Current Commentary

Obstacles to Studying Emerging Technologies

L. Elaine Waetjen, MD, Ram Parvataneni, MD, Shira Varon, MD, Naghmeh Salamat Saberi, MD, and Vanessa L. Jacoby, MD, MAS, for the University of California Fibroid Network (UCFN)

Laparoscopic radiofrequency ablation of uterine leiomyomas with a new Federal Drug Administration (FDA)-approved device, a device that delivers radiofrequency energy, is a novel procedure that aims to meet patient and physician demand for effective, minimally invasive leiomyoma treatment. However, as a new procedure, the durability of symptom relief, the safety in widespread use, and ultimately the comparative effectiveness of radiofrequency ablation of leiomyomas need further study. In June 2013, the University of California Fibroid Network, a collaboration of the five University of California Departments of Obstetrics and Gynecology, launched the Uterine Leiomyoma Treatment with Radiofrequency Ablation Study, an investigator-initiated early postmarket approval clinical trial of radiofrequency ablation of leiomyomas. In this commentary, we provide a review of the FDA approval process for medical devices using the device that delivers radiofrequency energy as a case study and describe significant limitations of this process that may adversely affect clinical care. We show how the deficiencies in the FDA process have challenged our ability to conduct independent early postmarket research evaluating the safety and long-term effectiveness of this novel technology. Our experience validates the Institute of Medicine's recommendation that advancements in surgical technology introducing new treatments without long-term effectiveness data, comparative study, or both should emerge onto the market under research conditions. Until the FDA requires more rigorous study of novel devices, we suggest ways of working together as a community of gynecologic surgeons to evaluate promising new technologies in early postmarket studies, putting research before widespread adoption of surgical innovation.

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Many women with uterine leiomyomas seek uterine-sparing surgical treatments that provide symptom relief with minimal risk and a rapid recovery time. Laparoscopic radiofrequency ablation of uterine leiomyomas with a U.S. Food and Drug Administration (FDA)–approved device, Acessa (a device that delivers radiofrequency energy), aims to meet this demand for effective, minimally invasive leiomyoma treatment. Approved in November 2012 with promising initial study results, long-term data on the safety and effectiveness of radiofrequency ablation of leiomyomas with this device are limited. In this commentary, we provide a review of the FDA approval process for medical devices using the Acessa device as a case study and describe significant limitations of this process that may adversely affect clinical care. We describe how the deficiencies in the FDA process have challenged our conduct of independent early postmarket research to evaluate the safety and long-term effectiveness of this novel technology as it emerges into surgical practice. Finally, we suggest strategies to address the deficiencies in the FDA process, including strategies to facilitate the early outcomes research that gynecologists need for patient care and clinical decision-making.

The FDA pathway to surgical device approval is distinct from drug approval. Before release onto the market, a new drug must be tested in comparative trials (level I evidence) to demonstrate that it is safe and at least as effective as an existing drug. Surgical devices, on the other hand, are triaged to "low risk," "moderate risk," and "high risk" by FDA reviewers

From the Departments of Obstetrics and Gynecology, University of California, Davis, School of Medicine, Sacramento, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, University of California Irvine, School of Medicine, Irvine, the Department of Reproductive Medicine, University of California, San Diego, School of Medicine, San Diego, and the Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, School of Medicine, San Francisco, California.

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Corresponding author: L. Elaine Waetjen, MD, University of California, Davis, Department of Obstetrics and Gynecology, 4860 Y Street, Suite 2500, Sacramento, CA 95817; e-mail: lewaetjen@ucdavis.edu.

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based on specific guidelines. Low-risk devices, for example crutches, can be released into medical practice without study. High-risk devices must undergo clinical trials, although not necessarily with a control group (ie, not with level I evidence), in humans to prove safety and effectiveness and often require postmarket evaluation after their release into medical practice. Moderate-risk medical devices are approved by the FDA through a process called the 510(k) mechanism created by the 1976 Medical Device Amendment to the Federal Food, Drug, and Cosmetic Act. The 510(k) application requires device-makers to demonstrate "substantial equivalence to a legally marketed device" in structure and function referred to as the "predicate" device.

