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IMPROVING THE SAFETY OF HIGH-RISK MEDICAL DEVICES

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Medical devices play an ever-increasing role in medical care. The pace of regulations to protect patient safety has not kept up with the development and marketing of new medical devices. In fact, patient safety protections have weakened in the last several years with the emphasis to get “innovative” devices on the market faster. As a result, there is, less premarket clinical study, and postmarket surveillance still remains weak.

It is helpful to begin with a brief historical perspective of medical device regulation. The Food and Drug Administration (FDA) first began regulating devices with the 1976 Medical Device Amendments (Amendments), after thousands of women were injured by the Dalkon Shield intrauterine device.¹ To accommodate the number of medical devices in common use prior to 1976, the FDA framework was rudimentary and meant to be expanded and strengthened. However, over forty years later the FDA framework still has not been completed and is being progressively weakened. In fact, the current trend of lowering evidentiary requirements for high-risk device approval through legislation such as the 21st Century Cures Act, new proposed rules and regulations, and a rudimentary adverse event reporting framework will pose increasing threats to patient safety.

The Amendments established three categories of risk for FDA device approval.² Only the highest risk category (Class III) goes through premarket approval (PMA), which is the most rigorous pathway and the only pathway to require clinical data.³ Approximately 1% of all devices enter the market via PMA.⁴ Furthermore, a landmark study in 2009 by Dhruva et al. found that only a small minority of PMA devices were supported by high-quality, randomized controlled trial

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1. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 315 (2008).

2. *Id.* at 316–17.

3. Sanket S. Dhruva et al., *Strength of Study Evidence Examined by the FDA in Premarket Approval of Cardiovascular Devices*, 302 JAMA 2679, 2679 (2009).

4. Sarah Y. Zheng et al., *Characteristics of Clinical Studies Used for US Food and Drug Administration Approval of High-Risk Medical Device Supplements*, 318 JAMA 619, 620 (2017).

(RCT) data.⁵ Very few of these trials were blinded, meaning they could not determine if the benefit was due to the device or to the well-known and powerful placebo effect of a procedure.⁶ Thus, many high-risk devices are currently used without evidence of benefit from high-quality, randomized controlled trials. Additionally, in 1976, many high-risk devices were classified as Class II, an intermediate risk category meant to be used for certain high-risk devices on a temporary basis. Forty years later, high-risk devices remain in the intermediate risk pathway, while some have been reclassified as lower risk Class II devices.

After entering the market via the original PMA process, high-risk devices can be modified through supplements to the PMA.⁷ These supplements generally do not require clinical data.⁸ Some high-risk devices enter the market via the 510(k) process, which uses the criteria of being “substantially equivalent” to a device already on the market and does not require clinical data.⁹ The FDA asked the venerable Institute of Medicine (IOM)¹⁰ for advice on how to improve the safety and effectiveness of the 510(k) process.¹¹ After careful study and consultation with many experts, the 2011 IOM report concluded that safety and effectiveness was not a criterion for market entry in the 510(k) process.¹² Therefore, there was no way to assure safety and effectiveness of 510(k) devices and the IOM report determined this pathway should be abandoned.¹³ In a startling and unusual move, the FDA renounced the findings of the IOM report, and the 510(k) process continues to be used for many high-risk devices today.¹⁴ For example, when the Lariat device intended to be placed inside the heart to tie off one of the cardiac structures (the left atrial appendage) entered the market via the 510(k) process, it was judged as being substantially equivalent to the preformed sutures used during

5. Dhruva et al., *supra* note 3, at 2683.

6. Zheng et al., *supra* note 4, at 622; *see also* Dhruva et al., *supra* note 3, at 2683.

7. *See generally* Zheng et al., *supra* note 4. *See also* Riegel v. Medtronic, Inc., 552 U.S. 312, 319 (2008).

8. Zheng et al., *supra* note 4, at 620.

9. Riegel, 552 U.S. at 319.

10. The IOM is now known as the National Academy of Medicine (NAM).

11. INST. OF MED., MEDICAL DEVICES AND THE PUBLIC'S HEALTH: THE FDA 510(K) CLEARANCE PROCESS AT 35 YEARS, at xi (2011), <https://www.nap.edu/read/13150/chapter/1#ii>. Named after Section 510(k) of the Federal Food, Drug, and Cosmetic Act, this is a process by which the majority of health care medical devices must be reviewed and approved by the FDA prior to entering the market. *Id.*

12. *Id.* at xi–xii.

