. For our thoracoabadominal system, we have a thoracic bifurcation and manifold main body graft, a visceral bypass, an infrarenal bifurcation, iliac limbs, iCast (Atrium Medical Corporation) bridging stents, and Medtronic bare-metal, self-expanding stents to

line the bridging stents. All of the devices in this system are included in the study. Although we also use many accessory devices, none of them are under study.

IDE IN PRACTICE

What kinds of documentation are required in each case, and are there any postprocedural/follow-up protocols mandated?

There are several case report forms that need to be documented with each case. We have case report forms that collect patient demographics, procedural data, discharge information, adverse events, protocol deviations, and follow-up data. For follow-up, we require imaging, physical exam, and adverse event evaluation performed at 1, 6, 12, 24, 36, 48, and 60 months. We report all patients on-study to the Vascular Quality Initiative. Additionally, we promptly report any unexpected serious adverse events, protocol deviations, or patient deaths to the FDA and the reviewing IRB.

The device needs to be modified according to the protocol unless we file an IDE supplement with prior approval from the IRB and FDA. In the event of an emergency in which a change is required to protect the well-being of a patient, a change can be made without prior approval, but a report detailing the emergency use or deviation must be filed with the IRB and FDA within 5 working days. A change that does not affect the scientific integrity or the safety of the patients can be made without prior FDA approval, but the FDA must be notified within 5 working days of the change.

How has practicing under the IDE changed the way you approach your cases?

I'm a big believer in gestalt. Surgeons develop their craft over many years and often make decisions in a complex and chaotic environment that they learn to see as an organized whole rather than the sum of its parts. The FDA requires that we document the decisions that we make in a very detailed way, which is important for both patient safety and advancing the state of the art. However, it has at times been a painful process as I learned to justify decisions that I used to make quickly and freely. I wouldn't say that treating patients under a PS-IDE has changed the way I practice, but it definitely has forced me to better communicate the clinical decision-making process and the risk-benefit ratio considered when treating a patient.

Is reimbursement different for cases performed under the IDE?

For Medicare reimbursement, a physician-modified IDE device may not be billed to Medicare unless CMS approves the clinical trial. For CMS approval, once the physician-modified IDE receives FDA and IRB approval, the FDA-approved clinical protocol may be submitted to CMS for Medicare approval of coverage and reimbursement. Under CMS rules, the physician should submit the FDA letter that includes the CMS category designation of an A or B denoting the risk profile of the IDE device. A Category A device has a safety profile that has not yet been established and is considered experimental. A Category B device has a risk profile that has been established. Stent grafts historically have been designated as Category B.

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This Medicare IDE approval process changed on January 1, 2015. Prior to that date, PS-IDEs were reviewed by regional Medicare Administrative Contractors. After January 1, the review was centralized with the goal that the review of IDEs would become more uniform throughout the United States.

Since centralizing the review process, few Category B feasibility studies, including PS-IDE feasibility studies, have been approved by CMS. This includes both early and traditional feasibility studies. According to CMS, many of the Category B IDE clinical studies were too early in the device development process to be approved under its regulatory criteria. However, CMS has approved Category A IDE feasibility studies. A CMS-approved Category A IDE approval allows for the reimbursement of the routine costs (eg, hospital costs) in the feasibility study. Unlike Category B devices, Category A devices and related costs are not coverable or reimbursable by Medicare.

If your IDE study is not approved by CMS, the absence of reimbursement includes the device, the procedure, and hospital-related costs. Physician-modified devices are unique in that they are not a device brought forward by industry, so if PS-IDEs are not reimbursed, it will make it very challenging for physicians to run a PS-IDE. In an effort to educate CMS, we requested a face-to-face meeting to fully

explain PS-IDEs. CMS was appreciative of the meeting because they were unaware of PS-IDEs. Further, CMS acknowledged that precedence has been set on the device classification of PS-IDEs that must be considered when evaluating coverage of PS-IDEs. Because the PS-IDE is a fairly new paradigm for CMS, they recommended that physicians might want to talk with CMS regarding the IDE study they are proposing in order to fully understand CMS IDE study criteria, historic precedence, and to educate CMS on the value proposition of a specific study.

Is the IDE transferrable if the physician moves to a new institution? If so, what additional measures might be required to do so?

Yes, an IDE is transferrable if the physician moves to a new institution. However, there are a few things that will need to be taken care of prior to commencing the IDE at a new institution. First, the physician will need to file a supplement with the FDA requesting the change. Second, the physician will need to have the study approved by the IRB at the new institution. Finally, the physician will need to perform a new Medicare coverage analysis with their new institution and get the proper approvals to undertake the study.

How long does the IDE last, and are there reviews by the FDA along the way?

In our case, the IDE was established to treat 15 patients with a periodic review with the FDA occurring after every fifth patient. There is not a specific time frame attached to our treating those 15 patients. We anticipate that once we enroll 15 patients, we will approach the FDA and ask for an additional set of patients.

ADVICE FOR OTHERS SEEKING IDEs

What are the first steps an interested physician should take in the process of seeking an IDE?

