

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

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An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials

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N Engl J Med 2017;376:1350-7.

DOI: 10.1056/NEJMr1512592

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MEDICAL DEVICES PLAY A CRITICAL ROLE IN THE LIVES AND HEALTH OF millions of people worldwide. From everyday household items such as oral thermometers to complex implantables such as deep-brain stimulators, patients and the general public rely on regulators to ensure that legally marketed medical devices have been shown to be safe and effective. Regulators expect data that are provided by device manufacturers to reflect the risk profile of the device. For example, a device that most consumers can use without instruction, such as reading glasses or elastic bandages, will require a very different evidence profile than a device, such as a portable ventilator, on which a patient's life could depend.

Although devices are manufactured and marketed worldwide, this review focuses on the strategy used by the U.S. Food and Drug Administration (FDA); special attention is paid to the ways in which the evaluation of devices is distinct from that of drugs. The entry of the FDA into the device arena was largely prompted by several deaths and claims by an estimated 200,000 women that they were harmed by the use of the Dalkon Shield, an intrauterine device (IUD) intended for contraception. Women who used this device had five times the risk of pelvic inflammatory disease as those using other IUD types, and several had uterine rupture or septic pregnancies. Congress responded by passing the Medical Device Amendments to the Food, Drug, and Cosmetic Act.^{1,2} These 1976 amendments established a risk-based regulatory framework for evaluating medical devices in the United States. Under this framework, the requirements that a device must meet to be lawfully marketed depend on the risk classification of the product, with risk being assessed as the potential for the device to present harm to the patient, including in circumstances in which the device could malfunction or be used improperly.

Most low-risk devices, which present a minimal potential for harm to the user (e.g., prescription eyeglasses, elastic bandages, and dental floss), are exempt from FDA review before marketing, although manufacturers are still subject to certain requirements. Manufacturers of most moderate-risk devices, such as condoms, nebulizers, and blood glucose meters, generally need to show that their device is substantially equivalent to another device already cleared by the FDA; in most cases, this is achieved through bench (nonclinical laboratory) testing and without clinical data.³ Higher-risk and innovative moderate-risk devices (approximately 4% of all medical devices), which are the primary focus of this article, generally require clinical evidence to show that the benefits of a technology outweigh its risks. Such information is often critical not only for showing the safety and effectiveness of the device but also for informing clinicians and patients about the preferred use of the device in the marketed clinical setting. This article seeks to illustrate the broad array of trial designs and clinical data sources that may be used to support the safety and effectiveness of these critical products.

TYPES OF TRIAL DESIGNS
AND CLINICAL DATA SOURCES

In clinical studies of pharmaceuticals, we might see double-blind, randomized, phase 3 trials assessing outcomes, sometimes in thousands of participants followed over a period of many months or years. There are many notable exceptions for situations in which a drug treatment has great clinical need that counterbalances its risks; in these contexts, we often accept smaller studies or less certainty because risk tolerance is higher in serious diseases for which current treatment options are inadequate. For some device studies, a similar approach is feasible. For example, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy, sponsored by Boston Scientific, randomly assigned 1820 participants with mild-to-moderate heart failure and a long QRS complex to receive either a standard implantable cardioverter-defibrillator (ICD) or cardiac-resynchronization therapy with a defibrillator (CRT-D) and followed them for an average of 2.4 years.⁴ The addition of cardiac resynchronization therapy was intended to increase the efficiency and effectiveness of cardiac contractions in a patient population with decreased exercise tolerance, increased left ventricular chamber size, and elevated risks of hospitalization and death. The trial showed a lower risk of heart-failure-related events with CRT-D than with ICD alone, resulting in an expansion of the approved label for Boston Scientific CRT-D devices,⁵ which had previously been restricted to patients with severe heart failure, and contributing to a subsequent expansion of the medical guidelines for CRT-D to include less-sick patients.⁶

