

Implantable Material and Device Regulation

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FROM THE EDITOR

How Differently Should the FDA Regulate Drugs and Devices?

Ariel Wampler, MD

In 2000, it was estimated that 20 to 25 million Americans had an implanted device,¹ but between 2003 and 2007, less than 1% of devices underwent the 2 large, human clinical trials mandated for US Food and Drug Administration (FDA) pharmaceutical approval.^{2,3} Only high-risk devices that are lifesaving or life-supporting are required to submit clinical data to demonstrate their safety and efficacy, also known as the premarket approval (PMA) pathway. Many devices are cleared through premarket notification (PMN), also known as the **510(k) pathway**, which is permitted for low-to-moderate risk devices or those that are, according to manufacturers, essentially equivalent to those already on the market.

Widespread **patient harm** due to medical devices has been chronicled in recent journalistic exposés,^{4,5,6,7} congressional hearings,⁸ and the 2018 documentary, *The Bleeding Edge*.⁹ Examples of such harms include cobalt poisoning due to artificial hips, inadequate or excessive delivery of insulin from implantable pumps, and spinal cord stimulators that deliver painful shocks. The device industry and its regulators are now facing **increased scrutiny** for lax premarket clearance standards,^{10,11} suspect advertising practices,^{12,13} undisclosed conflicts of interest,^{14,15,16,17} deficient postmarket surveillance,^{18,19} and inappropriate and inaccurate reporting of injuries and deaths.^{20,21,22,23}

The FDA must balance **timely access** to life-extending or life-improving technologies with rigorous safety. The US device approval process is already longer and more stringent than that of Europe, leading many physicians to lament their inability to offer pioneering solutions to disease and disability.²⁴ A 2010 industry survey reported that PMA devices take on average 54 months from first communication to reach American patients compared with 11 months for European patients. Similarly, PMN pathway devices take on average 31 months from first communication to be cleared in the United States compared with about 7 months in Europe.²⁵ Moreover, regulatory changes to further improve safety could make devices prohibitively expensive and therefore are unlikely to be supported by patients, physicians, and payers.^{26,27,28}

Device industry critics argue that most serious recalls have involved 510(k)-cleared devices²⁹ and that public protection requires that more devices undergo PMA, with submission of clinical data. Given that medications with adverse effects can usually be discontinued without additional risk, while device removal can cause serious

complications, it might be reasonable to expect implanted devices to meet even higher safety benchmarks than drugs. Additionally, patients harmed by FDA-approved drugs can sue pharmaceutical companies, but the *Riegel v Medtronic* Supreme Court precedent leaves those harmed by FDA-cleared devices without recourse to seek damages from device manufacturers.³⁰

Industry advocates, however, point out that less than 1% of all 510(k) and PMA devices that were cleared or approved between 2004 and 2009 have ever been subject to a Class I recall (utilized for major injuries or death).²⁵ Conducting clinical studies for implantable devices is often more complicated and expensive than for drugs and can be ethically problematic. For example, the closest equivalent to a placebo control pill would be sham surgery, which carries considerably more risk.³¹ Even with painstaking design and testing, devices can cause harm if used improperly; companies tend to argue that it's inappropriate for them to be held liable if physicians make poor patient-selection decisions or lack the motor skills needed to implant or operate a device. Device makers appreciate the need for evidence-based approval, but they call for FDA reviewers with more field-specific expertise, as well as for more transparent and predictable regulatory processes in order to efficiently bring their devices to US markets.²⁵

How might regulators exercise **sufficient caution** without stifling innovation? Which processes should be used to **mitigate bias** in device research and development and user education, when most experts have industry ties? Which entities should bear **ultimate responsibility** for prevention and compensation for patient harm from devices? This issue of the *AMA Journal of Ethics* invites clinicians, researchers, device representatives, and patient-safety champions to reflect on these and other questions.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

How Should Clinicians and Organizations Assess Risks and Benefits of First-in-Human Implantation of Investigational Devices?

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Abstract

The number of new medical devices cleared by the US Food and Drug Administration (FDA) through the 510(k) pathway that has subsequently been associated with safety risks has led to discussion of approaches to regulation and communication of device risks. As debate continues over whether the pathway needs to be altered, features of ethical use of 510(k)-cleared devices can include (1) heightened caution with respect to newly cleared 510(k) products until adequate data are gathered through postmarket surveillance, (2) facilitating informed consent by improving physician and patient knowledge of the 510(k) pathway, and (3) basing distribution of these devices on individual risk assessments while ensuring equitable access.