I would encourage physicians interested in seeking a PS-IDE to do three things. First, I would encourage them to reach out to a colleague who already has an approved IDE. I think they can give a realistic set of expectations of what the process is like. Second, I would encourage them to contact the SVS and obtain a copy of the PS-IDE template. I began writing my IDE

Figure 1. CTA of the type II TAAA before repair.

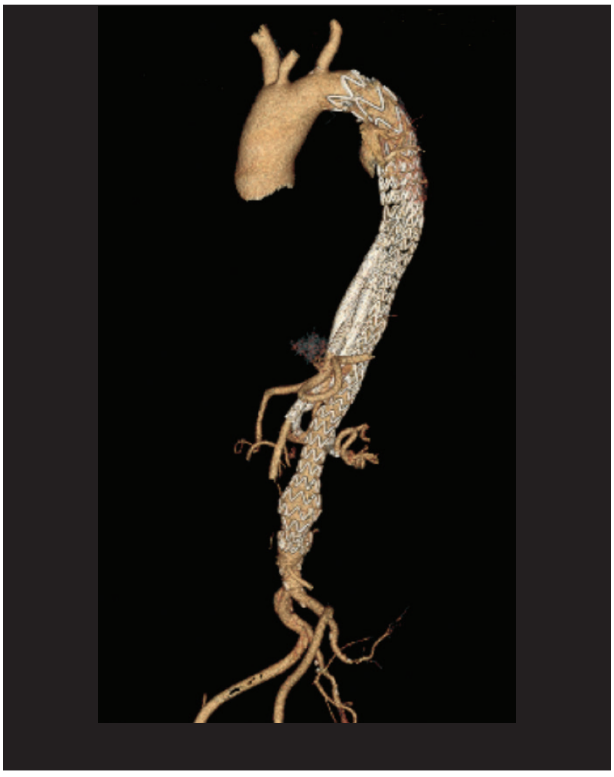

Figure 2. CTA of the type II TAAA at postoperative day 1 after repair with the Medtronic Valiant TAAA thoracoabdominal stent graft system (thoracic bifurcation and visceral manifold components only) as well as other Medtronic components.

application without the template and without a regulatory consultant, and it took longer than it should have. If I would have had the SVS template, I believe the process would have gone much faster. Finally, I would encourage them to visit the FDA's website to begin preparing the presubmission materials to engage the FDA early in the process. After all, the most important thing is to just get started.

In addition to the above advice, if the physician is interested in Medicare coverage and reimbursement, I recommend that you visit the Medicare IDE website at https://www.cms.gov/Medicare/Coverage/IDE/index.html. You will find general information regarding Medicare IDE approval criteria and also a checklist to help submit an application for Medicare approval.

What else do you wish you had done differently?

The one thing I would have done differently is I would have gotten my IDE earlier. The process was big and scary to me in the beginning, but now I have a good understanding of how it works. The FDA has been great to work with. Before I approached the FDA, I thought they would be adversarial. However, I have come to view them as a partner. The level of documentation required can sometimes feel overwhelming, but the FDA does everything they can to help you comply with the regulation. In the long run, we all want the same thing: to advance technology and provide better care for our patients.

CASE STUDY

A 67-year-old woman presented with a symptomatic type II TAAA. The maximum diameter of the aneurysm was 5.1 cm and had grown 0.8 cm in less than 6 months. The aneurysm was fusiform with no neck and extended from the descending thoracic aorta to just below the renal arteries. The patient had a duplicated right renal artery; both were small in diameter. She had a history of smoking, chronic obstructive pulmonary disease, hypertension, significant coronary disease, and a previous myocardial infarction.

The patient was not a candidate for open surgical repair of her TAAA due to the high risk of respiratory failure, paraplegia, cerebrovascular vascular accident, and cardiac complications from her existing comorbidities. She was not a candidate for the Zenith t-branch because the diameter of the proximal neck was 39 mm, and the t-branch device requires a diameter of ≤ 30 mm. The patient did not meet inclusion criteria for our device due to excessive thrombus in the proximal neck and branch vessels < 5 mm, so this patient was treated via the compassionate use provision. The compassionate use request was approved by the FDA and the local IRB.

The patient was treated with the Valiant thoracoabdominal stent graft system (Medtronic), including the investigational thoracic bifurcation and visceral manifold stent grafts. The four visceral vessels were stented, and the upper pole of the duplicated right renal was stented, as this artery provided good flow to the adrenals as well as the upper and lower poles. Despite the lower pole renal artery being sacrificed, the patient maintained good renal function. The rest of the case was completed using commercially available Endurant stent grafts (Medtronic) to seal into the distal aorta. The device was successfully deployed at the intended site, and a completion angiogram showed patency and good flow throughout the stent graft system. There was a type II endoleak, but this had resolved by the 1-month follow-up. The total procedure time was 383 minutes, with 76 minutes of fluoroscopy time. The patient received 177 mL of a contrast agent and had an estimated blood loss of < 500 mL. The length of stay was 7 days, and the patient was discharged to home. Pre- and postoperative CT angiograms (CTAs) are shown in Figures 1 and 2. ■