For many devices, however, practical limitations related to the device or disease condition require alternative approaches to conducting large, randomized, controlled, double-blind studies and increased flexibility in trial design and statistical analysis. For example, it may be infeasible to conduct a blinded trial of an implantable device because it is impractical or unethical to use a sham control for the target patient population owing to the risk of the implantation or procedure itself. For some devices, opportunities exist for leveraging alternative data sources, such as existing registries or modeling techniques, to allow regulators to have a good idea of the risks and benefits of the device without the need for conducting detailed trials. For the majority of devices, the benefits and risks

are expected to be manifest through registries and evolve as clinical techniques are refined and the technologies themselves are rapidly modified and improved. Such a continuous improvement cycle would be impossible if every device iteration required a full trial to test its safety and efficacy. The FDA has in many cases accepted a somewhat greater degree of uncertainty regarding those benefits and risks early in the life cycle of a device, while allowing patients access to potentially important technologies and supporting the iterative refinement of the technologies.

Table 1 and Table 2 provide brief examples of the types of clinical data that may be expected on the basis of the benefits and risks of the device and the potential to leverage alternative data sources. Because this article cannot cover the full range of devices, we have focused on two examples that illustrate ways in which the FDA has allowed flexibility in the gathering of clinical data to support device approval.

EXAMPLE 1 — USE OF MODELING AND ENGINEERING TESTS TO REDUCE CLINICAL TRIAL REQUIREMENTS

In some circumstances, a clinical trial is not able to answer the most critical questions related to the safety and effectiveness of a device and instead serves to provide secondary confirmatory information. An example is the Medtronic Revo MRI pacemaker system, which was approved in 2011 as the first pacemaker indicated to allow patients implanted with the device to undergo magnetic resonance imaging (MRI).¹⁶ (For representative cardiac-pacing devices over time, see Fig. 1.) Given that as many as 75% of patients with pacemakers can expect to have a clinical indication for MRI over the lifetime of their device,¹⁷ the availability of a device that would safely allow for such scans had the potential to have a strong positive effect on health. The greatest safety concern for pacemakers in the MRI environment is the potential for a cardiac lead to act as an antenna and to direct radiofrequency energy from the MRI scanner to the lead tip, heating the tip and potentially ablating cardiac tissue. The Revo MRI system was specifically designed to minimize this effect by changing some characteristics of the conductor geometry. The device was also modified in other ways, including to incorporate an MRI scan mode so that during MRI the device would deliver appropriate therapy and not interpret the electrical noise generated by the MRI scanner as cardiac activity.

