The STS-ACC Transcatheter Valve Therapy National Registry

A New Partnership and Infrastructure for the Introduction and Surveillance of Medical Devices and Therapies

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A novel, national clinical registry program for new transcatheter valve therapy (TVT) devices has been created through a partnership of The Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC). The STS/ACC TVT registry (NCT01737528) was developed in close collaboration with the Food and Drug Administration, the Center for Medicare and Medicaid Services, and the Duke Clinical Research Institute. The registry will serve as an objective, comprehensive, and scientifically based resource to improve the quality of patient care, to monitor the safety and effectiveness of TVT devices, to serve as an analytic resource for TVT research, and to enhance communication among key stakeholders. (J Am Coll Cardiol 2013;62:1026–34) © 2013 by the American College of Cardiology Foundation

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as an analytic resource for TVT research, and to enhance communication among key stakeholders.

The TVT registry was publicly proposed by professional society leadership with the endorsement of the FDA and panel members at the FDA Cardiovascular Circulatory Device Expert Panel meeting in July 2011. It became operational on December 1, 2011.

### Why We Need a TVT Registry

The FDA is the primary authority in the United States to regulate medical devices and is required by law to provide “reasonable assurance of safety and effectiveness.” Once regulatory approval of a medical device has been granted, post-market surveillance is performed to ensure that safe and effective use of the device continues in the general population. However, the infrastructure for gathering and analyzing device use in the U.S population has been problematic and inadequate. There have been calls for the “professional societies, the medical device industry, and the FDA to mobilize available resources to improve post-market surveillance” (1,2).

Transcatheter aortic valve replacement (TAVR) for aortic stenosis using the Sapien valve from Edwards Lifesciences, Inc., has received FDA approval for patients considered inoperable for surgery. On June 13, 2012, an FDA Advisory Panel voted in favor of extending approval of the Sapien technology to high-risk patients including the use of the transapical approach in addition to the transfemoral route of vascular access for device delivery (3). Full FDA approval was subsequently announced (4).

Other transcatheter therapies for valvular heart disease are being developed and the TVT registry has been designed to facilitate their incorporation. The process of adding new technologies, such as transcatheter mitral repair technology, involves significant planning including identifying data elements that must be captured in a fashion that is standardized, well-defined, and harmonized with the clinical trials leading to regulatory approval.

The introduction of new treatment options presents challenges that are magnified when the therapy represents a substantial transformation of both patient care and the process of care to deliver the new therapy. Rational dispersion of TAVR into centers with sufficient experience and patient volume may maintain the reported results of the PARTNER trial in inoperable and/or high-risk patients with aortic stenosis (5). An expert consensus document on transcatheter valve therapy has outlined the initial technology, the targeted patient population, the multidisciplinary heart team, the specialized facilities needed, and the critical need for a new type of device registry (6). Some of the proposed uses of the registry are described in Table 2.

The Center for Devices and Radiological Health at the FDA has embarked on a substantial effort to strengthen post-market device surveillance. They and others have encouraged the use of professional clinical registries for post-approval studies (7,8). The TVT registry will provide the data gathering and analysis infrastructure to enable comprehensive monitoring of device safety and performance throughout the device life cycle in all patients being treated with this technology. The TVT registry will also incorporate “unique device identifiers” being introduced in 2013 by the FDA as another effort to improve the safe and effective use of medical devices (9).

When new and potentially high-risk technologies come to market, the FDA mandates the medical device companies to carry out PAS. Traditionally, manufacturers have devoted considerable effort and expense to develop a registry to fulfill PAS requirements that is often created as a stand-alone project, uses separate data elements and endpoints, and has little coordination with other registry efforts. This has led to predictable inconsistencies in cardiovascular data reporting and safety surveillance efforts. Furthermore, industry studies have typically not been open to independent data analysis, and potential conflicts of interest exist when a manufacturer conducts studies of its own device.

The TVT registry represents a new model combining the needs of the medical device industry, regulatory and reimbursement agencies, clinicians, hospitals, patients, researchers, and professional societies. The STS National Database and the ACC’s National Cardiovascular Data Registry (NCDR) have the ability to coordinate the development and execution of this national registry and have developed other mature national registries with well-defined protocols for data collection and audits to ensure high quality.

### Unique and Innovative Aspects of the TVT Registry

The TVT registry will have multiple innovations.

**Immediate focus on critical issues.** Initial TAVR clinical trials and FDA panel experts have identified the risk of stroke, paravalvular regurgitation, outcomes differences between sexes, vascular complications, and device durability as key issues. The TVT registry has been designed to further clarify these issues.