The FDA's standard for establishing substantial equivalence to approve moderate-risk devices ranges from accepting descriptive information to requiring performance data. The now controversial power tissue morcellator used for laparoscopic hysterectomies was approved through the 510(k) pathway based on descriptive information of substantial equivalence to predicate devices. Despite public disclosure laws, the scientific basis for determining substantial equivalence between predicate and newly approved devices is not always publically available or clearly described.[1] As consumers of power morcellators, we searched the FDA web site (http://www.fda.gov/MedicalDevices) to identify their predicate devices. Through a series of "substantially equivalent" devices, the Internet trail ends at the Cook Tissue Morcellator, approved in 1991. This first power morcellator, designed for laparoscopic removal of organs, references "surgical instrument motors and accessories/attachments" as predicate devices, specifically two tissue punches and a motorized tool for clearing joint fluid in arthroscopy. To track the predicate devices for the Acessa device, we again used the FDA web site and determined that the substantially equivalent devices to which Acessa were compared were used in other tissues, for example, to ablate liver metastases. On this web site, we were unable to establish the original predicate device and thus any data for its use in humans.

Because this approved radiofrequency energy device has introduced an entirely new laparoscopic gynecologic procedure, laparoscopic radiofrequency ablation of leiomyomas, the 510(k) application for this device required performance data. Before FDA approval, the Acessa device was examined in a phase III noncomparative trial (level II evidence) of radiofrequency ablation of leiomyomas to assess the efficacy in reducing abnormal uterine bleeding and the reintervention rates at 1 year. One hundred thirty-five women with leiomyoma-related abnormal uterine bleeding underwent radiofrequency ablation with this device and were followed for 1-year clinical outcomes. Published in *Obstetrics & Gynecology* in May 2013,[2] the trial showed that radiofrequency ablation reduced leiomyoma symptoms by approximately 56%, uterine volume by approximately 45%, and heavy vaginal bleeding by approximately 35%. Retreatment for persistent leiomyoma problems was less than 1% during the 1 year of follow-up.

There are significant concerns regarding the safety and effectiveness of devices that are approved through this streamlined 510(k) process.[3] Many recalls of devices deemed "moderate risk" and approved through the 510(k) process have been associated with major complications; the devices have posed more than a moderate risk to patients.[1] In 2011, an Institute of Medicine report concluded that the 510(k) pathway is fundamentally flawed and recommended that the FDA develop a new pre- and postapproval regulatory pathway to ensure patient safety.[4] The FDA has been working to respond to some of the concerns raised about their evaluation processes.[5] For example, section 522 of the Federal Food, Drug and Cosmetic Act revised in 2011 requires postapproval studies for moderate- and high-risk devices with potential for significant complications (eg, implantable devices).[5] Regulating an environment that both encourages innovation and protects patient safety is challenging, and physicians need to be aware of the limitations of the FDA approval process for the new technology we use.

Without a rigorous regulatory pathway, surgical innovation with novel technology undergoes a series of stages from introduction into practice based on limited data, to physician adoption into practice, to public acceptance including insurance coverage. Only after acceptance is there formal, independent research where safety and effectiveness are objectively evaluated in comparative clinical trials.[6] The history of gynecology is filled with new technology and practices that have proven to enhance our care of women such as the development of and advancements in laparoscopy and operative hysteroscopy. However, history has also demonstrated how adopting novel technology before careful study can lead to patient harm such as vaginal erosions from the ProtoGen suburethral sling[7] or lead to increased medical costs without substantial improvement in care such as robot-assisted sacrocolpopexes.[8] The clearest recent example of patient harm from the widespread adoption and acceptance of an understudied FDA-approved surgical device is the use of transvaginal mesh kits for vaginal prolapse procedures. Had these

novel devices, predicated on descriptive comparisons with the flawed ProtoGen suburethral sling, been studied more rigorously before they were adopted into general clinical practice, it is likely that many of the kits would have been eliminated before widespread use or best surgical practices would have been more quickly defined. Rigorous study of this novel technology, before widespread adoption and acceptance, could have reduced the significant morbidity from mesh complications.

As a new procedure, the durability of symptom relief, the safety, and ultimately the comparative effectiveness of radiofrequency ablation of leiomyomas require further evaluation. Investigating how this radiofrequency energy device functions in real-world gynecologic practice, outside the limited patient population of trials conducted by the device company, where surgeons are carefully trained and inclusion criteria are strict, is critical. Radiofrequency ablation of leiomyomas and devices that deliver the radiofrequency energy need independent studies to evaluate long-term effectiveness, to assess for possible unanticipated risks, to describe surgeon learning curves, and to define the characteristics of patients who may benefit the most from this minimally invasive option. We as gynecologists need this information to counsel patients about this surgical innovation in the context of other treatment options. Ultimately, randomized, comparative trials (level I evidence) with long-term follow-up are required to provide gold standard evidence on the effectiveness and application of radiofrequency ablation of leiomyomas.