13. *Id.*

14. Press Release, U.S. Food & Drug Administration, FDA to seek public comment on IOM recommendations (2011) (on file with agency).

laparoscopic surgery, even though this is a surgery that is not done in the heart.¹⁵

The 21st Century Cures Act, passed in December 2016, further weakened the evidence requirements for high-risk devices. This legislation is intended to allow the FDA to accept anecdotal evidence in support of high-risk device approval. Congress stated more emphasis would be placed on post approval studies (PAS). However, our prior work has shown that PAS are often not initiated at the time of device approval, although that is the stated intent of the FDA.¹⁶ Few PAS studies are completed and even less are published in peer review medical journals.¹⁷ The FDA has never issued a warning letter or levied any penalty related to study delays, inadequate progress on PAS, or failure to comply with PAS requirements.¹⁸ The lowering of thresholds for premarket evidence to support safety and effectiveness of high-risk devices, along with severely limited postmarketing evidence collection, all leads to increased chances of serious adverse events due to dangerous devices.

Making this situation even more unsafe and scary for patients, there is an extremely weak adverse event (AE) reporting system, such that only 3%–6% of all AE are even reported.¹⁹ Physicians are not required to report adverse events, and the barriers for well-intentioned physicians to report AE are high. Besides doing the right thing, there is no incentive to report AE, and even when one wants to report, the system is difficult to access and time-consuming. Legislation to mandate physician reporting of AE, the Medical Device Guardians Act, was introduced in the 2016 and 2017 Congresses.²⁰ When hospitals report AE, they generally report them to the device company and not directly to the FDA. The device companies do have mandatory reporting, but it is at their discretion to decide if the event, even a serious

15. Saurav Chatterjee et al., *Safety and Procedural Success of Left Atrial Appendage Exclusion with the Lariat Device: A Systematic Review of Published Reports and Analytic Review of the FDA MAUDE Database*, 175 JAMA INTERNAL MED. 1104, 1107 (2015). A Netflix documentary released in July 2018, *The Bleeding Edge*, tells the story of how many unsafe medical devices have gotten on the market and the serious, adverse consequences. *The Bleeding Edge*, NETFLIX (July 2018), <https://www.netflix.com/search?q=the%20bleeding%20&jbv=80170862&jbp=0&jbr=0>.

16. Ian S. Reynolds et al., *Assessing the Safety and Effectiveness of Devices After US Food and Drug Administration Approval: FDA-Mandated Postapproval Studies*, 174 JAMA INTERNAL MED. 1773, 1774–78 (2014).

17. *Id.*

18. *Id.* at 1776.

19. In 2012, physicians “report[ed] only 1% of adverse events.” Gina Shaw, *Most Adverse Events at Hospitals Still Go Unreported*, HOSPITALIST (July 2012), <https://www.the-hospitalist.org/hospitalist/article/125141/most-adverse-events-hospitals-still-go-unreported>.

20. Medical Device Guardians Act of 2016, H.R. 5404, 114th Cong. (2016).

AE such as death, was related to the device. Karaca-Mandic, Ma, and Marinovic found that companies did not meet their requirements for reporting of serious AE 10% of the time, without any consequences from the FDA.²¹ Thus, while device manufacturers may claim their device is safe, that assurance is greatly weakened by the failure of our adverse event reporting system to capture most events.

We know there is no reporting of many dangerous device-related AE. Some have come to light due to litigation, press accounts, and AE data collected in foreign countries—many of which have a much stronger system for collecting this data and making it available. Repeatedly, it has taken several years before AE information, which comes from the companies or involved institutions, was released to the public and physicians. This included information relating to widespread and serious device safety issues, such as duodenoscopes, inferior vena cava filters, intracardiac cardioverter-defibrillator (ICD) leads, and metal-on-metal hips. Manufacturers and hospitals delayed making the AE publicly known, notifying doctors and patients, and recalling the dangerous devices.²² The widespread lack of tracking of AE means that the patient harm and deaths known to be related to medical devices is likely a small fraction of the actual harm. Furthermore, the AE data that is collected is either very difficult to access due to the FDA's antiquated collection system, known as the Manufacturer and User Facility Device Experience (the MAUDE), or is kept secret by private organizations, such as the professional society registries that track devices. While there are research papers written based on selective analyses of data from these registries, the data is not publicly accessible and access is restricted. For example, Centers for Medicare and Medicaid Services (CMS) pays billions of dollars for the implantation of defibrillators and left ventricular assist devices, but it cannot access the registry collecting data about these same devices.

21. Paul Ma et al., *Drug Manufacturers' Delayed Disclosure of Serious and Unexpected Adverse Events to the US Food and Drug Administration*, 175 JAMA INTERNAL MED. 1565, 1566 (2015); Rita F. Redberg, *Improving Manufacturer Reporting of Adverse Events to the US Food and Drug Administration*, 175 JAMA INTERNAL MED. 1566, 1567 (2015).

