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Transcatheter Valve Therapy Registry Is A Model For Medical Device Innovation And Surveillance

ABSTRACT Heart valve diseases are increasingly prevalent, especially in people older than age seventy. Many of these elderly people have other comorbid conditions, making them poor candidates for surgical treatment of heart valve diseases. Since 2011 such patients have been eligible to receive new nonsurgical heart valve treatments approved by the Food and Drug Administration (FDA) and covered by Medicare. This article examines the Transcatheter Valve Therapy Registry, which captures clinical information on all US patients undergoing new nonsurgical heart valve treatments. The registry has patient-level data from more than 27,000 patients treated with the novel devices. Patient- and procedure-related data are gathered from hospitals, patient-reported outcomes are assessed pre- and postprocedure, and longer-term data on mortality and repeat hospitalization are provided by linking the registry’s data to Medicare patient data. The registry is a model of collaboration among professional societies, the FDA, the Centers for Medicare and Medicaid Services, hospitals, patients, and the medical device industry. It has been used to support Medicare coverage decisions, expand device indications, provide comprehensive device surveillance, and establish national quality benchmarks. Beyond having it serve as a collaborative model, future goals for the registry include shortening the FDA-approval timeline for devices, providing data for decision-making tools for patients, and public reporting of hospital performance.

As the US population ages, valvular heart disease poses an increasing public health burden. The need to develop therapeutic strategies prompted the introduction of a new class of medical devices including catheter-based valve replacement and repair in the past three years.

The gold standard for treatment of heart valve abnormalities has been open-heart surgery. For some elderly and high-risk patients, though, this surgical approach either is not feasible or has risks that are prohibitive.

Less invasive, nonsurgical procedures to treat heart valve diseases are termed transcatheter valve therapies. These therapies use a catheter delivery system inserted into the body from an artery or a vein and guided by medical imaging to place the heart valve device while the heart continues to beat.

The clinical trials for the therapies initially focused on patients who were inoperable or had a very high risk with surgery. The safety and effectiveness of three devices were proven in industry-sponsored clinical trials in the United States and other countries. Following these tri-
als, the Food and Drug Administration (FDA) approved the devices, and the Centers for Medicare and Medicaid Services (CMS) determined that the devices would be covered.

Such new treatments have large gaps in knowledge, which limits the ability of clinicians and patients to make informed and personalized decisions. To overcome the knowledge gaps associated with the devices, the Transcatheter Valve Therapy Registry was created to address patient care goals in a timely fashion, objectively, and with actionable knowledge.3

The Registry

The Transcatheter Valve Therapy Registry enrolls all US patients receiving novel heart valve devices at all sites—that is, hospitals, where the treatment is available. For each patient, more than 300 pre- and postprocedure data elements are gathered and entered into the registry by hospital personnel. The data elements include the indication for the procedure; patient characteristics; procedural results and complications; in-hospital, thirty-day, and subsequent yearly outcomes; and patient health status measures. The registry data collection form and dictionary are available at http://www.tvtregistry.org.

The Society of Thoracic Surgeons and the American College of Cardiology, two professional societies, collaborated to create and administer this new registry. The two societies, the FDA, CMS, and the medical device industry collectively determined which data elements to be included in the registry. Harmonizing data elements and definitions with emerging standards was a top priority since different definitions have been used over the years in describing patient characteristics, procedure complications, and other important data elements.4

All patients receiving these medical devices are added to the registry, including those in whom the new technology is used “on label”—that is, according to FDA-approved indications—and “off label”—that is, when clinicians have patients who fall outside the FDA-approved indications, which is a common occurrence in clinical practice. This provides data to fill the knowledge gap that exists for off-label uses and allows an objective assessment of whether off-label uses are achieving reasonable safety and effectiveness goals in patient populations not studied in premarket pivotal trials.

The completeness and accuracy of data entered by hospital employees have been addressed by multiple mechanisms.5 For this registry, automatic data completeness and value checks are used. A pilot audit program has been designed, and an external auditing group is under contract to begin the audit of 8 percent of participating hospital sites in 2015. Auditing will include the accuracy of sixty-five data elements deemed to be of critical value by the registry steering committee. A novel streamlined adjudication process is used for key data elements to verify that outcomes are uniformly and accurately reported. Site data managers have access to support staff, attend an annual national meeting, and are provided with web-based educational seminars.