**Long-term and quality-of-life outcomes.** The TVT registry will be linked to CMS claims data to evaluate longitudinal patient outcomes, including hospitalizations and survival. This strategy has been successfully used by the STS and NCDR registries to examine long-term coronary revascularization outcomes (10–12). Moreover, after the
CMS coverage criteria, the TVT registry also includes collection of quality-of-life measures. The primary measure will be the Kansas City Cardiomyopathy Questionnaire (KCCQ), a valid and reliable measure of patient-reported symptom burden, functional status, and quality of life that is sensitive to clinical change and has been used in TAVR patients (13).

**Risk models tailored for the TVT population.** Models of outcomes will be developed and validated using TVT registry data that will be used for benchmark comparisons of risk-adjusted outcomes among centers, and can potentially provide personalized risk estimates to support informed decisions by patients and clinicians regarding the likelihood of benefits and complications.

** Appropriateness of use.** Data collected over years can be analyzed for the appropriateness of the procedure correlating patient characteristics with post-procedural outcomes. With the procedure indications thus defined, it will then be possible to effectively monitor for potentially appropriate or inappropriate “indication creep.”

**Expansion of indications for use.** The TVT registry will gather data on device use in ways not originally intended using clinical research protocols imbedded in the registry. “Valve-in-valve” (the placement of TVT valves in degenerated surgical bioprostheses) and alternative vascular access (i.e., transapical, transaortic, trans-subclavian, and transiliac) are uses of TAVR technology not part of FDA-approved indications from November 2011 and not covered by the CMS national coverage decision (NCD) from May 2012 for the Sapien valve use in inoperable patients. Part B of the CMS NCD provides reimbursement of procedures performed as part of a CMS-approved research study (14). After months of developing a new model for a TVT registry-based IDE study, the STS and ACC submitted to CMS and FDA a research proposal to study alternative access for inoperable patients. The FDA has recently approved the IDE study (G120291); the clinical trial number has been issued (NCT01787084); CMS has approved the research proposal; and the study will soon be initiated and be open to all qualifying and compliant TAVR sites in the United States. This unique study is also constructed so that the scientific evidence developed can be used by the FDA to expand indications.

**Nested PAS studies.** Data for FDA-mandated PAS will be nested within the TVT registry and will satisfy the FDA requirements placed on the sponsor. The registry design can accommodate differences in the scope of data collection and operation as requested by the FDA for the sponsor. The
entire TVT registry population may be used for future PAS studies.

**Linkages to Other Registries and Relationship to Randomized Clinical Trials**

The TVT registry is a registry focused on new transcatheter technologies, is not a comprehensive disease-based registry, and, by itself, cannot be used to compare treatment alternatives or to establish appropriateness or one treatment versus another. Links can and will be made to the STS Adult Cardiac Surgery Database to compare open surgical techniques to TVT techniques. For other patients who have neither surgery nor TVT, there will be the need to gather data on medical management from PINNACLE (Practice Innovation and Clinical Excellence), a NCDR registry of out-patient quality improvement, or other sources.

Registries, such as the TVT registry, can support observational studies but are not a substitute for randomized clinical trials (RCT) when needed to control for selection bias. However, the network of hospitals involved in the TVT registry may be useful for the recruitment and conduct of RCTs. Data from the TVT registry may be helpful in planning RCTs, and/or may be useful within an RCT conducted using the TVT registry sites/infrastructure, leading to a more efficient clinical trial.

**The TVT Registry Defined**

The TVT registry is placed in the context of the FDA’s medical device regulatory process (Fig. 1) and is a next generation of prospective registries implemented with the introduction of new technologies into real-world practice. Initially, the registry will contain data on only 1 TAVR device but it eventually can include all future approved technologies in the TVT domain.

The TVT registry is a national registry in the United States. More than 50,000 TAVR procedures have been completed after commercial release in 46 countries worldwide. Reports in 2011 from registries in Canada (15), Italy (16), Germany (17), France (18), and the United Kingdom (19) included 2,817 patients. Subsequently, in 2012, the German Registry (GARY) has been described in detail with >15,000 datasets entered (20). Most recently, the Transcatheter Valve Treatment Sentinel Pilot Registry, a prospective independent consecutive registry, reported 4,571 patients undergoing TAVI between January 2011 and May 2012 in 137 medical centers of 10 European countries (21). The groundwork for TVT worldwide registries has been laid.

In a paradigm shifting approach to surveillance, the FDA has recently initiated efforts to facilitate and promote the development of international registry consortia with the goal to augment the infrastructure for evidence generation,
synthesis and appraisal of device performance, and clinical outcomes throughout the product life cycle. Notably, in 2011, the International Consortium of Orthopedic Registries was created, consisting of 29 orthopedic registries from 14 nations and capturing 3.5 million procedures involving orthopedic implants worldwide (22). The FDA also initiated efforts to develop an international consortia of cardiovascular registries (23).

