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VIEWPOINT

Medical Device Innovation: Prospective Solutions for an Ecosystem in Crisis

Adding a Professional Society Perspective

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Barriers to medical device innovation compromise timelines and costs from bench to bedside. Fragmented strategies by individual competitors are no longer sustainable. Pragmatically focused pre-competitive collaboration across stakeholders approaches innovation as an ecosystem. Desiloing experience and expertise encourages high-impact infrastructure efficiencies unique to pre-competitive constructs. Alignment of processes and objectives across the regulatory, reimbursement, clinical research, and clinical practice enterprises, with particular attention to the total product life cycle and continuous accrual of safety information, promotes more predictable equipoise for speed of access relative to residual safety concerns. Professional societies are well positioned to convene pre-competitive dialogue, facilitate alignment, and add perspective to equipoise within the innovation ecosystem. (J Am Coll Cardiol Intv 2012;5:790–6) © 2012 by the American College of Cardiology Foundation

Novel cardiovascular devices have been associated with improved patient outcomes for increasingly large populations while ongoing innovation continues in response to unmet needs for a broad array of disorders. Especially in the United States, however, device innovation has been impeded by a number of contemporary barriers. Among these barriers are constrained financial resources, rising research costs, concerns with predictability of regulatory processes, as well as several important advances in medicine that have had unanticipated effects on innovation. We propose specific avenues where alignment and leveraging of professional society and federal agency resources could provide unique efficiencies, enhance predictability of equipoise between speed of innovation and safety concerns, and promote processes that actively incentivize both innovation and ongoing accrual of safety information.

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Regulatory Efforts to Facilitate Medical Device Innovation

There have been several initiatives to streamline the process of regulatory approval of drugs and devices.

- The combination of rising research and development costs and reduced drug and device approvals in the United States between 1994 and 2004 led the U.S. Food and Drug Administration (FDA) to launch the Critical Path program (1), which focused on inadequacies of the clinical research enterprise that impede new therapy development.
- During this time, international regulatory agencies in the Global Harmonization Task Force, jointly with industry, sought to focus regulatory device evaluations on essential principles of safety and performance (2).
- In 1997, the FDA Modernization Act codified the construct of "least burdensome" approaches

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to medical device evaluation, including dialogue with FDA review teams early in planning for investigational device exemption (IDE) clinical trials, or "pre-IDE dialogue."

- In 2010, the FDA Center for Devices and Radiologic Health launched the Medical Device Innovation Initiative to facilitate speed to market of transformative technologies (3).

Despite these efforts, medical device innovation, particularly in the United States, has reached a crisis stage. Widespread concerns include late bedside access to important technologies in the United States ("device lag") and a shift in industry research and development priorities to markets outside the United States due to cost and regulatory and infrastructure barriers ("industry exodus").

Conversely, there are those who criticize medical device regulations as too lax and propose raising the threshold of pre-market evidence (4,5). This view has been amplified by recent safety issues that were not identified by pre-market studies, such as drug-eluting stent thrombosis and failures of pacemaker leads and implantable defibrillators.

These divergent views point to the critical issue: the lack of a consistent approach that balances the pace of medical device innovation with sufficient safety data relevant to real-world clinical practice. The absence of transparent, predictable processes for establishing equipoise around how fast is fast enough, how safe is safe enough, and for specific new device technologies leads instead to confusion, risk aversion, redundancy, and delays contrary to the best interests of advancing the public health.

Concern regarding the adequacy of the current 510(k) regulatory processes was recently the subject of an Institute of Medicine report, which concluded that the 510(k) process, through which most devices are approved, "lacks the statutory basis to make it a reliable screen of safety and effectiveness . . . as long as the standard for clearance is substantial equivalence to any previously cleared device" (6). Defining "innovation" as "improving the quality of, efficiency of, or access to health care," the committee continued: "the 510(k) process was not designed to reward . . . or encourage innovation" although it is "generally more economical, faster, and less burdensome than the PMA [premarket approval] process for both industry and the FDA."

Stakeholders in medical device innovation include patients, medical practitioners, professional societies, researchers, research organizations, device manufacturers, the investment community, hospitals and healthcare organizations, insurers, federal regulatory and reimbursement agencies, and the U.S. Congress, which passes the legislation governing and funding those agencies. Perspectives vary from the bedside to federal agencies to the economic drivers of the medical industry. Such different perspectives make simple questions such as "how safe is safe enough," "how fast is fast enough," and what really is the "cost of delay" seem unsolvable.