Table 1. Considerations for Device Trials.*

Characteristic of Device Trials	Rationale	Example
Device trials tend to enroll fewer participants than drug trials.	End points designed to show a “reasonable assurance of safety and effectiveness” tend to lead to modest sample sizes. In other cases, practical challenges limit the feasibility of conducting larger studies.	The Second Sight Medical Products Argus II Retinal Prosthesis System, indicated for providing visual function to blind participants with severe-to-profound retinitis pigmentosa, is an implanted device approved under the FDA Humanitarian Device Exemption program. ⁷ In the study, 30 patients were enrolled and served as their own controls. A larger, randomized, controlled trial was impractical owing to the low prevalence of end-stage retinitis pigmentosa with no or bare light perception. On the basis of the data provided, the FDA determined that the probable benefits outweighed the risks and that the device provides an important option for patients who previously had no FDA-approved treatments.
Many device trials assess iterative improvements on previous-generation devices.	Although some devices are truly new, the nature of device development is iterative improvement on existing technologies as clinical experience grows and the science advances. In many cases, clinical data are required to evaluate the benefits and risks of the new device but not necessarily as extensive as for the original device.	Many modern trials of drug-eluting coronary stents are designed to show noninferiority to earlier-generation stents. The Boston Scientific SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System was approved in 2015 on the basis of a 1684-participant randomized trial comparing SYNERGY with the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System. ⁸
Device design or procedure may be modified during the trial.	In some cases, early clinical events or feedback from physicians or patients may lead to changes in the device or the procedure. Validation of the changes may require additional clinical data beyond the original plan but may not require an entirely new study if it can be shown that data on the original device or procedure are appropriate to leverage.	The ReShape Medical Integrated Dual Balloon System is a dual intragastric balloon approved in 2015 for weight reduction. ^{9,10} After all participants were enrolled in the randomized pivotal study, the device was modified to reduce the observed rate of gastric ulcers. The revised device was used in crossover participants and additional participants in a single-group cohort study and showed a substantial reduction in ulcer rate. The FDA used this information to support the safety of the modified device in its approval decision.
Device trials are less likely to be blinded or randomized than drug trials. ¹¹	For many device trials, blinding or randomization is impractical owing to the nature of the device or the condition under study. For other studies, FDA experience with the device type allows for single-group studies that compare results with agreed-upon performance goals or established objective performance criteria.	Surgically implanted prosthetic heart valves have a long history of use, and studies supporting their marketing approvals are generally single-group studies that compare results with objective performance criteria. ¹² The FDA has described the number of participants and duration that should be studied to support the safety and effectiveness of a new valve, providing consistency and transparency to future device developers and providing an alternative to much larger, randomized, controlled trials that would otherwise be needed to assess low-level events.
Adaptive designs are increasingly common.	Adaptive trial designs are becoming more common for device studies because they allow sponsors to obtain essential data with as few participants and as short a follow-up period as necessary. Such methods may allow the investigators to alter the sample size, to stop the trial early for success or futility, or to modify the study in other ways on the basis of accruing data.	The AtriCure Synergy Ablation System was approved for the treatment of atrial fibrillation after a study with a Bayesian adaptive design. On the basis of strongly positive results assessed during the prespecified interim analysis, conducted when 55 participants had been enrolled, the study was stopped early for success. ¹³
In some cases, existing data can partially or fully substitute for prospective trial data.	The FDA considers the clinical data that are available external to prospective studies for the specific purpose of supporting marketing applications. This is particularly relevant for consideration of expanded indications for approved devices in cases in which there is a body of evidence supporting the “off-label” use and in which it could be difficult or even unethical to randomly assign participants.	The Medtronic Duet External Drainage and Monitoring System, intended for draining and monitoring of cerebrospinal fluid from the lumbar subarachnoid space, was granted an expanded indication under the FDA de novo program ¹⁴ on the basis of extensive bench testing along with clinical data available in the published literature, which included primary and secondary safety and effectiveness end points with significant outcomes for more than 800 patients treated with the device. The FDA determined that, given the worldwide clinical experience, the data and information provided supported use of the device for the expanded indication. ¹⁵

* In addition to the considerations described in the table, modeling data, registry data, and electronic-health-record data may reduce or replace requirements for clinical-trial data.

Given that heating would be most likely to occur in rare, worst-case conditions that would be difficult to predict clinically, relying on a clinical trial as the primary validation of safety would have required many thousands of participants. Instead, FDA approval rested primarily on robust mathematical modeling that was validated with bench studies and studies in animals. The modeling data, which simulated thousands of combinations of device and patient geometries and MRI scan conditions, provided strong evidence that even worst-case conditions would be very unlikely to result in detrimental lead heating. Owing to the novelty of this approach, Medtronic conducted a confirmatory unblinded clinical trial in which 464 participants with an indication to receive a pacemaker were implanted with the device and randomly assigned to receive a protocol-defined MRI or not.

As expected from the modeling results, the clinical trial showed no evidence of clinically relevant MRI-induced lead heating, as assessed by changes in the pacing capture threshold. The clinical trial was not focused on the primary safety and effectiveness aspects of the device — that is, whether the device paces and senses appropriately (independent of MRI exposure) and maintains its mechanical integrity. Given FDA and industry experience with basic pacemaker technology, these elements were leveraged from similar approved devices from the same manufacturer and confirmed with standard electrical and mechanical bench testing. Given that the new lead design had the potential to affect lead durability, a 5-year study of lead performance involving 1810 patients was required after approval. This approach of gathering a modest clinical data set to confirm robust bench and modeling data has been used to support a number of subsequent approvals for pacemakers and ICDs that allow MRI. As our experience with relying on modeling as a primary data set grows, premarketing clinical studies for next-generation devices may not even be necessary.

In this context, patients who participate in a postapproval study would be informed about the reasons for the study as part of the consent process for participation. However, as an approved device, the pacemaker was considered to have already shown a reasonable assurance of safety and effectiveness sufficient to support approval, and there is not an expectation of specific information to be provided to the patient regarding the fact that the device is new.