The University of California Fibroid Network is a collaboration of the five departments of Obstetrics and Gynecology within the University of California system: University of California San Francisco, University of California Davis, University of California Los Angeles, University of California Irvine, and University of California San Diego whose mission is to improve the care of women with leiomyomas and to conduct independent research in leiomyoma treatment outcomes. In June of 2013, we launched an investigator-initiated postmarket clinical trial of radiofrequency ablation of leiomyomas, the Uterine Leiomyoma Treatment with Radiofrequency Ablation Study. We designed this single-arm study to address gaps in important knowledge about radiofrequency ablation of leiomyomas not addressed in the FDA 510 (k) process to approve the Acessa device. Our goals are to study radiofrequency ablation outcomes among a typical clinic population of women with leiomyomas rather than the more restricted population enrolled in the initial trials. For example, we included women with larger uteruses and larger leiomyomas than in the initial phase III trial. We included women who, although not infertile, may desire future childbearing to evaluate pregnancy outcomes, which would likely occur during widespread adoption of radiofrequency ablation of leiomyomas. We also planned to study the learning curve of surgeons with different minimally invasive surgical skill levels to provide competency evaluation recommendations for performing the procedure.

Over the past 18 months, the Uterine Leiomyoma Treatment with Radiofrequency Ablation Study has encountered numerous obstacles. The various systemic problems that have hindered our study's progress demonstrate inefficiencies in our health care system that challenge early research of new technology released through the 510(k) approval process.

New surgical technology must pass through a hospital value analysis committee that is charged with evaluating the financial effect of purchasing new devices. A number of our hospitals were concerned there would be no cost recovery for the disposable radiofrequency energy device. In their experience, insurance carriers decline novel procedures and their accompanying technology as "investigational." Given the research mission of our hospitals, radiofrequency ablation of leiomyomas was approved under study conditions, on a limited basis, and only after formal written guarantee of reimbursement for all procedural and equipment costs by each patient's insurance carrier. Between July 1, 2013, and March 1, 2015, the Uterine Leiomyoma Treatment with Radiofrequency Ablation Study has submitted 84 requests for coverage of laparoscopic radiofrequency ablation of leiomyomas to insurance carriers and received 60 denials. We have submitted 33 appeals and have received 19 denials of appeals (five are pending). The main reason for denying coverage has been that radiofrequency ablation of leiomyomas is still considered experimental. For example, Health Net states "Studies to date are limited with small patient size and lack of long term results. Further studies are needed to determine the long-term efficacy of this procedure and to evaluate the efficacy and safety of this procedure relative to other treatments for uterine fibroids" (Health Net, National Medical Policy, Policy Number NMP532, August 2014).

For radiofrequency ablation of leiomyomas that represents both a new device as well as a new surgical procedure, another problem we encountered in the Uterine Leiomyoma Treatment with Radiofrequency Ablation Study has been the time lag between FDA approval and the development of new International Classification of Diseases, 9th Revision and Current Procedural Terminology codes more specific to

laparoscopic radiofrequency ablation of leiomyomas. During the first 6 months of seeking insurance carrier approval, we used the general billing codes of laparoscopic procedure on the uterus "not otherwise specified." However, the cost recovery of this code was insufficient to cover the disposable radiofrequency energy device. In early 2014, a new code, more specific to radiofrequency ablation of leiomyomas, was published and, with it, the opportunity for our hospitals to set a standard charge that would cover the device. Although this more specific code alleviated our hospitals' financial concerns, we found that the coding change confounded the insurance carriers. For example, Medi-Cal (California's Medicaid) and Medicare included radiofrequency ablation of leiomyomas as a covered benefit in March and July of 2014, respectively, but under the older codes. Until the newer codes had been fully updated, we continued to receive denial letters from Medi-Cal and Medicare.

The Uterine Leiomyoma Treatment with Radiofrequency Ablation Study investigators and our patients interested in participation have been addressing these problems over the past 18 months through various strategies. For example, one of our participants appealed her insurance denial to the California Department of Insurance Independent Medical Review that overturned the insurance carrier's denial decision. We have seen a slow increase in insurance carriers covering radiofrequency ablation of leiomyomas over the past 6 months. The increase in coverage for radiofrequency ablation of leiomyomas is likely based on a number of factors. First, four additional journal articles by Halt Medical have been published in the last year: two were 24- (112 participants) and 36- (104 participants) month follow-ups of the original phase III trial (level II evidence) that showed reintervention rates of 5% and 11%, respectively,[2,9,10] and a representation of the phase III trial.[11] A randomized clinical trial in Germany found lower surgical complication rates with radiofrequency ablation of leiomyomas compared with laparoscopic myomectomy in 50 women.[12] The trend in more insurance carriers covering radiofrequency ablation of leiomyomas is also likely related to the development of more specific billing codes, the announcement of Medi-Cal and Medicare coverage for the procedure, repeated requests and appeals for coverage from doctors and patients, and peer pressure between insurance carriers.