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The Regulatory Process And Postapproval Period

The regulatory process for US market approval of new high-risk devices has several components. The first component is conducting premarket trials of medical devices. These pivotal trials are used to gain FDA approval by demonstrating the safety and effectiveness of the devices compared to existing treatments. However, these trials are often conducted in specialized centers treating only very carefully selected patients who represent a fraction of the total population that may benefit from treatment.

Later steps in the post–regulatory approval period involve broader issues and goals, including how to improve patient outcomes, refine appropriate patient selection criteria, monitor device safety, potentially expand the indications for use of the device, and develop benchmarks of hospital performance. The registry helps address these issues and goals by collecting comprehensive patient-level data in order to function as a rapid learning system and to meet the needs of multiple stakeholders (patients, clinicians, hospitals, regulatory agencies, payers, and medical device companies).5

Traditionally, each stakeholder has used separate approaches to gather data. For example, the FDA may require medical device companies to conduct postapproval studies.6 Additional tools may be used for monitoring device safety. CMS may use another approach, coverage with evidence development, to assess whether new treatments meet its goals.7 Professional societies may develop separate clinical registries to gather data to develop practice guidelines. This “Tower of Babel” of different and separate data collection systems is inefficient, costly, and ill fated.

In contrast to the Tower of Babel approach, the FDA made the development of national and international device registries for selected products a key pillar of its strategy to strengthen the national system for medical device postmarket surveillance.8 This registry system should have patient data on virtually all procedures, real-world generalizability, scalable and reusable infrastructure, continuous accrual of
information for near real-time analysis, and the use of structured data with standardized nomenclature and definitions. For example, structured data on a patient’s symptoms of heart failure require entry into one of four well-defined data fields—that is, categories of severity that are widely used in cardiovascular medicine. (An unstructured approach would be for the local physician to describe a patient’s symptoms using free text and any adjectives the physician chooses to use.) Such a registry system would be capable, as it matures, of providing assessments of the benefits and risks of medical devices, identifying potential safety signals, reducing the burden and cost of device performance surveillance, and facilitating the clearance and approval of new devices or new uses of existing ones.

CMS made participation in a national registry a condition of coverage for the nonsurgical, transcatheter aortic valve replacement technology in a national coverage determination in 2012. In 2014 CMS issued a national coverage determination (a process by which Medicare determines that it will pay nationally for a new benefit or service) for nonsurgical, transcatheter mitral valve repair and made participation in a national registry a condition of coverage. The participation of CMS in the registry also set the stage for subsequent linkage of patients in the registry to CMS administrative claims to track long-term patient outcomes.

The Medical Devices
Abnormalities of the aortic and mitral valves are the most commonly encountered abnormalities of heart valves in adults. The most common problem of the mitral valve involves the valve not closing completely—that is, being regurgitant or incompetent in preventing backward flow of blood. The most common problem of the aortic valve involves the valve not opening completely—that is, being narrowed or stenotic.

The medical devices treating these abnormalities may be a completely new valve or a device that repairs the valve. The registry currently captures transcatheter aortic valve replacements for aortic stenosis and transcatheter mitral valve repair technology for mitral regurgitation.

Patients being treated are currently categorized by whether or not they are candidates for surgery and their estimated risk of conventional surgery as determined by a local heart team. The Society of Thoracic Surgeons has an established database that has captured twenty-five years of outcomes from patients undergoing surgical operations in the United States, and an algorithm was developed to predict the outcome risk for individual patients having surgical valve replacement or repair.

Patients thought to be inoperable or who have prohibitive risk for surgery were the first to receive transcatheter aortic valve replacements and transcatheter mitral valve repairs. Since this initial FDA approval, the transcatheter aortic valve replacement procedure has been extended to patients thought to be at high risk, but not prohibitive risk, for surgery. The registry captures the reasons they are felt to be inoperable or at high risk.

Exhibit 1 shows the timeline on which these treatments became available and the activities of the registry.