In the future, computer-based modeling may change the way we think about device validation in other ways, allowing for much smaller clinical trials, or may change the way we think about running trials, in that some “clinical” information may be derived from simulations. Device manufacturers are increasingly developing stochastic engineering models that may have the capability to simulate clinical outcomes for “virtual patients” by modeling a relationship between bench outcomes and clinical end points. If it can be shown that these virtual patients are similar, in a precisely defined way, to real patients, future trials may be able to rely partially on virtual-patient information, thus lessening the burden of enrolling additional real patients. The Medical Device Innovation Consortium, a public–private partnership among industry, nonprofit organizations, and federal agencies (including the FDA), is exploring ways to facilitate how computer modeling and simulation may become a validated and accepted part of a clinical trial.¹⁸ For devices for which some uncertainty remains after such premarketing studies, postapproval registries may be a helpful tool to provide additional confirmation of device performance, as discussed below.

EXAMPLE 2 — USE OF EVIDENCE FROM CLINICAL EXPERIENCE

Registry studies have the potential to play a critical role in device-approval decisions as a source of evidence from clinical experience (“real-world” clinical data). An example is the Transcatheter Valve Therapy (TVT) Registry, which is managed by the Society of Thoracic Surgeons and the American College of Cardiology.^{19,20} This registry collects data on nearly all transcatheter aortic-valve replacement (TAVR) procedures performed in the United States in order to study the short-term and intermediate-term outcomes of such procedures. Data quality is maintained through both an automated data-assessment system and an audit program.²¹ The SAPIEN transcatheter heart valve (THV) from Edwards Lifesciences (Fig. 2) was initially approved, on the basis of the results of a 358-patient randomized, controlled trial,²² for transfemoral insertion in patients considered to be inoperable for open-heart surgery and subsequently, on the basis of a second, 699-patient randomized, controlled trial,²³ for transfemoral or transapical insertion in high-risk candidates for open-heart surgery.

After approval, clinical data from the TVT

Table 2. Intervertebral Body Spinal Fusion Devices (“Spinal Cages”) — Historical Perspective.

Device Trial or Data Requirement	Rationale	Example
Extensive (full) clinical trial	The original devices, which are permanent implants, were considered to be high risk. Unknown safety and effectiveness profiles of these devices and lack of previous-generation devices necessitated prospective clinical studies.	Approval of the original devices was based on prospective trials that generally studied fusion in patients with degenerative spinal pathologic features at one or two adjacent spinal levels, as compared with standard-of-care treatments. Today, prospective trials are still generally expected for new spinal cages that combine the use of a drug or biologic component, because the risk profile of those devices may be complex.
Limited clinical information	Today, we have a much better understanding of the risk profile for spinal cages that do not include a new drug or biologic component, and the FDA now considers these devices to be moderate risk. Generally, a manufacturer can show that a new spinal cage is “substantially equivalent” to a currently marketed device without conducting a new clinical trial. However, some clinical data may be required to support a new element of the device design or a change to the indicated population.	Manufacturers have leveraged existing clinical data (e.g., literature and clinical experience) to support expansions to the indications for use. For example, the indications for intervertebral body spinal fusion devices approved for use with autograft bone graft have been expanded to allograft bone graft (i.e., cancellous or corticocancellous bone) on the basis of such data.
Information with respect to previous-generation devices	In some cases, minor changes and iterative improvements in a device that is fundamentally well understood can be supported solely through nonclinical testing and experience with similar devices.	Today, minor changes to the device designs, such as anatomical footprint and implant orientation, can be supported through nonclinical testing. Some changes to the fixation mechanism have been based on information with respect to previous-generation devices in conjunction with mechanical testing that shows that the new device performs equivalently.

