Hearing on the Safety of Medical Devices and FDA Oversight
Testimony of Frederic S. Resnic, MD MSc
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Chairman Kohl, Senator Corker and the members of the subcommittee, I would like to thank you and your staffs for the privilege to present my perspective on challenges facing the effective monitoring of medical device safety in the United States.

The focus of my remarks today will be on:

1. Understanding the infrequent but very severe impact of medical device failures
2. Identifying existing barriers to effective post-market surveillance of medical device failures and safety risks.
3. Proposing a new paradigm, based on continuous automated surveillance to monitor clinical registries, to provide timely and meaningful information to regulators, the public and medical device manufacturers to substantially improve the safety of medical devices.

I am a practicing interventional cardiologist with Brigham and Women's Hospital and Harvard Medical School in Boston where I utilize many innovative and high risk medical devices in my daily medical practice. Complementing this practical experience, I have degrees in engineering and medical informatics, and I lead a research program funded by the National Institutes of Health and supported through research contracts by the FDA focused on strategies to monitor the safety of medical devices through continuous surveillance of health information registries and databases. I am here to present my opinions on how the U.S. could greatly improve the nation's medical device safety system to assure that patients are treated with technologies and approaches that are as safe as possible; recognizing that no device can be absolutely free of risk of failure. Please note that I am relaying my expert opinion and do not necessarily represent those of the medical center, medical school or the sponsors of my research.

To begin, I believe that the FDA Center for Devices and Radiologic Health (CDRH), and specifically their epidemiology and post-market surveillance divisions have made great progress over the past several years in addressing gaps in the safety net for medical devices. However, there is much yet to be done to adequately protect the public against infrequent, but potentially dangerous complications or failure of such devices. I also believe that the medical device manufacturer industry has recognized, over the past several years, the critical importance of comprehensive safety surveillance both for improving their products and also to reduce the significant business risk of any delay in recognizing and addressing a safety concern for one of their products. Given this alignment of interests, I believe there is a shared responsibility and a unique opportunity for the government including the FDA, device manufacturers, and scientific leaders in medical device safety surveillance to collaboratively examine and optimize the tools and strategies to assure the safety of patients receiving medical devices in the U.S.

The Hazards of Medical Device Failures and Safety Risks:

Key points:

1. Medical device safety failures are infrequent but often have severe consequences for affected patients.
2. Due to limited available usage information, there is often a significant time lag between the first reports of a medical device failure and when action is taken.
3. Within the last three years there have been numerous high risk medical device failures leading to injury and death of numerous U.S. patients.

The first issue to consider is risk of medical device failures that, while rare, can be devastating and represent a preventable public health risk in the United States. Within the past three years there have been several high profile medical device safety failures that have led to significant recalls, direct and indirect injuries for patients including additional procedures, and loss of life due to the failure of the device. Among the most recent have been the recall of the DePuy ASR XL Acetetabular Hip System in August 2010 on the basis of an analysis of the National Joint Registry of England and Wales in which the DePuy hip suffered a 13% risk of requirement for hip revision within 5 years; far greater than the rates seen with other hip implants. Unfortunately, this finding was not new. In fact, a high failure rate was noted in the Australian National Joint Replacement Registry and the manufacturer had voluntarily stopped selling the device in Australia in December 2009. It is estimated that thousands of U.S. patients underwent hip replacement with the DePuy system in the U.S. after the initial concerns were raised by the Australian study and before the formal recall was undertaken. As an aside, this particular product had been approved through the 510(k) pathway in 2003 and was not subject to specific clinical trial testing to confirm its safety or efficacy before market approval. *[see Johnson and Johnson Website: http://www.jnj.com/connect/news/all/depuy-orthopaedics-voluntarily-recalls-asr-hip-system, accessed April 2, 2011]*