New Technologies

TRANSCATHETER AORTIC VALVE REPLACEMENT
The first transcatheter aortic valve replacement technology to be submitted and gain approval from the FDA was the Sapien transcatheter heart valve from Edwards Lifesciences Corporation. A US trial demonstrated a highly significant survival advantage of this procedure over medical therapy in patients with severe aortic stenosis who had been deemed inoperable by heart surgeons. The FDA approved the use of the device in 2011 with the restriction that the procedure had to be performed by an approach through the femoral artery in the leg. The second trial demonstrated similar outcomes of transcatheter aortic valve replacements when compared to surgery in patients deemed high-risk surgical candidates, which led the FDA to extend approval in 2012 of the device for use in high-risk surgical patients when performed by either the femoral artery or an “alternative access” approach (that is, a site of inserting the valve delivery system when the femoral artery site was not feasible). The next version with a smaller delivery profile, Sapien XT, was approved in 2014.

The second FDA-approved transcatheter aortic valve replacement technology was the CoreValve from Medtronic Inc. Approval occurred in 2014. The pivotal trial showed that the CoreValve produced superior results and lower mortality compared to traditional surgery.

TRANSCATHETER MITRAL VALVE REPAIR
The third technology included in the registry was the first approved transcatheter mitral valve repair technology. The MitraClip from Abbott Vascular treats patients with significant, symptomatic mitral regurgitation. FDA approval in 2013 followed a series of trials on the device. The MitraClip is approved for patients with degenerative mitral regurgitation who are at prohibitive risk for open surgical mitral valve repair or replacement. Shortly after FDA approval, CMS issued a national coverage determination open-
ing the way for Medicare coverage consistent with the FDA label and required participation in a registry. Illustrations of the devices are available in the online Appendix.

Registry Achievements
The registry has created a data repository of all approved relevant technologies. As of December 2014 more than 27,000 patient records representing virtually all patients treated with these medical devices for aortic stenosis and mitral regurgitation in the United States have been entered into the registry. Transcatheter aortic valve replacements are now available in 354 US hospitals, and transcatheter mitral valve repairs are available in 100 US hospitals.

The registry includes patient input. Before and after the procedure, patients use a standardized questionnaire to report their health status (symptoms, functional state, and health-related quality of life). Patient representatives and advocacy groups are also part of a stakeholder advisory committee and provide unique guidance on how the results can be made useful for patients and families. A Patient-Centered Outcomes Research Institute grant was awarded in late 2013 to the Duke Clinical Research Institute, which uses the registry data to enable the development, testing, and distribution of a tool to assist patients and families to make informed decisions for both transcatheter aortic valve replacement and open-heart surgery. By using the experience of the thousands of patients having received these devices and collected in the registry, future patients will be able to make better decisions based on data and individualized assessments of risks and benefits.

The registry, unlike other cardiovascular treatment registries, tracks long-term outcomes rather than only the immediate outcomes of procedures and surgery. A registry of implantable

### Exhibit 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1948</td>
<td>First surgical heart valve replacement performed in United States by Harken</td>
</tr>
<tr>
<td>1948–2012</td>
<td>Open-heart surgery is exclusive gold standard</td>
</tr>
<tr>
<td>2002</td>
<td>First transcatheter aortic valve replacement (TAVR) performed in France by Cribier</td>
</tr>
<tr>
<td>2005–12</td>
<td>US trial (EVEREST 2) of MitraClip enrolled 279 patients from September 2005 to November 2008</td>
</tr>
<tr>
<td>2007</td>
<td>CE Mark approval—that is, conformity with European community standards—of the two TAVR technologies: CoreValve and Sapien</td>
</tr>
<tr>
<td>2008</td>
<td>CE Mark approval of transcatheter mitral valve repair (TMVR) technology, MitraClip</td>
</tr>
<tr>
<td>February 2011–September 2012</td>
<td>US trial of CoreValve: 506 inoperable and 795 high-risk patients enrolled</td>
</tr>
<tr>
<td>2011 July</td>
<td>FDA advisory panel recommends Sapien approval; Transcatheter Valve Therapy (TVT) Registry begins to be organized</td>
</tr>
<tr>
<td>2011 November</td>
<td>FDA approves Sapien for inoperable patients with valve inserted via the femoral artery</td>
</tr>
<tr>
<td>2011 December</td>
<td>TVT Registry becomes operational</td>
</tr>
<tr>
<td>2012 May</td>
<td>CMS issues national coverage determination covering TAVR under coverage with evidence development</td>
</tr>
<tr>
<td>2012 October</td>
<td>FDA extends Sapien approval to high-risk patients using femoral or other access</td>
</tr>
<tr>
<td>2013 September</td>
<td>FDA extends Sapien using registry data to inoperable patients for all vascular access</td>
</tr>
<tr>
<td>2013 October</td>
<td>TVT Registry: 10,000 patient records entered</td>
</tr>
<tr>
<td>2013 October</td>
<td>FDA approves MitraClip for prohibitive-risk, degenerative mitral regurgitation patients</td>
</tr>
<tr>
<td>2013 November</td>
<td>TVT Registry creates a new module for mitral valve transcatheter technologies</td>
</tr>
<tr>
<td>2014 January</td>
<td>FDA approves CoreValve for extreme-risk patients, and TVT Registry includes it</td>
</tr>
<tr>
<td>2014 June</td>
<td>FDA extends CoreValve for high-risk patients</td>
</tr>
<tr>
<td>2014 June</td>
<td>FDA approves Sapien XT, a next-generation TAVR device</td>
</tr>
<tr>
<td>2014 June</td>
<td>TVT Registry modified to include Sapien XT</td>
</tr>
<tr>
<td>2014 August</td>
<td>CMS issues national coverage determination for TMVR under coverage with evidence development</td>
</tr>
<tr>
<td>2014 December</td>
<td>TVT Registry: more than 25,000 patient records entered</td>
</tr>
</tbody>
</table>