Registry and other sources indicated that a considerable number of inoperable patients who did not have suitable anatomy for transfemoral insertion could benefit from TAVR through alternative access (i.e., nontransfemoral access). In 2013, Edwards Lifesciences submitted deidentified data from the TVT Registry, along with data from peer-reviewed medical journals and THV registries in Europe, to support an expansion of the approved indication by removing references to specific anatomical access points. The data included several thousand procedures performed with the use of alternative access points and clearly supported the conclusion that there were no adverse effects of the use of THVs on either device performance or the overall benefit–risk profile on the basis of the access point. Use of this extensive “real-world” clinical data was instrumental in allowing the FDA to rapidly approve this label expansion, avoiding the time delay of a randomized, controlled trial for this substantial group of patients with an otherwise fatal disease and an unmet clinical need.²⁴

High-quality registries and electronic health records hold enormous potential to serve as efficient tools to answer premarketing and postmarketing questions. For example, registry data have been used as historical controls and have also allowed the FDA to reduce or replace postapproval study requirements. Registry data may

also serve as the basis for statistically derived objective performance criteria. Future devices may be compared with those criteria to show acceptable clinical performance, thereby eliminating the need for a control group. In the longer term, we expect to see randomized studies embedded within registries, leveraging that existing infrastructure and minimizing the burden for study start-up and execution. For example, a next-generation unapproved device that requires a clinical trial to support approval could be studied under a protocol designed to have its data requirements aligned with an existing registry that gathers high-quality outcomes data for approved devices of that type. Investigational sites already participating in the registry could leverage their experience and existing processes to easily participate in the premarketing trial. Such an approach could simplify data gathering, auditing, and analysis by relying on methods already in place for the registry.

FUTURE CHALLENGES AND OPPORTUNITIES

The most important factor for successful marketing approval, practitioner adoption, and safe use of higher-risk and innovative moderate-risk medical devices is robust clinical evidence. However, the most appropriate, least burdensome paths for gathering clinical data to support marketing ap-