A second recent device failure was the Medtronic Sprint Fidelis implantable defibrillator lead, which was recalled in October 2007. This device was recalled after release of the report indicating that the fracture of the lead may have been a contributing factor in the death of five patients. Again, this product had been approved for market release without any pre-market clinical testing to assure safety or efficacy. Medtronic had originally notified physicians in March 2007 of a limited number of reports regarding higher than expected Fidelis lead fracture rates, but on the basis of Medtronic's own analysis of a 100 patient registry, concluded that the Fidelis lead performed in-line with other ICD leads. However, even a cursory review would indicate that this post-market study was severely underpowered to detect any difference in lead fracture rates and should not have been used to reassure patients, providers or the FDA regarding lead fracture rates. Ultimately 268,000 Fidelis leads were sold and implanted world-wide, with a great number implanted in the U.S. *[Maisel W. N Engl J Med; March 6, 2008]*

Other notable medical device safety failures include the Guidant ICD battery failure (2005), the the Cordis Cypher Drug Eluting stent (2005) and the Boston Scientific Taxus drug eluting stent (2004). Both of these stent recalls were, in fact, distinct from the overall controversy regarding overall risk of heart attacks with drug eluting stent (2006) which resulted in an emergent FDA public hearing on the safety of these devices. In each case the lack of a coherent clinical data registry made the identification of the existence, extent and severity of the problems much more difficult to estimate.

Key Challenges to Existing Medical Device Safety Surveillance:
Key points:

1. Current systems are passive and depend on voluntary reporting of adverse events
2. The GAO estimates that only 0.5% of all device adverse events are reported to FDA
3. Medical devices do not yet have a unique identifier in administrative or claims data complicating efforts to systematically study their use and safety
4. Other challenges such as learning curve effects, and rapid product lifecycle are unique to medical devices and will challenge current plans such as the FDA Sentinel Initiative.

The systems currently used to assure that medical devices are safe are primarily a patchwork of voluntary and passive event reporting mechanisms administered through the FDA. These systems, including MAUDE, MDR and MedSun principally rely upon incident reports to the FDA, which then sifts through these reports to look for clusters or trends. With more than 125,000 incident reports submitted per year by hospitals, physicians and manufacturers, these systems provide a great deal of critically important information to the FDA regarding the safety of devices, and are invaluable for gathering detailed information regarding the circumstances leading to rare or unexpected events. Despite significant efforts by FDA to encourage comprehensive reporting of medical device complications and failures, the actual proportion of experienced medical device failures is very low. In fact, the GAO has estimated that less than 0.5% of actual device failures or complications are reported, thus tremendously limiting the information available to make judgments regarding the relative balance of safety risk and health improvement that a medical device might provide to patients. [*Gross TP, Kessler LG. Stud Health Technol Inform 1996l28:17-24*] In addition, this passive reporting system provides information only about the problems reported, but does not give any information regarding the usage of the device; the "denominator" information, so that the rate of a specific device failing can be compared with other similar devices or some benchmark for acceptable performance. It is also critical to note that the approval of medical devices, even through the most rigorous pre-market randomized trial, can not effectively address the very low frequency safety risks that may be experienced only once the device is available for use in much larger "real-world" patient populations that occurs in the post-approval timeframe.

In 2008 the FDA launched a major effort to connect large healthcare dataset owners throughout the country as part of a "Sentinel" initiative, in order to have timely access to post-approval data for approved medical products. *[Platt R, Wilson M, Chan KA, Benner JS, Marchibroda J and McClellan M. N Engl J Med; 361(7) August 2009]*. However, the unique requirements of medical device safety surveillance will clearly challenge the current planned structure of the Sentinel program. In fact, despite several years of planning and evolution, the Sentinel program has yet to address medical device safety at all.