Important recent advances in the United States include better clinical outcomes and improved safety reporting. Both have affected device innovation, requiring larger trials to show benefit and creating a generally risk-averse environment. Other landscape changes affecting time and expense associated with device innovation in the United States include eventuation of comprehensive protection of electronic health information, meticulous standards for coding and billing for healthcare services, and the maturation of cardiovascular device markets outside the United States, enabling them to contribute high-quality research data.

To revitalize device innovation, we must first recognize that it is a highly interconnected "ecosystem," wherein regulatory and reimbursement processes, clinical trial infrastructure, public expectations, and investment decisions dynamically interact. To address the full spectrum of challenges will require frank communication among all stakeholders. Professional societies are well positioned to help orchestrate a neutral ground for such dialogue, as well as to help cultivate a collaborative, precompetitive focus on the most critical barriers with a pragmatic emphasis on working together to create both short- and long-term solutions.

Abbreviations and Acronyms

CMS = Center for Medicare and Medicaid Services

CSRC = Cardiac Safety Research Consortium

EHR = electronic health records

FDA = Food and Drug Administration

IDE = investigational device exemption

NCDR = National Cardiovascular Data Registry

Safety Concerns, Residual Risk, and the Cost of Delay

Safety concerns are the primary counterpoint to the pace of device innovation. Improvements in safety reporting, however, have not been balanced with management of clinical, commercial, public, media, and medicolegal concerns surrounding safety events. The value of improved safety reporting may be undermined if it creates a risk-averse atmosphere that impedes important further innovation.

Considerable work needs to be done to transform both key processes and perception to address medical device safety as a continuum. The U.S. legislatively mandated "reasonable assurance of safety" is frequently misinterpreted as meaning that approved devices are absolutely safe. Expectations must be clarified that no device is perfectly safe (7) and that rarer or longer term safety unknowns must be progressively uncovered with rigor in both the pre- and post-market. The international regulatory construct of "residual risk" assessment (8,9), where any level of defined device benefit is balanced with any still-undefined safety concerns, provides a fertile and practical focus for aligning

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regulatory milestones, reimbursement decisions, statistical models, public expectations, and business models over the total product life cycle.

To define the boundaries of residual risk, computer simulations, pre-clinical bench testing, and animal models may be informative to clinical trial designs (10,11). Continuity of safety information accrual across pre- and post-market human trials aligns well with statistical approaches, including the FDA's recent guidance on Bayesian methods for device applications (12). As a continuum, residual risk unresolved by pre-market randomized trials should provide the basis for suitable post-market studies (13), rather than impeding device approval and bedside access per se.

Residual risk as a continuum could reach further through the innovation ecosystem to align approval decisions with public perception and reimbursement decisions. If a device of great clinical benefit has only short-term, but reasonable safety information, conditional status of approval aligned with limited reimbursement might facilitate the speed of access while informing the public of an exciting new technology with both great potential and significant unknowns. As subsequent post-market registries, global trials, or other high-quality data reduce confidence intervals around rare safety events and provide longer term outcome data, a more unconditional approval status could be awarded in parallel with pre-determined decisions to increase reimbursement, all aligned with greater public reassurance of device safety. This kind of multisector alignment along the lines of accrual of safety information would incentivize, rather than impede, innovation.

The "cost of delay" is often excluded from the balance between speed of innovation and the need for adequate safety information (14). Established models for the financial impact of delays on revenues do not include clinical calculation of lives lost, rehospitalizations, and other morbidities related to delayed access to better technology. With growing quality of human data from outside the United States, for selected high-impact devices, statistically robust assessments of the clinical cost of delay may importantly add to the determination of equipoise for "reasonable" assurance of safety and effectiveness approval decisions. Integration of the clinical cost of delayed access into a more comprehensive calculus of the continuum of residual risk for approval decisions represents an important potential by-product from the advance of high-quality global research efforts.

Safety as a continuum and the accrual of data informing residual risk assessment crystallizes 3 central directions to revitalize medical device innovation: 1) predictable determination of equipoise between speed of innovation and residual safety concerns; 2) promoting efficient operational research infrastructure supporting item 1; and 3) orchestration of ongoing, collaborative pre-competitive dialogue. We address 5 potential solutions along these lines as listed in Table 1.

