Application of Investigational Device Exemptions regulations to endograft modification

Dorothy Abel, BSBME, and **Andrew Farb, MD,** *Silver Spring, Md*

For patients with complex aortic aneurysms that cannot be treated effectively with currently approved endografts, physicians have made fenestrations in marketed devices and constructed branched grafts by creatively implanting available endograft components. For the most part, these procedures are being done outside of clinical studies by individual physicians. Although these novel approaches may be useful in the treatment of individual patients, the current ad hoc use of physician-created fenestrated and branched devices may not result in the unbiased capture and reporting of data regarding short- and longer-term outcomes. As a result, unsubstantiated conclusions regarding the safety and effectiveness of these procedures may be drawn. Well-designed and executed clinical studies are necessary to adequately assess the benefits and risks of these techniques. Because these interventions involve the use of significant risk devices, these studies need to be conducted under United States Food and Drug Administration-approved Investigational Device Exemptions (IDE) applications. Although this regulatory process adds complexity to the application of these creative techniques, the IDE regulations assure that patient protection measures are followed and data are captured to assess safety and effectiveness. This approach creates opportunities to advance the development of innovative, beneficial devices and procedures to treat complex aortic aneurysms. (J Vasc Surg 2013;57:823-5.)

The first fenestrated endograft to treat abdominal aortic aneurysms with short infrarenal neck lengths was approved for use in the United States (U.S.) by the U.S. Food and Drug Administration (FDA) in April 2012. Even with the approval of this device, which is custom-designed and imported for each patient, many patients with complex aortic aneurysms cannot be treated effectively or expeditiously with currently approved endografts. In response, physicians have developed techniques to make fenestrations in marketed endografts and to construct branched grafts by creatively implanting available endograft components. Most of these procedures are being done outside of clinical studies on an ad hoc basis by individual physicians treating individual patients.

The current creative endograft uses are reminiscent of the "homemade" devices of the 1990s, where off-the-shelf stents and vascular grafts were sewn together to create endografts to treat aortic aneurysms. Although there may have been benefits for individual patients and physicians from the uses of these early devices, the lack of rigorous, well-designed clinical studies may have delayed the transfer of knowledge to efficiently advance endograft technology. Ultimately, systematically captured information obtained from the use of homemade endografts, under sponsor-investigator research studies, led to an evolution in implantation techniques and patient selection, followed by improvements in industry-supported clinical study protocols and device designs. The long-term data from these studies have also revealed the limitations of homemade devices compared with devices manufactured by industry.

As was the case with the homemade endografts, the current ad hoc use of physician-created fenestrated and branched devices may not result in the unbiased capture and reporting of complete and accurate data regarding device use and short-term and longer-term procedural outcomes. As a result, unsubstantiated conclusions may be drawn about the safety and effectiveness of these procedures. Furthermore, appropriate human subject protection measures, such as the use of an informed consent form that adequately communicates the unknown risks that may be associated with these procedures, may be deficient or absent outside of a formal clinical study.

Recognizing the potential for improved patient treatment given the promising results reported to date, the practice of physically modifying or constructing branched endografts is ready to move into a phase of rigorous clinical investigation. As these investigations advance from single-center feasibility studies to multicenter studies involving larger numbers of patients, they will provide invaluable information to expand the treatment options for patients with complex aortic aneurysms.

THE INVESTIGATIONAL DEVICE EXEMPTIONS REGULATIONS AND CLINICAL STUDIES

Clinical studies, defined as any standardized, systematic collection of safety or effectiveness data, or both, in the

From the United States Food and Drug Administration.
Author conflict of interest: none.
Reprint requests: Dorothy Abel, BSBME, U.S. Food and Drug Administration, 10903 New Hampshire Ave, WO66-1204, Silver Spring, MD 20993-0002 (e-mail: dorothy.abel@fda.hhs.gov).
The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
0741-5214/$36.00
Published by Elsevier Inc. on behalf of the Society for Vascular Surgery.
http://dx.doi.org/10.1016/j.jvs.2012.12.025

U.S. are subject to the Investigational Device Exemptions (IDE) regulations, which for significant-risk studies involve the submission of an IDE application for approval by the FDA.[1] To explore why IDE applications are needed for the use of physician-modified endografts and the creation of branched devices in vivo, there are three key questions to consider:

- Is it optimal to justify the use of these devices under the "practice of medicine," and therefore miss the opportunity to collect device performance and clinical outcome data in a clinical study?
- Are the studies exempt from the IDE regulations?
- Are these significant-risk studies?