Among the challenges specific to medical devices which greatly complicate post-market surveillance, include the absence of unique device identifier information for the monitoring of medical device safety. In contrast to medications, the absence of a unique device identifier (UDI) severely limits the utility of existing healthcare administrative claims datasets, which form the core of routinely collected data used by the Sentinel network. Secondarily, most complex and high risk medical devices are refined and improved through a rapid product lifecycle,

making it essential to have extremely timely analysis and interpretation of any potential safety signals before a device is replaced by a next generation product. Also, unlike medications there is a complex interplay between the experience of the surgeon or proceduralist implanting or using a high risk medical device and the potential harm the device might cause, through effects such as "learning curves" and team or healthcare center training levels. Finally, for novel medical devices, there may be few alternatives against which to compare in terms of adverse events, making assessments of relative safety very challenging. All of these attributes of medical devices will challenge the current strategies for connecting existing healthcare clinical and administrative datasets to provide meaningful, timely and effective medical device safety surveillance.

A Better Approach – Automated Continuous Safety Surveillance:

Key points:

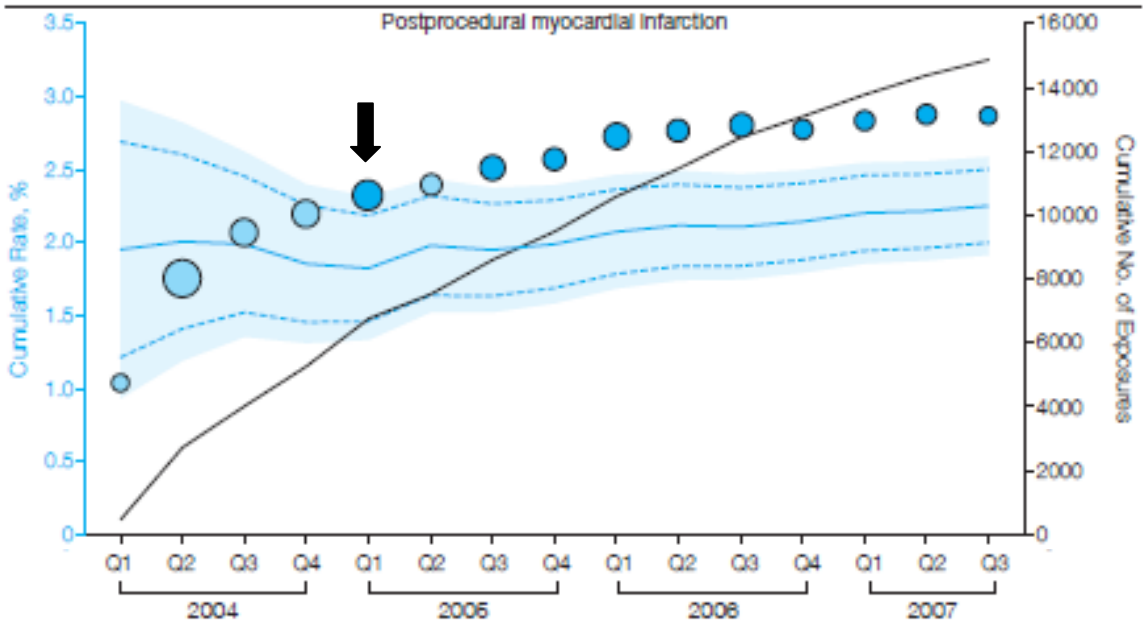
1. Recent studies have demonstrated that automated surveillance tools can effectively detect low frequency safety signals not discovered through other means.
2. Such approaches can greatly reduce the time to discover safety risks thereby sparing additional patients the exposure to the device.
3. Best available methods to maximize detection of true safety signals while minimizing risk of "false alarms" can be incorporated in such automated surveillance tools.

Despite these challenges to monitoring device safety, I believe there is a path to achieve an organized, coordinated and rational approach to post-market medical device safety surveillance that would not stifle innovation nor delay the release of important healthcare advances to the public. This strategy would be based on the use of available and emerging computerized tools to support continuous surveillance of health information registries to detect unexpected safety signals in a timely manner. I believe such a strategy could be sustainably funded through the use of existing fees assessed during the medical device approval process without incurring additional costs to the medical device manufacturer industry. Specifically, I believe that the use of continuous monitoring tools, constantly looking for evidence of safety signals for high risk medical devices is an immediately feasible strategy that would dramatically improve the current voluntary or passive approach of medical device post-market safety assurance. These monitoring tools already exist, and incorporate the best available statistical methods to account for some of the complexity of medical device safety surveillance, such as the differences in risk between patients, learning curves or interactions of the device with other medical conditions or medications used.