Potential Directions and Solutions

Professional society involvement: education; perspective; and collaboration. Professional societies have advanced the field of medicine with the development of practice guidelines, quality metrics, and electronic data capture of quality registries. Examples of interactions supporting federal agencies with professional society electronic data capture systems include the use of the ACC-NCDR (American College of Cardiology National Cardiovascular Data Registry) infrastructure to support the Center for Medicare and Medicaid Services' (CMS) continuing evidence decision on implantable defibrillators, and the current interaction between FDA, CMS, ACC-NCDR, and the Society of Thoracic Surgeons' Adult Cardiac Database for the Transcatheter Valve Therapy Registry. To date these activities have focused exclusively on post-market practice of medicine—on guidelines, not on guidance documents.

As the key repositories of physician specialists, professional societies must expand physician focus and education into pre-market regulatory and reimbursement issues to complement such post-market interests. The bedside perspectives of unmet needs, therapeutic options, patient advocacy, and equipoise in risk versus benefit concerns are critical to reasonable determination of safety and benefit equipoise for pre-market pivotal clinical trial objectives and, hence, to the predictability of approval for any particular device. Additionally, more widespread insight into the early stages of device evaluation would enhance physician-patient interactions, such as informed consent for procedures and management of patient and public expectations for specific device safety issues.

Well-informed physicians could enhance pre-IDE dialogue by helping regulators and manufacturers find common ground and equipoise. One unanticipated consequence of very early pre-IDE meetings between industry and regulatory has been to marginalize the role of the clinician outside of a handful of clinical trialists (15). Without academic clinician involvement, the positions of regulators and industry tend to become contentious. The determination of what is "reasonable" assurance of safety and effectiveness—including endpoint selection, statistical confidence, comparators—ultimately centers on the question of risk and ben-

Table 1. 5 Directions for the Future of Device Innovation

1. Better integration of professional societies and clinical perspectives
2. Alignment with regulatory requirements
3. Alignment with reimbursement processes
4. Alignment of clinical practice and clinical research data
5. Globalization of new device evaluation

efit. Knowledgeable physician involvement, from the most basic, pre-competitive issues related to disease states to the details of specific procedures and devices could shift this dialogue from contentious to collaborative. Professional societies must encourage and educate physician members to support interactions with federal agencies and medical industry, either as selected experts or in transparent expert panels.

Beyond educating their own membership, professional societies could also provide a convening function to facilitate pre-competitive dialogue. These societies have frequent contact with the manufacturing industry and federal regulatory and reimbursement authorities, and through their members, direct contact with patients and hospitals throughout the United States. Societies also have established experience with program planning and transparency.

Beyond education and convening, unique and already operational professional society resources could be leveraged on behalf of other areas currently creating barriers to innovation in the United States, particularly the high cost and slow enrollment typifying U.S. research sites. Registries, such as the ACC-NCDR and Society of Thoracic Surgeons' databases constitute continuous electronic data streams funded by clinical revenues, and institution of enhanced quality control measures has resulted in more reliable data. With only modest augmentation, such national electronic infrastructure could be leveraged for pre- or post-market randomized trials or registries, providing uniform terminology and definitions across studies while concomitantly increasing the speed and reducing the cost of dedicated research activities.

Greater professional society attention and involvement could help revitalize the innovation ecosystem, facilitate more informed and transparent dialogue around central questions, such as safety equipoise, and leverage infrastructure efficiencies to streamline trial processes. However, there are potential pitfalls to be avoided in endorsing this approach. Traditionally, societies have not been structured to coordinate multilevel long-term collaborations that include both industry and federal agencies, and society-driven databases have not been sufficiently granular to address specific device safety concerns. Even more importantly, the role of professional societies must be carefully structured to avoid creating new barriers or adding further complexity or inefficiencies. Thus, although such societies formally endorse best practice guidelines and govern the processes that produce them, it would be neither desirable nor appropriate to require such endorsement of approval decisions per se.

Alignment with regulatory processes and objectives. Pivotal IDE trials that promote device approval, clinical benefit data that support reimbursement decisions, and clinical trials that drive best practice guidelines are often conceived and executed independently. It would be far more efficient and at least as informative to integrate these objectives using a common operational infrastructure and align studies sequentially over the total product life cycle (Fig. 1) to accrue residual risk data. In this way, suitable prospective use of randomized and registry study designs could predictably and adaptively provide pre- and post-market data suited to any specific device needs for approval, reimbursement, and market uptake via clinical adoption.