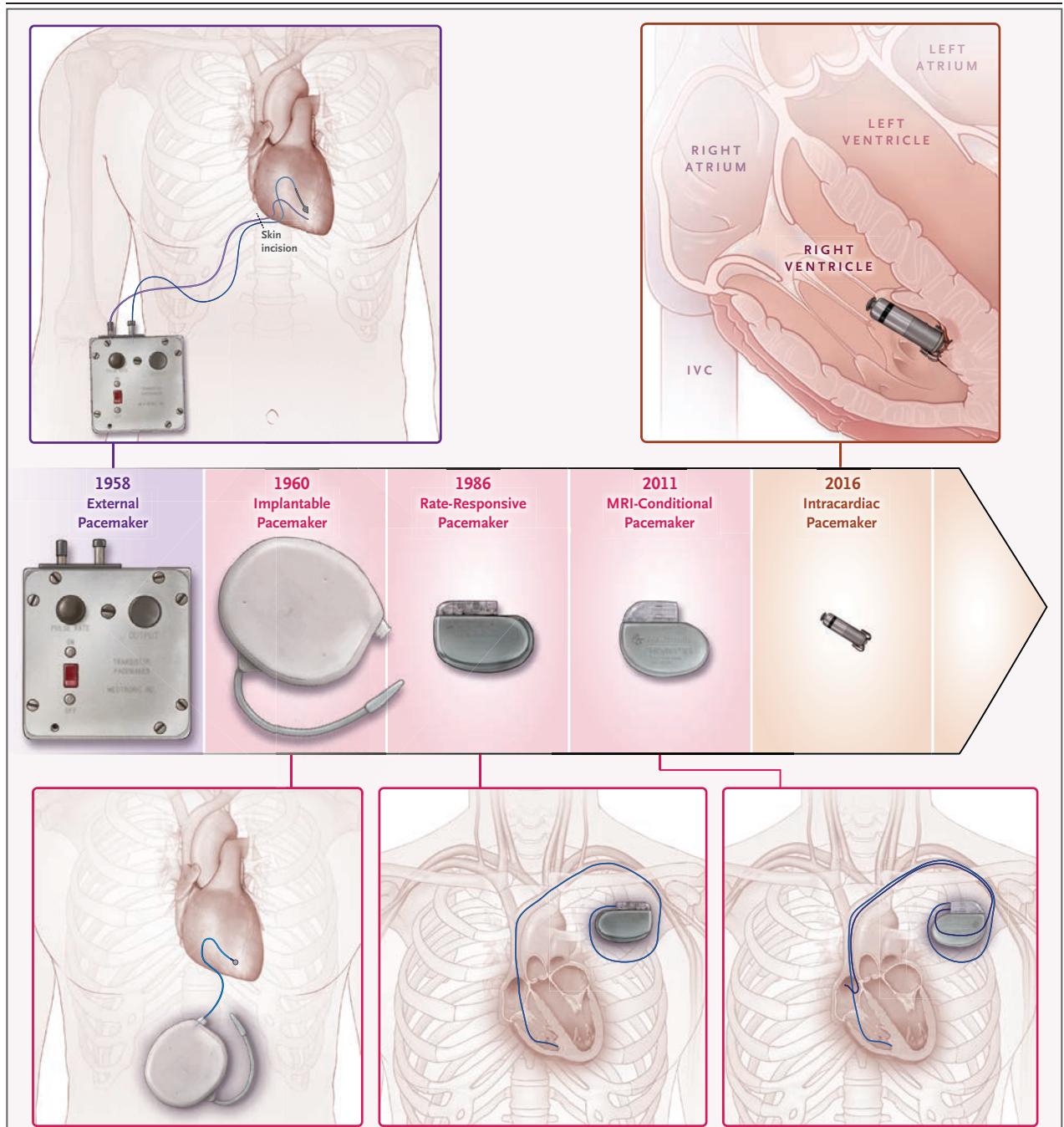
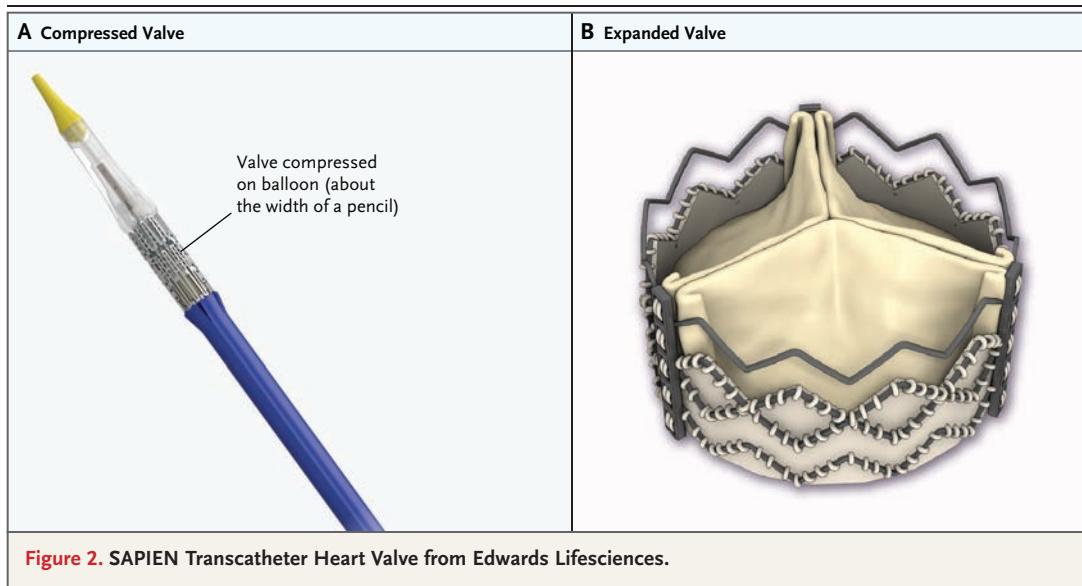


Figure 1. Representative Cardiac-Pacing Devices over Time.
 Shown are devices developed by Medtronic. IVC denotes inferior vena cava.

proval for medical devices are as varied as the devices themselves. Because the U.S. regulatory standard for approval is reasonable assurance of safety and effectiveness whereas most other countries use a safety and performance standard, generally more clinical data must be collected and larger clinical studies must be conducted to sup-

port U.S. marketing approval. The FDA works with sponsors to develop a clinical trial design and statistical analysis approach that is best tailored to the technology, the medical need being addressed, the feasibility of data collection, and the benefits and risks to affected patients. In some cases, the FDA expects and is provided



with clinical data from trials that are similar in design to a “gold standard” drug trial — large, blinded, randomized, controlled trials. For many devices, however, such designs are impractical or unnecessary. Often, the clinical data are confirmatory to extensive bench studies, studies in animals, and modeling studies that provide essential information on safety and effectiveness.