In research recently published by my group in the Journal of the American Medical Association, we developed and tested a computerized safety surveillance system and applied this tool to a statewide registry of cardiac procedures in MA. Our study monitored the adverse events of more than 74,000 heart stent procedures performed between 2005 and 2007 and identified two out of seven medical devices which experienced 20% to 50% higher rates of heart attacks or major bleeding following the procedure as compared with similar products in matched patient groups. In Figure 1, below, the accrual of matched patients from the registry allows us to compare, head to head, one device against identical patients receiving an alternative device. Within 18 months of the start of this monitoring, we detected the significantly increased rates of

heart attacks for one type of drug eluting stent as indicated by the red plotted points . This exploration was the first such study to demonstrate the feasibility of applying continuous surveillance to a detailed medical device specific registry. [*Resnic FS, Gross TP, Marinac-Dabic D et al. JAMA; 304(18): November 2010 – included as Appendix 1*]

Figure 1: Risk of Heart Attack following treatment with Taxus Drug Eluting Stent (DES): The graph plots the propensity matched analysis of the cumulative incidence of heart attacks following implantation of at least one Taxus DES. Circles indicate the cumulative observed event rates for patients receiving Taxus DES. The dark arrow indicate the point at which the automated system detected a significantly higher rate of heart attacks for the Taxus stent as compared with other DES. Please see Appendix 1 for full description of analysis.

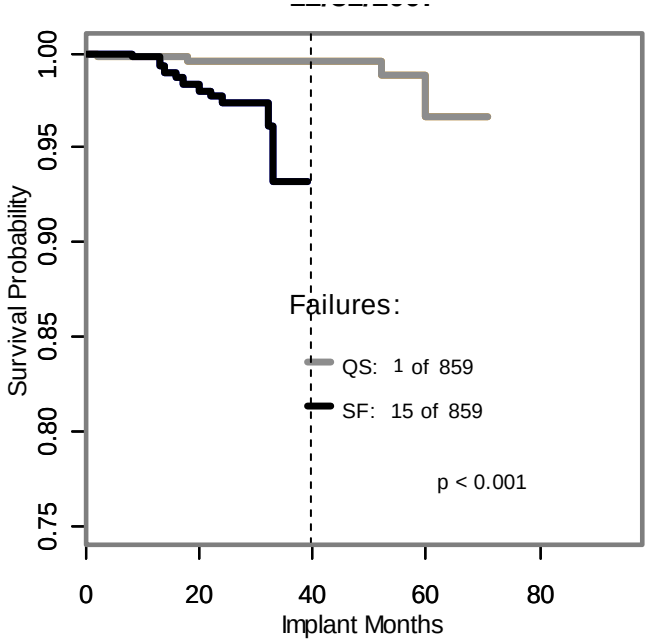


In response to this research, international experts in healthcare safety and quality including Dr. John Rumsfeld, Acting National Director of Cardiology for the Veterans Administration Healthcare System, and Dr. Eric Peterson Associate Director of the Duke Clinical Research Institute have called for broadly applying the approach of using automated surveillance to medical outcomes registries as a principle way to improve the safety surveillance of medical devices in the United States. *[Rumsfeld JS and Peterson ED. JAMA 304(18): November 2010]*

In a separate study, Dr. Robert Hauser, a leading advocate for cardiovascular device safety used the same computerized surveillance system to show how quickly automated surveillance could have identified the increased risks of the Fidelis implantable defibrillator lead fracture, had the system been monitoring the accruing data at just four academic medical centers. In this study, the system was able to identify Fidelis lead fractures 14 months before the traditional methods of analysis were able to show a difference. This time savings, if acted upon promptly by FDA, could have spared thousands people from having these systems implanted. Importantly, this

early warning would have also spared the manufacturer, Medtronic, from having a relatively small problem snowball into an enormously complex safety issue.