Practice of medicine. The FDA regulates the marketing of medical devices, not the practice of medicine. Section 1006 of the Food, Drug, and Cosmetic Act specifically states that "Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." One interpretation of the Food, Drug and Cosmetic Act is that it may be acceptable to create branched endografts under the practice of medicine. However, making fenestrations in a device that has received Premarket Approval could be interpreted as creating a new investigational device that would be subject to additional FDA oversight.

The FDA approves a device for marketing for a specific use(s).[2] The manufacturer's product labeling, which contains the instructions for use (IFU), presents a general description of the patient population for which the device is intended and the disease or condition that the device will diagnose, treat, prevent, cure, or mitigate. The labeling also describes how the device should be used to obtain clinical outcomes consistent with the data provided to support FDA approval.

Off-label use is a term applied to the use of an approved device under the practice of medicine outside of the IFU. The decision to use an approved device off-label or to use a modified version of an approved device in treating a patient is not necessarily inappropriate but is typically supported by less information than with on-label use. Specifically, when a physician constructs a branched or fenestrated endograft, it cannot be assumed that the data collected to demonstrate the safety and effectiveness of the device when used on-label or in its unmodified state are applicable. The prior nonclinical testing and clinical studies would not have addressed the off-label or device modification aspects of these innovative uses, such as performing tests that incorporate conditions that reflect the anatomy and physiology associated with complex aortic aneurysms or the effects of combining or modifying devices.

Creative uses of endografts may be associated with higher rates of major adverse events, particularly in the hands of inexperienced operators, compared with the anticipated rates with on-label uses of unmodified devices. The differences in expected outcomes may be acceptable given the typically higher-risk patients being treated but should be assessed through clinical studies to establish appropriate expectations by the treating physicians and potential patients.

The information available from presentations and publications on creative endograft use consists largely of retrospective observations and analyses rather than prospective clinical studies. Although ad hoc device use can provide insight into the promise and limitations of these techniques, definitive data from appropriately designed and conducted clinical studies are needed to guide informed decisions for the treatment of complex aortic aneurysms.

Exempted investigations. Some clinical studies, such as the study of approved devices that are being used on-label, are exempted from the IDE regulations. A clinical study of physician-modified endografts or a study of the combination of off-the-shelf components to treat aneurysms involving arterial side branches or bifurcations would be an investigation of a new device or an off-label use, so would not be exempted.

The testing of a modification to a device or of a combination of two or more legally marketed devices is only exempted from the IDE regulations if the testing is not for the purpose of determining safety or effectiveness and does not put patients at risk. Because there are risks to patients associated with the creative use of endografts, clinical studies of these uses would not be exempted from the IDE regulations, even if the data were not intended to support a marketing application to the FDA.

Significant-risk determination. Significant-risk devices are those that present the potential for serious risk to the health, safety, or welfare of a patient. A significant-risk device may be an implant, a life-supporting or life-sustaining device, or a device of substantial importance in diagnosing curing, mitigating, or treating disease or in otherwise preventing impairment of human health. By definition, studies of endografts that are subject to the IDE regulations are significant-risk studies.

A clinical study of a significant-risk device in the U.S. requires prior FDA approval, through the submission of an IDE application, and Institutional Review Board approval before initiating study subject enrollment.

IDE APPLICATION

The IDE regulations list the information to be included in an IDE application. The IDE sponsor needs to provide sufficient information to justify the proposed study based on reports of prior investigations of the device, an appropriate investigational plan, and adequate patient protection measures. Other required elements of an IDE application address records and reports, study monitoring, and manufacturing information.