Source: Authors’ analysis.
cardiac defibrillators designed in the past is considered in the opinion of some as an example of a less successful device registry, in that it lacked prospective long-term outcome assessments. The registry of transcatheter valve therapies has already been used to successfully link patient-specific data to Medicare claims in order to provide one-year mortality and rate of recurrent hospitalization data. The link between the registry and Medicare claims can be used going forward to provide even longer-term data.

The registry will also enhance the cardiac field’s ability to compare effectiveness of different treatments for valve disease. Registry data were analyzed in association with data from the Society of Thoracic Surgeons’ national database to compare transcatheter aortic valve replacements with surgical aortic valve replacement.24

The registry provides data and analytics to the FDA, CMS, and device companies to facilitate improvements in the robustness, timeliness, and cost of evidence generation to meet regulatory and coverage standards. The current uses of registry data by the FDA are discussed below.

Postmarket studies for all three technologies are now imbedded in the registry. This allowed a much more comprehensive postmarket study process and eliminated the need for an expensive, separate postmarket study infrastructure.6

The FDA has expanded the indication for use of the Sapien valve using registry data.25 Specifically, the Sapien device was approved for implantation using alternative insertion techniques in patients deemed inoperable for open-heart surgery.

The registry strengthens the national system of medical devices postmarket surveillance by including unique device identifiers.6 Novel automatic adverse signal detection algorithms for these medical devices will shortly undergo a pilot test on registry data. These efforts should make it easier to monitor device safety and improve the efficiency of recalls if needed. Adverse events are reported to the registry by hospital sites, and the accuracy of this process will be assessed with audits in 2015.

The registry has been expanded to include the investigational Sapien 3 valve. This data collection is part of a continued access trial that is an extension of the pivotal trial of this medical device.26 Up until this development, the registry had been used only for FDA-approved, commercially available devices.

The registry is one of several ongoing FDA initiatives to establish international registries for specific high-impact treatments and disease states that may serve as models to accelerate the evolution toward a modern electronic worldwide clinical and device surveillance data infrastructure.27,28

The registry was a key part of a coordinated effort by the FDA, CMS, relevant professional societies, and the medical device industry to guide and assess the process of rational dispersion of this technology to only qualified hospitals.29 Both transcatheter aortic valve replacement and transcatheter mitral valve repair procedures require special skills, novel facilities, and a multidisciplinary team not commonly required in most cardiovascular therapies. In October 2014 all participating sites in the registry received a report of their site outcomes, including national benchmarks to use in comparing their performance to that of others.

Assessing the performance of sites and publicly reporting their results has multiple challenges that must be addressed before scientifically valid and clinically meaningful results can be released. Mortality rates must be adjusted to patient characteristics since the condition of a patient is a major determinant of mortality rates and other outcomes from these procedures. Over the course of the first two years of the registry’s existence, data were collected to enable a risk-adjusted mortality rate algorithm to be developed and validated. Site performance in 2015 can now be reported with this essential adjustment. There are other challenges in the assessment of site performance including the determination of statistically significant and clinically meaningful differences in performance. The volume of procedures being performed may or may not influence a hospital’s performance, and this relationship must and will be studied in 2015. A factor to balance with site volume is reasonable patient access to a hospital performing these procedures. Most patients cannot travel to remote nationally prominent centers that treat large volumes of patients.