Figure 2: Monthly prospective propensity matched survival analysis comparing Sprint Fidelis to control implantable cardio-defibrillator leads. The durability of each lead type is plotted against the months following implant. By 40 months of analysis(dashed line) 1.7% (15of 859) of Fidelis leads had fractured (black line) whereas only 0.1% (1 of 859) alternative ICD leads had fractured; representing a more than 10 fold device failure rate.



Importantly, the automated surveillance system tested in the studies above incorporate a variety of statistical approaches to maximize the detection of safety signals, while attempting to minimize the number of "false alarms" generated by the system. Systems such as this also are capable of monitoring hundreds simultaneous medical devices, so as to maximize the efficiency of using such systems. Additional explorations are currently underway linking a network of orthopedic implant databases as well as within the VAHS clinical data repositories, and should provide further information on the opportunities as well as limitations of automated surveillance approaches to medical device safety signal detection.

The Critical Need for National Medical Device Registries

Key points:

1. Detailed clinical registries provide the necessary granular clinical information needed to support automated safety surveillance.
2. There is no current process or regulation to assure that all high risk devices are followed in detailed clinical registries.
3. The best such registries in the U.S. are currently initiated, funded and maintained by non-profit professional medical societies or large healthcare provider systems.
4. Aligning resources and incentives in a public-private partnership, such as the INTERMACS registry of cardiac support devices may serve as a template for future medical device registries

Of course, having reliable tools able compare the relative performance and safety of medical devices marketed in the United States is a critical component for improving the safety net for medical devices, but is not enough to improve safety without reliable datasets to monitor. We must have accurate, reliable, and increasing bodies of information in useful and accessible datasets on which to base this model of continuous safety surveillance. Fortunately, voluntary detailed clinical registries capable of providing the necessarily detailed clinical information already exist in the selected medical fields, covering hundreds of high risk devices. In many countries, such registries are a mandatory component of the healthcare system and required for all high risk implant procedures. Examples of such registries include the Australian and UK joint replacement registries, from which the risks associated with the DePuy implant were discovered.

In the U.S. however, such registries have been developed primarily through non-profit professional organizations originally intended to analyze and improve the quality of care delivered, and not specifically for medical device surveillance. The American College of Cardiology, in conjunction with several partner professional organizations, have established leading detailed clinical datasets as part of their National Cardiovascular Data Repositories (NCDR), covering the fields of interventional cardiology (coronary stents, angioplasty balloons, vascular closure devices), a registry for ICD's, a registry for carotid stents, and will soon be launching several registries covering additional cardiovascular fields and their associated devices. The largest of these registries, CathPCI, includes over 3.1 million patient level records with device level information from over 1,100 participating facilities in the United States. In addition to the American College of Cardiology programs, the Society of Thoracic Surgery has a comprehensive clinical registry with detailed information on cardiac surgical implants. New efforts by professional societies within orthopedics, opthamology, and surgical material implants are also underway.

Creating and maintaining these detailed clinical registries is challenging and expensive. Today many of our registries are supported by voluntary submissions from health providers requiring hospitals to bear all of the costs of collecting and submitting the case level information. However, emerging standards for electronic health records including the "meaningful use" regulations being implemented over the next several years will provide unprecedented opportunities for securely mapping clinical information to distributed clinical registries. This

health care information revolution will dramatically increase the ability to extract the necessary information, and should greatly reduce the cost of collecting detailed medical device safety information to permit surveillance from hospital-based and clinical practice based health information systems.