Another benefit of alignment with the regulatory total product life cycle framework is the natural potential of ongoing dialogue about process improvement. Shared globally, professional society facilitated perspectives could become more informed as to how different international regulations influence both speed of access and degrees of safety uncertainties (16). The Institute of Medicine has recommended that the FDA formalize such a quality assurance initiative, including comparisons with international regulatory decisions (6).

A useful example of collaboration along these lines is the Cardiac Safety Research Consortium (CSRC), a public-private partnership developed under the FDA's Critical Path Program (17). Through think-tank meetings, the CSRC addresses scenarios where rare but catastrophic cardiac safety concerns create barriers to innovation. The CSRC then produces both white papers and research projects promoting collaborative pre-competitive solutions. Programs to date include drug-device safety interactions, such as dual antiplatelet therapy and drug-eluting stent thrombosis, the safety of atrial fibrillation ablation, the impact of vascular access on antithrombotic bleeding risk,

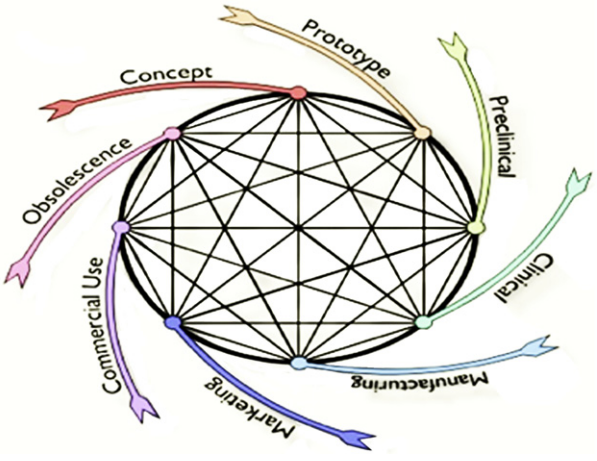

Figure 1. The Total Product Life Cycle Approach to Medical Device Development and Regulation

Medical device development is an iterative process that rapidly incorporates pre-clinical, clinical, and manufacturing experience into next-generation concept and design. Reprinted, with permission, from the U.S. Food and Drug Administration, CDRH Innovation Initiative White Paper. Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHInnovation/UCM242528.PDF.

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and electrocardiographic technologies detecting drug-induced corrected QT-interval prolongation (18,19).

Alignment of CMS processes. Reimbursement decisions are critical to all phases of new device innovation. Ambiguities in decisions on reimbursement for Category B investigational devices have direct impact on site-based participation in clinical trials, as hospitals are poorly resourced to absorb nonreimbursed expenses. Post-approval reimbursement decisions affect clinical adoption rates, as well as manufacturer revenues. Disconnects between pre- and post-market approval milestones and reimbursement decisions thus affect both data accrual and revenues that foster further innovation. In the United States, the FDA and the Center for Medicare and Medicaid Services operate in relative isolation both in their processes and in the objectives of data collection to show reasonable assurance of safety and effectiveness or metrics of clinical benefit, respectively.

Aligning processes and designing trials informative to both FDA and CMS could lower research and development costs and accelerate timelines for new devices. In September 2010 in the *Federal Register,* parallel review for new devices were announced (20). This step represents an opportunity and a paradigm to bridge federal agencies into a more efficient and predictable system of approval and reimbursement while preserving their independent jurisdictions.

Examples of CMS and professional society alignment include continuing evidence or "pay for data" decisions for defibrillators and, most recently, for percutaneous aortic valves (1,21). A unique feature of the national coverage decision for valves includes the expansion of coverage if the FDA's approved indications are extended over time—another example of efficiencies through alignment. For continuing evidence, mandatory data entry into NCDR registries provides an integrated data platform supporting utilization and device safety assessments, including longer-term follow-up in older patients through linkage to the Medicare database. Recent enhancements in monitoring and auditing of data entry continue to improve data quality. As the value of further improvements is more widely appreciated through educational programs and peer-review publications, the stage is set to support new policies for incremental reimbursement aligned with accrual of residual risk information throughout the total product life cycle. Where today safety data are the most notable barrier in the device ecosystem, such alignment could create incentivized safety data accrual and could, literally, incentivize innovation.

Align clinical and research infrastructures. Historically, the clinical care and clinical research enterprises have been separate entities. Although research requires meticulous attention to informed consent, information privacy, and protocol-related details, a completely separate research infrastructure is redundant. Statistical modeling to include more real-world populations in device trials is an important step toward narrowing the gap between studied patients and real-world practice (22,23). Beyond statistical models, however, it is critical for the clinical and research enterprises to converge at an operational level.