The FDA also recognizes that, for some technologies intended to address important unmet needs, it may be appropriate to accept a greater degree of uncertainty in order to expedite the availability of the device for patients, relying on postmarketing data to provide greater certainty about the safety or effectiveness of a device. This is the concept behind the FDA Expedited Access Pathway for “breakthrough” medical devices.²⁵ For other devices that are already available in other geographic locations or for other indications, there may be existing data — from registries or studies outside the United States — available to support approval. Advancements in the science of patient input are also needed to help ensure that clinical trials are designed to assess what matters most to patients and to facilitate patient enrollment in studies. In this spirit, we have been working with patient groups and other groups to foster the evaluation of patient preferences for benefits and acceptability of risks of devices for particular diseases to inform device-approval decisions. In the future, we see such data generation helping to inform the development of medical-device clinical trials and becoming a routine part of those trials.^{26,27}

The FDA has taken a number of actions to expedite the safe initiation of clinical trials in the United States and to collaborate with trial sponsors, the professional–provider community, and patients to design better trials — ones that are robust, reasonable, and efficient. However, to make well-informed decisions, practitioners, patients, and payers often need additional data on the benefit–risk profile of the device as compared with available alternatives, as well as a deeper understanding of the device derived from greater patient exposure in clinical practice. Because generating such evidence before marketing may inappropriately delay patient access to important technologies in some cases or may not be within FDA authority to require, it is critical that other stakeholders, such as the industry and the practitioner communities, support and provide additional evidence in the form of trials, registries, or analyses of data from health records. This challenge is not unique to the United States. Strategic investments and collaboration to establish a medical-device national evaluation system that are currently under way could improve the efficiency, timeliness, and comprehensiveness of postmarketing evidence generation.^{28–30} Such partnerships on a national and an international level are needed to ensure that appropriate data collection continues throughout the life cycle of a medical device as part of a learning health care system so that patients and practitioners are fully informed as to how best to use these technologies to support improved patient health and quality of life.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the following FDA scientists for their contributions to the information provided in this article: Martha Betz, Robert Califf, Erin Cutts, Vincent Devlin, Andrew Farb, Steve Kurtzman, John Laschinger, Bernard Lepri, Herbert Lerner, Mark Melkersson, Pablo Morales, Caroline Rhim, Laura Thompson, Ingmar Viohl,

Changfu Wu, and Xiaolin Zheng; Anne M. Gillis, M.D., of the Libin Cardiovascular Institute of Alberta and Alfred E. Buxton, M.D., of Beth Israel Deaconess Medical Center in Boston for advice regarding the information presented in Figure 1; and Ryan Mathre and Melanie Vincent of Medtronic and Sylvia Wrobel of Edwards Lifesciences for providing images to support this article.