22. Steven B. Danik et al., *Timing of Delayed Perforation with the St. Jude Riata Lead: A Single-Center Experience and a Review of the Literature*, 5 HEART RHYTHM 1667, 1667 (2008); Ratika Parkash et al., *Failure Rate of the Riata Lead Under Advisory: A Report from the CHRS Device Committee*, 10 HEART RHYTHM 692, 694–95 (2013); James Walsh, *St. Jude's Durata Lead is Facing New Questions*, STAR TRIB. (June 5, 2013, 6:58 AM), <http://www.startribune.com/st-jude-s-durata-lead-is-facing-new-questions/210107621/>; *Concerns about Metal-on-Metal Hip Implants*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm241604> (last updated Dec. 28, 2017).

There are great opportunities to better protect patient safety by improving our oversight of high-risk devices, especially for an implanted device. Discovering a safety problem with an implanted device carries a greater risk for patients. Unlike a drug discovered to be associated with adverse events, which can simply be stopped, an implanted device must either be removed in a risky procedure or left in the body with the attendant risk. Thus, high-quality RCTs to assure safety and effectiveness for high-risk devices prior to approval would go a long way to improve patient safety and to ensure we are not recommending unnecessary or harmful devices to patients. Once devices are approved, even on the flimsiest of data, they become entrenched in our clinical practice, and it is very hard to change the culture. For example, percutaneous coronary interventions, such as coronary stents, have never been shown to be superior than medical therapy in a blinded Randomised Controlled Trial (RCT) for stable coronary artery disease.²³ In fact, the recent ORBITA trial was the first blinded trial to be done, and it found there was no benefit to a real stent compared to a sham stent.²⁴ This trial found that people who thought they got a stent, but did not, did just as well as people who did receive a stent in terms of treadmill time, quality of life measures, and relief from angina.²⁵ My accompanying editorial called for a change in practice and the current guidelines based on this high-quality trial, but these needed changes have not occurred.²⁶ This first blinded trial of percutaneous coronary interventions (PCI) occurred more than a quarter-century after FDA approval of the Gianturco stent in 1992.²⁷ This approval was based on a single arm study of a little over 300 patients.²⁸ Several people died during the stent procedure, and more went on to have bypass surgery.²⁹ These patient outcomes were compared to patients enrolled in an National Institutes of Health (NIH) registry of angioplasty patients more than five years prior. Based on this low-quality study, stents were launched into common medical use,

23. See generally Rasha Al-Lamee et al., *Percutaneous Coronary Intervention in Stable Angina (ORBITA): A Double-Blind, Randomised Controlled Trial*, 391 LANCET 31 (2018).

24. *Id.* at 32, 36. ORBITA is the acronym for the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty with stable angina. *Id.* at 32.

25. *Id.* at 37.

26. David L. Brown & Rita F. Redberg, *Last Nail in the Coffin for PCI in Stable Angina?*, 391 LANCET 3, 4 (2018).

27. COOK, INC., SUMMARY OF SAFETY AND EFFECTIVENESS FROM THE GIANTURCO ROUBIN CORONARY STENT 1 (1992).

28. *Id.* at 10.

29. *Id.* at 18–19.

and millions have been placed in persons all over the world.³⁰ Before ORBITA, there were several studies that showed no benefit of PCI on reducing myocardial infarction (heart attacks) or deaths, but the practice continued largely unabated.³¹ The most recent (and first blinded) trial of PCI found that there was no benefit to actual PCI compared to a sham PCI, and there were risks to the PCI procedure.³² However, again, this high-quality RCT has been met with scathing attacks largely from the interventional cardiology community.³³ It is very difficult to change practice and minds once a practice becomes established in the medical culture, as PCI has. Ironically, it was complications from a coronary stent that led to the Supreme Court decision in *Riegel v. Medtronic*, which established that preemption prevents patients who have suffered serious injury or death from suing a PMA device manufacturer.³⁴

There is great opportunity for patients, physicians and health professionals, and regulatory agencies to improve patient safety of medical devices. Patients and clinicians must demand high-quality evidence and FDA approval before use of high-risk devices. Adverse event reporting must become part of the medical culture, and the data must be easy to report and access. Innovation is important, but evidence is needed to know if a device is innovative or is actually dangerous. Once devices reach the market, it is so hard to slow down the use of ineffective or even dangerous devices. Thus, it is essential to rebalance our current system to make patient safety the highest priority.

30. Liz Szabo, *Stents Open Clogged Arteries of 1M Americans Annually*, USA TODAY (Aug. 6, 2013), <https://www.usatoday.com/story/news/politics/2013/08/06/bush-stent-heart-surgery/2623111/>.

31. William E. Boden et al., *Optimal Medical Therapy with or Without PCI for Stable Coronary Disease*, 356 NEW ENG. J. MED. 1503, 1509–11 (2007).

32. Brown & Redberg, *supra* note 26, at 3. See generally Al-Lamee et al., *supra* note 23.

33. Tricia Ward, *ORBITA: Sham PCI Trial Sends Stents and CardioTwitter Reeling*, MEDSCAPE (Dec. 12, 2017), <https://www.medscape.com/viewarticle/889670>.

34. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 324–25 (2008).