The TVT registry is listed in the U.S. National Institutes of Health clinicaltrials.gov (NCT01737528) as part of this database of clinical studies conducted worldwide.

**Patient Composition and Enrollment in the TVT Registry**

In the past, studies reported from some registries were difficult to interpret because of potential selection bias and lack of knowledge of the overall population. The TVT registry with its expected inclusion of most, if not all, treated patients in the United States should eliminate this concern.

Several factors will likely result in a high rate of enrollment. The CMS NCD includes a requirement that TAVR will be covered for Medicare beneficiaries only if the patient is enrolled in a prospective national registry (14). Furthermore, institutions need a site-specific analysis of their programs compared to benchmarks from a nationwide experience. PAS studies may be required to use a national registry. Figure 2 shows the growth of formal participation of the TVT registry, and Figure 3 shows the number of patient records submitted from the initial TAVR procedure. As of August 7, 2013 there have been 245 sites in the United States formally enrolled in the TVT registry.

Clinical registry data collection is considered a part of an institution’s quality assessment and improvement process and therefore does not require specific written informed patient consent. The TVT registry complies with the relevant regulations relating to the protection of human research subjects, and this protocol is part of the TVT registry that has undergone and had been given approval by an independent institutional review board review from Chesapeake Research Review Inc. There is no added procedural risk to patients through involvement in the TVT registry. Patient data used in potentially CMS-approved studies on such topics as valve-in-valve and alternative access approaches are collected using only data elements included in the original TVT registry and undergoing variations in the use of TAVR as decided by the clinicians caring for the patients. No risk or procedures beyond those required for routine care will be imposed. Conversely, if the goal of such studies is to expand a device’s indication, then a formal IDE may be necessary and this carries additional responsibilities and compliance issues that have been the subject of extensive discussions between the TVT registry and the FDA. Finally, participation in a specific prospective, FDA-regulated PAS may
require both institutional review board approval and written informed consent if the PAS involves collecting specific elements of personal health information or data for research purposes.

**Registry Data Elements**

The TVT registry data collection form and dictionary are available at the TVT registry website (www.tvtregistry.org). Version 1.1 has online data entry that became active in July 2012.

Although TAVR technology has led to some unique data elements, most elements and definitions are commonly included in other clinical registries. In the design of the TVT registry, particular attention was given to data elements and definitions that are harmonized with TAVR trials. The Valve Academic Research Consortium is a multiple stake holder group that has created consistent endpoint definitions and consensus recommendations for TAVR clinical research programs (24–26). These efforts have been valuable to the TVT registry focused on use of these technologies in real-world settings.

Echocardiographic data post-TAVR are also important parameters that will be captured in the TVT registry to assess prosthetic durability, but are currently not incorporated in clinical management guidelines (27).

**Data Entry, Monitoring, and Auditing**

Participating sites will submit complete periprocedural and short-term follow-up data on all patients who undergo a TAVR procedure. Outcomes beyond the first year will be captured through linkage with the CMS database.

The TVT registry will have an extensive data quality program including multiple mechanisms to monitor completeness and accuracy. These include site training and support by TVT registry staff, data “cleaning” by data integrity checks utilizing range validation and other measures, auditing at the site level portions of data, and adjudication of selected 30-day and 1-year outcomes. Collection of source documents and verification of pre-specified key events can be added specifically for PAS studies. Audit strategies will be executed by the FDA for the TVT registry. The Duke Clinical Research Institute will also provide event adjudication services for pre-specified events and other operational support.

**Reporting**

The TVT registry will provide feedback to sites including quarterly quality national benchmarking. Participants will have access to a repository of their own data and tools to evaluate their local practice and conduct user-specified local data queries. Heart teams will be encouraged to review
outcome reports for opportunities for improvement (28). The TVT registry will also issue annual reports at professional meetings of TAVR and future TVT technology that will include volume and outcomes. CMS-approved studies as described in part B of the NCD will be reported as specified in the protocol. The PAS studies will be reported as determined by its research and publications committee.

**Funding**

The investment to enable the creation of the TVT registry began 2 decades ago as STS and ACC founded their respective national clinical databases. The development of the TVT registry has been funded by STS and ACC. The on-going funding must maintain the independence of the governance and day-to-day activities of the registry.