Our experience conducting this radiofrequency ablation of leiomyomas clinical trial has provided us unique insight into the cascade of challenges in studying new devices approved through the FDA 510(k) process. Approval by this process is approval for release onto the market after which the device company is not always under obligation to provide or fund further study of their device. Most often devices are adopted into clinical practice with the expectation that they will become accepted over time and insurance companies will eventually cover their costs. Any additional research on the device must be funded independently, and the current standard is to require individual patients or insurance companies to cover the costs of the new surgical procedure in which the device is being investigated, yet because these devices are FDA-approved without comparative trials or long-term follow-up, insurance carriers are correct in classifying them as investigational and hospitals are understandably reluctant to purchase them without specific billing codes to extract adequate reimbursement. Ironically, until there is acceptance of new technology in the marketplace, independent investigators like the University of California Fibroid Network are significantly limited in conducting early postmarket studies.

We have two main recommendations to address these challenges and improve the available evidence to support the use of new surgical devices.

First, our main recommendation aligns with the Institute of Medicine report on the 510(k) process: to replace the current process "with an integrated premarket and post-market regulatory framework that effectively provides a reasonable assurance of safety and effectiveness through the device life cycle."[4] We would recommend that the FDA apply a similar rigor to evaluating devices as they do for drugs. Ideally, comparative studies (level I evidence) or at least large clinical trials (level II evidence) with long-term safety and effectiveness information should be required before widespread use of any new device. Although some may debate this recommendation based on concern that higher research standards might squelch investment in technologic advancement as a result of the high risk-to-reward ratio associated with gaining FDA approval,[13] the advantages could be faster and more widespread adoption of the device into clinical practice, a potential reduction in marketing costs resulting from widespread pre- and postmarketing studies that would raise surgeon and patient awareness of the new technology, and the avoidance of legal consequences from unknown adverse outcomes. More rigorous studies would satisfy both physicians and insurance carriers of the best indications, costs, and benefits of the new device and procedure.

Second, until change in the FDA approval process for moderate-risk devices, the surgical community needs to consider other means for independent

early study of novel technology. Specifically, we need to reverse the historical process of putting critical research after adoption and acceptance of surgical innovation. Sponsored by collaborations between private and public interest groups, FDA-approved novel surgical technology should emerge into clinical practice under research conditions. In particular, through professional organizations and societies, in collaboration with patients, we could develop specific protocols that acknowledge the "investigational" status of promising new surgical treatments and provide solutions to the financial concerns and coding issues that currently challenge early postmarket research. A kind of precedent for such collaboration exists in the Pelvic Floor Disorders Registry developed by the American Urogynecologic Society in response to the complications from transvaginal mesh placement. Organizing collaborations like this before release of technology onto the market could streamline the early collection of "real-world" evidence and minimize unexpected harm.

The University of California Fibroid Network plans to continue studying outcomes of radiofrequency ablation of leiomyomas. Although we have elected to keep enrollment open for the Uterine Leiomyoma Treatment with Radiofrequency Ablation Study despite the challenges, we recognize that this will delay the timeline for reporting our 3-year effectiveness of radiofrequency ablation of leiomyomas; those results will not be available to gynecologic surgeons until 2019. In the meantime, the University of California Fibroid Network has launched the observational arm of our clinical trial, the nationwide Uterine Leiomyoma Treatment with Radiofrequency Ablation Registry (web site: http://fibroids.ucsf.edu), to further assess safety and efficacy of the device in the postmarket setting. We invite physicians who are performing and patients who are undergoing radiofrequency ablation of leiomyomas to join the Uterine Leiomyoma Treatment with Radiofrequency Ablation Registry and provide basic information on indications, complications, and 3-year effectiveness.

For now, forming registries to study new technology as it emerges onto the market is one small, feasible step toward more rigorous research. Working together as a community of gynecologic surgeons to document outcomes together, we can evaluate how to incorporate radiofrequency ablation of leiomyomas and other exciting new technology into our practices. In this way, we can begin to surmount some of the imperfections in the FDA approval process.

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