For physician-sponsored endograft studies, justification for the study would be based primarily on the clinical expertise of the individual submitting the IDE, historical information on the development of the techniques proposed, and a description of the benefits and risks of alternative treatment options. Clinical mitigation strategies (ie, strategies included in the clinical protocol intended to minimize the

frequency or severity of potential adverse events) are also critical to support the study, particularly when limited nonclinical testing is available. The rationale for the conduct of the study should be tailored to the specific patient population to be enrolled, for example, patients at high risk for complications if treated with open surgical repair.

The clinical protocol for a modified endograft IDE should contain information similar to that provided under manufacturer-sponsored IDEs. For example, the protocol should clearly describe:

- The patients to be enrolled in the study;
- The lesion types and locations to be treated;
- The duration of the study (most endograft IDEs specify 5-year follow-up for each patient);
- All devices to be used in the study (eg, devices used in constructing the modified endograft, covered stents, bare stents) and how the endograft will be modified, if applicable;
- The potential risks that may be associated with the treatment and how the risks will be minimized; and
- The data to be captured, differentiating between protocol-required data and optional information.

Incorporation of appropriate monitoring and oversight will be important and may include the use of a clinical events committee and a data and safety monitoring board.

The informed consent document for a physician-sponsored endograft study should contain the required elements as outlined in 21 CFR Part 50 Subpart B—Informed Consent of Human Subjects. For these studies, prospective study subjects should be informed of potential benefits and risks that may be associated with study participation and that there could be unforeseeable risks due to limitations in available data and experience with the device. The benefits and risks associated with the standard of care (eg, open surgical repair) should also be addressed.

Guidance on the preparation and submission of an IDE can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm.

The preparation of an IDE application and the conduct of an IDE study can be challenging, requiring a skilled research staff. Consultation with the device manufacturer and physicians who have experience with the IDE process may be helpful. In addition, it is recommended that a sponsor-investigator interact with the FDA through the presubmission process when preparing the IDE application. This process allows for informal discussion and feedback to address key components that need to be included or revised in the IDE submission.

Information on the presubmission process may be found in the draft guidance "Medical Devices: The Pre-Submission Program and Meetings with FDA Staff" at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm. Once finalized, this guidance will represent the FDA's current thinking on this topic.

REIMBURSEMENT UNDER IDES

The FDA provides recommendations to the Centers for Medicare & Medicaid Services (CMS) with respect to whether an IDE application is for an experimental (category A) or a nonexperimental/investigational (category B) device. A category A device is an innovative device for which initial questions of safety and effectiveness have not been resolved and the FDA is unsure whether the device type can be safe and effective. Category B refers to a device for which the underlying questions of safety and effectiveness of that device *type* have been resolved or it is known that the device type can be safe and effective.

CMS uses the FDA categorization of a device as a factor in making Medicare coverage decisions. CMS may consider for Medicare coverage certain nonexperimental/investigational (category B) devices being studied under an FDA-approved IDE application. To date, FDA has categorized all endografts as nonexperimental/investigational devices when used in IDE-approved clinical studies. The FDA makes no recommendations to CMS regarding off-label use of approved endografts.

Additional information on FDA categorization and CMS coverage can be found at http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&rgn=div6&view=text&node=42:2.0.1.2.5.2&idno=42.

CONCLUSIONS

Modified endografts and creative implantation procedures have been developed to address unmet clinical needs in the treatment of complex aortic aneurysms in patients at a high risk for morbidity and mortality if treated with open surgery. As clinicians increasingly apply these contemporary endovascular techniques, appropriate patient protection and care should be applied. Data from well-designed and executed clinical studies are needed to optimize patient selection, treatment, and follow-up. Although the IDE process adds complexity to the use of novel endovascular therapies, it should aid in the development of improved technology and techniques for patients with complex aortic aneurysms.

AUTHOR CONTRIBUTIONS

Conception and design: DA, AF
Analysis and interpretation: DA, AF
Data collection: Not applicable
Writing the article: DA, AF
Critical revision of the article: AF
Final approval of the article: DA
Statistical analysis: Not applicable
Obtaining funding: Not applicable
Overall responsibility: DA

REFERENCES

1. Abel DB. Investigational device exemptions. Endovasc Today 2003:51-2.
2. Abel DB, Smith AC. Medical device labeling. Endovasc Today 2008: 101-2.

Submitted Oct 8, 2012; accepted Dec 22, 2012.