Funding for operational expenses associated with TVT registry will predominantly be from site fees, namely, paid for by institutions with TVT programs. The FDA will provide some resources for monitoring the quality of data entered by sites through audits, particularly associated with PAS studies. Device PAS studies that are nested within the TVT registry will be appropriately funded by the sponsor. Investigator-initiated research will be able to access the data in the TVT registry with funding from private and public agencies. Funding for IDE studies may include support from industry, but strict firewalls have been placed to maintain the independence, impartiality, and scientific credibility of the professional societies in designing, conducting, and reporting trials. Both ACC and STS have formal rules for engagement with industry involving data use, scientific integrity, governance, marketing, and promotion (29–32).

**Governance**

The primary independent governing body is a steering committee of representatives from STS and ACC. Representatives from the Duke Clinical Research Institute, the National Heart, Lung, and Blood Institute, the FDA, and the CMS are nonvoting ex-officio members of the steering committee. The steering committee shall provide strategic direction for the TVT registry, monitor all activities, and have ultimate authority and responsibility for the scientific integrity and appropriate use of the TVT registry data for research and publications.

The research and publications subcommittee will oversee all activities related to research and publications using TVT registry data. Industry-sponsored PAS will have a separate research and publications committee. All committee members are required to submit relationship with industry information.

The stakeholder advisory group will provide input, guidance, and feedback to the steering committee on pertinent clinical and scientific topics. Members selected by the steering committee will represent stakeholders, including government entities, patient advocates, device manufacturers, and insurers.

**Challenges for the TVT Registry**

The principle challenges of the TVT registry include demonstration of its added value versus maintaining the status quo, justifying the burden of data collection, validating the completeness and quality of data, and being a professional “good shepherd” of using these data for objective, bias-free, and scientifically based reports. Furthermore, the TVT registry must be linked to other professional registries to enhance the efficiency of data entry, reduce redundancies, and to enable comparative effectiveness research and regulatory decision making.

National clinical registries are becoming part of the cost to offer high-end therapies such as ventricular assist devices, implantable defibrillators, and now TAVR. The burdens associated with entering high-quality data from hospitals are recognized and potentially will be reduced with medical information technology infrastructure improvements.

The costs of the TVT registry will need to be periodically assessed with transparency of the expenses and demonstration of the value of the deliverables. For industry, the transition from the prior PAS model to the use of the TVT registry must also have an on-going evaluation and process of improvement. The structure and governance of the TVT registry provides for this process and involvement of industry.

The quality of the data in the TVT registry is a top priority, and the means to monitor, audit, and adjudicate have been outlined. The reliance on CMS administrative data for longitudinal outcomes must be further studied. The implementation of novel and potentially more efficient means of event adjudication must be assessed in peer-reviewed scientific publications. New challenges are expected in implementing and optimizing the new pathway for clinical protocols that will provide CMS reimbursement and gather data for potential FDA decisions to expand indications for use of an approved device. This replaces the prior system of “off-label” use of devices with no pre-specified data collection and analysis, no pathway to potential expansion of indications, and challenges to the reimbursement and regulatory systems.

While a rational dispersion of new technology is appropriate, there are many unexplored and potentially unintended consequences of this new model of novel technology dissemination and centrally based control. For example, the need for a CMS-approved research protocol to allow use of an alternative access site to place an approved TAVR device starts to cross into the traditional realm of clinician control of procedural techniques. The CMS and FDA controlled research protocol pathway for the use of new approved technologies in narrowly defined off-label uses may result in more frequent appropriate use with a better understanding of these applications from registry-based data collection and analysis, but
the bureaucratic burdens, costs, and time delays need to be minimized. Finally, there will always be outliers not covered by research protocols for common off-label uses. The challenge is significant to refine this new model to optimize rational device dispersion, appropriate reimbursement, and effective regulation without compromising the need for clinicians and patients to individualize care within the broad context of scientific evidence presented in guidelines derived from population-based recommendations.

**Future Perspective**

The TVT registry is an ambitious undertaking with a potential to have a major impact on patient health care and safety, clinical research, evaluation throughout the device life cycle, and informed decision making by clinicians, patients, policy makers, payers, and regulators. Successful implementation of this model can be replicated broadly in other medical specialties and other areas of medical care. The TVT registry has been developed and implemented in the midst of on-going developments in the FDA’s vision for the novel approaches to medical device evidence generation, synthesis, and evaluation, CMS’s deliberations on national coverage decisions, and the medical device industry’s adaptation to these changes (33,34). The data infrastructure created offers the ability to catalyze the joint initiatives of CMS and FDA (35). The professional societies have also embraced a new level of responsibility in coordinating and implementing these changes as well as being the voice and advocate of patients and clinicians. The launch of the TVT registry is only the beginning of a new model that will be refined and improved in the years to come.

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