Perhaps the most innovative example of bringing multiple stakeholders together into a coordinated effort to study newly introduced medical devices has been the INTERMACS registry, a public private partnership involving the National Institutes of Health, Center for Medicare Services, FDA, industry representatives and academia. The INTERMACS registry was established in 2006 to capture the clinical data and outcomes of all patients receiving mechanical heart support pumps in the U.S. Importantly, CMS created the incentive for participation in INTERMACS by requiring that every patient's information be entered into an audited national registry as a condition for reimbursement for the procedure. INTERMACS has provided a model for the collection, timely analysis and dissemination of information that improves care for these complex patients. Since its inception, INTERMACS has provided tremendous information on the safety and effectiveness of mechanical heart support therapies on groups of patients who were not studied in the initial randomized pre-approval trials, enabling rapid dissemination of knowledge and moving the care of these patients forward at a rapid pace. Importantly, INTERMACS also serves as a ready infrastructure to support the post-approval study of every new generation of mechanical cardiac support device since the initiation of the registry, saving the manufacturers significantly by avoiding the requirement to establish redundant systems of data collection, auditing and analysis. *[Miller MA, Ulisney K and Baldwin JT J. Am Coll Cardiol 2010;56(9):738-740]*.

The INTERMACS experience provides a template that could form the basis for future prospective surveillance for all high risk medical devices, in that it aligned the incentives of healthcare providers with the needs of the public health and public policy organizations to collect, analyze and disseminate device level analyses using detailed clinical registry information for all patients receiving a new device. Looking ahead, developing similar public-private partnerships to collect detailed clinical information in the form of clinical registries, and coupling these data sources with the tools for automated prospective surveillance, as described above, will provide the best mechanism to minimize the health risk of new medical devices.

Also notable in the push toward more comprehensive medical device active surveillance, relying on such detailed clnical registries, is the leadership of the FDA CDRH in bringing together dataset owners to participate in critically important collaborative device safety pilot projects. A recently launched initiative within CDRH, called the Medical Device Epidemiology Network or MDEpiNet focuses on developing the best methods to study these types of emerging data resources, and seeks to establish a variety of public-private partnerships to make the greatest use of these device specific registries.

Summary and Specific Recommendations:
In summary, the post-approval monitoring of medical devices in the United States requires significant enhancement to avoid preventable injury and death to patients treated with high risk medical devices that ultimately fail. Current passive event reporting systems are inadequate to provide the critical information to regulators, public health officials, physicians and patients as to the relative safety and performance of new medical devices. Unique and specific challenges for studying medical devices, such as the lack of unique device identifiers, intrinsic learning curve effects, and interactions between devices, medications and medical conditions may challenge current advanced monitoring strategies such as the Sentinel initiative. Pilot studies have demonstrated that advanced automated safety surveillance tools can simultaneously monitor numerous medical devices for multiple safety outcomes to identify low frequency safety signals. Such systems could prevent exposure of patients to devices which would put them at uniquely increased risk. In order to facilitate such a broad surveillance network, regulators and industry must look to well organized clinical registries with sufficient detail to support post-market surveillance of specific high risk medical devices.

In order to achieve the goals outlined above, I would respectfully ask the committee to consider the following recommendations:

1. FDA, in collaboration with CMS, should mandate that detailed information regarding high risk medical device use and clinical outcomes be universally submitted to selected national clinical registries.
2. The registries should be operated by independent academic or professional society organizations as part of public-private partnerships, informed and guided by MDEpiNet and the Sentinel Initiative and other federal stakeholders.
3. FDA should redirect resources currently spent by the medical device industry on condition of approval studies to support the national medical device safety registries.
4. Automated safety surveillance tools should be uniformly applied to the device registries to continuously and prospectively monitor each registry for the most severe as well as most common complications and failures of each high risk medical device.
5. The results of the automated surveillance should be provided, in real time, to both the FDA, to complement existing event reporting systems, as well as to manufacturers to support refinements in product design.

Thank you again for the opportunity to share my thoughts on this very important topic with this committee.