Among the innovative aspects of this registry is the collaborative model of different stakeholders to create, operate, and fund it. The FDA and CMS participate as ex officio members of the registry steering committee. A stakeholder advisory committee provides input to the steering committee from patients, hospitals, and the medical device industry.

Challenges

The registry is in the spotlight of being, on the one hand, an example of a learning system and, on the other hand, existing within the ethical and legal boundaries of sharing patient-level data, albeit deidentified for most applications. The primary goal of clinical registries, including the Transcatheter Valve Therapy Registry, is to
enable quality assessment and improvement as part of hospital operations. This goal is built into registries’ design and the reporting of results. Patient-level data can also be used to create new knowledge to further improve patient care. Recent publications have discussed the ethical and regulatory aspects of clinical registries and their mixed role in supporting quality improvement and research.30–32 Safeguarding privacy is a top priority for the two professional societies that manage the registry.

Patients do not have to provide written informed consent for their data to be included in the registry and used to create new knowledge. The societies submitted a research protocol to a central Institutional Review Board (IRB) regarding the use of the data. The societies received a waiver of informed consent under the Common Rule based on the IRB finding that the registry constitutes a minimal risk to the patient.30 Because the societies, as sponsors of the registry, have IRB approval and a waiver of informed consent and because the data are already routinely collected, individual sites participating in the registry do not under federal law need to obtain local IRB approval prior to enrolling in the registry. However, specific research proposals such as that involving prospective gathering of additional data elements not routinely collected as part of clinical care would likely need appropriate IRB approval.

The collection of data for the registry places a work and cost burden on hospitals. While some data elements in the registry are reliably and easily extracted from the electronic health record (EHR), most are not. The current state of EHRs is not optimized for data export to national registries. It is hoped that funding and policies for EHR systems will be aligned to increase clinical registries’ ability to provide rapid, accurate, and shared patient-level data.

A reduction of the number and type of the registry data elements has occurred, but there remain more than 300 data elements. Further simplification of the data collection forms will occur as the technology matures and understanding of issues such as patient selection becomes more optimal. A first reduction in the number of data elements could not be done until it was determined they did not provide value such as being needed to develop the risk-adjusted algorithm for procedure mortality.

The sustainability of the registry is a challenge. One of the reasons for almost universal participation of clinical sites in the registry was CMS’s decision to cover the therapies listed in the registry through a national coverage determination. However, once evidence is mature, coverage requirements for continued registry participation would need to be reviewed. This leads to the need for a sustainability strategy of the registry based on demonstration of value to the various stakeholders.

The initial funding model was based on investment of the two professional societies involved, site fees, and industry fees for data collection for postapproval studies of the devices and potential expansion of indications for their use. Site fees paid by hospitals are $25,000 for the first year and $10,000 for subsequent years. The benefits to hospital sites included reports on their program’s outcomes with risk adjustments, meeting CMS requirements for coverage, and a variety of educational and data tools to enable local quality improvement processes. The funding model in the future may be modified as the registry plays a central role in device surveillance and premarket approval studies.

US health policy makers also must support sustainability. Coverage models that reward quality of care should include participation in data gathering and sharing to create actionable knowledge to implement further improvements in the quality of care.

Conclusion
The Transcatheter Valve Therapy Registry represents a novel multistakeholder collaboration that facilitates and accelerates the learning process during the introduction of revolutionary new treatments for heart valve abnormalities. The learning process begins with individual patient data, grows into big data with advanced analytics, and then translates into actionable improvements in clinical care as well as improvements in patient-centric medical device regulation.

John Hernandez is an employee of Abbott Vascular, Larry Wood is an employee of Edwards Lifesciences Corporation, and Richard Kuntz is an employee of Medtronic.

NOTES
2 Holmes DR Jr, Mack MJ.
18 To access the Appendix, click on the Appendix link in the box to the right of the article online.
27 Food and Drug Administration. Medical Device Epidemiology Network Initiative (MDEpiNet) [Internet]. Silver Spring (MD): FDA; [cited 2015 Jan 8]. Available from: http://www.fda.gov/MedicalDevices/ScienceandResearch/EpidemiologyMedicalDevices/MedicalDeviceEpidemiologyNetworkMDEpiNet/default.htm