Electronic data capture tools may enable such convergence at the site level. Historically, electronic databases have served administrative, quality reporting, and oversight roles. These databases include the Medicare database; the New York, Washington, and Massachusetts state databases; and the Swedish national SCAAR (Swedish Coronary Angiography and Angioplasty Registry) database. These and other longitudinal clinical databases have provided observational data on stent thrombosis and femoral closure devices useful for both regulatory and practice guidelines purposes.

Electronic information capture, particularly health records (EHR) and quality registries, provides a single point of data entry for both clinical and research purposes. The FDA's Sentinel Initiative, launched in May 2008, is a Critical Path collaboration with academic groups to develop "a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events linked to the use of its regulated products" (24) using EHR from millions of patients. Using the Veterans Administration Medical Centers EHR, a bidirectional query system for FDA safety concerns is in place via the CART CL (Cardiovascular Assessment, Reporting and Tracking for Cath Labs) database (25,26).

The ACC-NCDR includes a portfolio of registries for acute coronary syndromes, cardiac catheterization and percutaneous coronary intervention, implantable defibrillators, carotid artery revascularization, and pediatric and congenital heart disease. These registries are procedural and episodic care-based, but they can readily be merged with longer term data, such as Medicare, to mine outcomes, such as mortality, rehospitalizations, myocardial infarctions, as well as pharmaceutical and cost data; the result is rich clinical information in cohorts far larger than any clinical trial at a fraction of the cost (27). The Society of Thoracic Surgery (STS) Adult Cardiac Surgery Database has recently been successfully linked to the SSDMF (Social Security Death Master File). The STS and ACC-NCDR databases have been linked to each other as well as to the SSDMF and CMS administrative databases to compare intermediate-term outcomes for coronary revascularization in the ASCERT (ACCF-STS Database Collaboration on the Comparative Effectiveness of Revascularization Strategies) trial. In another example, the SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial (28) has used the National Cardiovascular Research Initiative to import data directly from the NCDR Cath-PCI registry into a prospective, randomized trial of vascular access in women. Such direct data linkage from already active NCDR sites saves 60% of study coordinator work per patient enrolled.

Another efficiency in using such centralized infrastructure is the de facto application of consistent nomenclature and definitions for descriptors, results, and outcomes. Such consensus definitions have particular value for the accrual of safety information, as has been exampled by the use of the Academic Research Consortium (29) stent thrombosis definitions and the integration of the Academic Research Consortium valve definitions into the ACC-STS TVT registry.

Involve the global cardiovascular community. Much attention has been directed to the "exodus" of medical device research and manufacturing from the United States and to the late arrival of devices for clinical practice in the United States. In part, this is due to the inefficiencies, rising costs, and dropping reimbursements that currently characterize the U.S. arena and that urgently need to be addressed. However, it is important to recognize that this shift also reflects the very positive advance of device research outside of the United States, including the rising markets in India and Asia-Pacific. Global dissemination of good clinical practice standards and investigator education on protocol compliance now produces high-impact peer-review literature based on high-quality data. As regulatory authorities continue to work on global convergence and harmonization of device approval principles and processes, this shift also signals the very real potential of global device evaluation strategies.

This advance mandates a new vision of how American stakeholders participate in the global cardiovascular community. Although selected nations may have more interest in earlier device access despite greater risk and others have more interest in later access with lower residual risk, it seems likely that patients and doctors would support the emergence of devices without undue hazard or delay as a matter of optimal global public health (30). A global clinical view of "how safe is safe enough" could be useful to regulatory authorities considering new device approvals in the context of public health within their jurisdiction. Toward this end, global manufacturing, international regulatory harmonization, and collaborations around cardiovascular clinical research and surveillance are to be encouraged. Professional societies are crucial to this international conversation.

Conclusions

Many contemporary impediments to innovation actually represent important advances in medicine and in health care—in clinical outcomes, safety reporting, electronic infrastructure, and global research quality—that can encourage rather than impede cardiovascular device innovation. Pre-competitive collaborations that foster efficiencies can help offset the effect of more difficult barriers, such as resource constraints. Such solutions, which remove redundancy, integrate and align objectives of regulatory approval, reimbursement, and best clinical practice, are well suited in the current era of economic fragility. Professional societies are uniquely positioned to help facilitate such transformation and revitalize the medical device innovation ecosystem.

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