REFERENCES

- Public Law 94-295. Medical device amendments of 1976. May 28, 1976 (<http://www.gpo.gov/fdsys/pkg/STATUTE-90/pdf/STATUTE-90-Pg539.pdf>).
- Rados C. Medical device and radiological health regulations come of age. *FDA Consum* 2006;40:58-65.
- The 510(k) program: evaluating substantial equivalence in premarket notifications [510(k)] — guidance for industry and Food and Drug Administration staff. Silver Spring, MD: Food and Drug Administration, 2014 (<http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf>).
- Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-38.
- Summary of safety and effectiveness data for PMA P010012/S230. Silver Spring, MD: Food and Drug Administration, 2010 (http://www.accessdata.fda.gov/cdrh_docs/pdf/P010012S230b.pdf).
- Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012;60:1297-313.
- Summary of safety and probable benefit for HDE H110002. Silver Spring, MD: Food and Drug Administration, 2013 (http://www.accessdata.fda.gov/cdrh_docs/pdf11/H110002b.pdf).
- Summary of safety and effectiveness data for PMA P150003. Silver Spring, MD: Food and Drug Administration, 2015 (http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150003b.pdf).
- Summary of safety and effectiveness data for PMA P140012. Silver Spring, MD: Food and Drug Administration, 2015 (http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140012b.pdf).
- Ponce J, Woodman G, Swain J, et al. The REDUCE pivotal trial: a prospective, randomized controlled pivotal trial of a dual intragastric balloon for the treatment of obesity. *Surg Obes Relat Dis* 2015;11:874-81.
- Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA* 2012;307:1838-47.
- Johnson DM, Sapirstein W. FDA's requirements for in-vivo performance data for prosthetic heart valves. *J Heart Valve Dis* 1994;3:350-5.
- Summary of safety and effectiveness data for PMA P100046. Silver Spring, MD: Food and Drug Administration, 2011 (http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100046b.pdf).
- De novo classification process (evaluation of automatic Class III designation) — draft guidance for industry and Food and Drug Administration staff. Silver Spring, MD: Food and Drug Administration, August 14, 2014 (<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm273903.pdf>).
- De novo summary for DEN120017. Silver Spring, MD: Food and Drug Administration, 2012 (http://www.accessdata.fda.gov/cdrh_docs/reviews/DEN120017.pdf).
- Summary of safety and effectiveness data for PMA P090013. Silver Spring, MD: Food and Drug Administration, 2011 (http://www.accessdata.fda.gov/cdrh_docs/pdf9/P090013b.pdf).
- Kalin R, Stanton MS. Current clinical issues for MRI scanning of pacemaker and defibrillator patients. *Pacing Clin Electrophysiol* 2005;28:326-8.
- Computational modeling and simulation (CM&S): paving the way for evaluation of 21st century medical devices. Minneapolis: Medical Device Innovation Consortium, 2015 (<http://www.MDIC.org/computer-modeling/>).
- Rumsfeld JS, Holmes DR Jr, Stough WG, Edwards FH, Jacques LB, Mack MJ. Insights from the early experience of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *JACC Cardiovasc Interv* 2015;8:377-81.
- Carroll JD, Shuren J, Jensen TS, et al. Transcatheter valve therapy registry is a model for medical device innovation and surveillance. *Health Aff (Millwood)* 2015;34:328-34.
- Hospital registry data quality process. Washington, DC: American College of Cardiology (<http://cvquality.acc.org/NCDR-Home/About-NCDR/Data-Quality/Hospital-Registry-Data-Quality-Process.aspx>).
- Summary of safety and effectiveness data for PMA P100041. Silver Spring, MD: Food and Drug Administration, 2011 (http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041b.pdf).
- Summary of safety and effectiveness data for PMA P110021. Silver Spring, MD: Food and Drug Administration, 2012 (http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110021b.pdf).
- FDA approval expands access to artificial heart valve for inoperable patients. Silver Spring, MD: Food and Drug Administration, September 23, 2013 (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm369510.htm>).
- Expedited access for premarket approval and *de novo* medical devices intended for unmet medical need for life threatening or irreversibly debilitating diseases or conditions — guidance for industry and Food and Drug Administration staff. Silver Spring, MD: Food and Drug Administration, April 13, 2015 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>).
- FDA. Patient preference information — submission, review in PMAs, HDE applications, and *de novo* requests, and inclusion in device labeling — draft guidance for industry, Food and Drug Administration staff, and other stakeholders. Silver Spring, MD: Food and Drug Administration, May 18, 2015 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf>).
- Medical Device Innovation Consortium (MDIC) patient centered benefit-risk project report: a framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology. Minneapolis: Medical Device Innovation Consortium, 2015 (http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf).
- Strengthening our national system for medical device postmarket surveillance. Silver Spring, MD: Food and Drug Administration, September 2012 (<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm301924.pdf>).
- Daniel G, McClellan M, Colvin H, Aurora P, Khaterzai S. Strengthening patient care: building an effective national medical device surveillance system. Washington, DC: The Brookings Institution, 2015 (<https://www.brookings.edu/research/strengthening-patient-care-building-an-effective-national-medical-device-surveillance-system/>).
- Krucoff MW, Normand S-L, Edwards F, et al. Recommendations for a national medical device evaluation system: strategically coordinated registry networks to bridge clinical care and research: a report from the Medical Device Registry Task Force and the Medical Devices Epidemiology Network — draft for public comment. Silver Spring, MD: Food and Drug Administration, August 20, 2015 (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM459368.pdf>).

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