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Case

A hospital purchasing committee is considering contracting with a company that produces an artificial lumbar spinal disc. The literature cited within the disc manufacturer's proposal claims that, compared to lumbar fusion, the benefits of the disc include earlier hospital discharge, a quicker return to work, and fewer opioids to manage postoperative pain. Several members of the committee, however, raise the concern that the disc could collapse and migrate, which would require further surgeries.

The US Food and Drug Administration (FDA) cleared the disc via the 510(k) pathway, which does not require clinical testing data. Instead, clearance is based on "substantial equivalence" to a predicate device on the assumption that the benefit-risk profile of the new device will be similar to the predicate device's profile. A new device is substantially equivalent to the predicate device if the new device has the same intended use as the predicate device and either (1) has the same technological characteristics as the predicate or (2) has different technological characteristics but does not raise different questions of safety and effectiveness and the information submitted for clearance demonstrates comparable safety and effectiveness.¹

Several members of the committee disagree about whether the 510(k) process provides sufficient assurance of device effectiveness and safety and, on that basis, disagree about entering into a purchasing contract with the device manufacturer. It should be noted, however, that in the presentation of the hypothetical case, no information is provided on the predicate or differences between the predicate and the current product (although it might be reasonable for the committee to seek out that information before making its decision).

Commentary

This case raises several practical and ethical questions about 510(k)-cleared devices, including how clinicians and organizations should weigh the benefits and risks of 510(k)-cleared devices, how patient safety should be optimized, what constitutes adequate informed consent for implantation, and how devices should be disseminated.

Benefit-Risk Analysis

A 2018 study found that physicians rated the following factors most highly when choosing whether to use implantable devices: better outcomes for patients, the longevity of the implant, design and ease of both implant and instrumentation, scientific evidence of better outcomes, length of follow-up in scientific studies, and product reputation.² When new implantable devices are **cleared by the FDA** via the 510(k) pathway, it therefore raises a particular challenge to physicians and hospital purchasing committees, since many of these factors might be unknown.

Although the 510(k) clearance process is an important mechanism for allowing incremental changes to devices, safety issues related to 510(k) clearance have been identified in some systematic assessments of the device market. A study in *JAMA Internal Medicine* found that, of all the devices recalled from 2005 to 2009 because of serious risks, 78% were approved through the 510(k) regulatory process or were exempt from regulatory review.³ The nature of 510(k) clearance—which can be issued on the basis of a finding of substantial equivalence to another approved or cleared device—leads to uncertainty in any **assessment of patient safety** for 510(k)-cleared devices because complicating factors abound. For example, some 510(k)-cleared devices rely on the use of more than one predicate by combining functions of different predicate devices (called *multiple predicates*) or by relying on one predicate to support equivalence of intended use and another to support equivalence of technological characteristics (called *split predicates*). These complexities have reportedly made the device safety profiles less certain.⁴ Additionally, manufacturers can use as a predicate a device that was cleared because it was substantially equivalent to another device, which might have been substantially equivalent to yet another device, and so on, which has been called *predicate creep*. In such cases, there might be substantial differences between a new device under consideration and whichever product in the predicate chain was the last product that was formally assessed in clinical trials of device effectiveness or safety.⁵ Finally, manufacturers are permitted to use devices that have since been recalled as a predicate, raising safety concerns about newly cleared devices.⁶

Optimizing Patient Safety

Clinical decision making must account for the fact that relevant safety information and other factors important for patient decision making are unknown. One approach to addressing this dilemma would be for hospitals to avoid bulk purchasing of 510(k) medical devices that lack key clinical data at the time they reach the market. Instead,

purchasing committees could make these decisions on a case-by-case basis for patients whose physicians can justify the benefit of the incremental changes offered by these devices. This precaution is especially important when major potential risks loom with the device—for example, with the artificial lumbar spinal disc in question, the risk of subsequent surgeries may negate any potential benefits, as subsequent surgeries would mean more time in the hospital, more time away from work, and possibly more opioids for the management of postoperative pain over the long term. While hospitals might incur greater costs by not purchasing the devices in bulk, purchasing on a case-by-case basis can help avoid secondary costs—such as the use of hospital beds for additional procedures—if the device turns out to lead to worse outcomes for patients. When organizations do purchase on a case-by-case basis, physicians should understand the nature of the clinical testing (if any) used to bring a device to market and be able to clearly pass that information along to patients.

Updating the information available to prescribers and hospital formulary committees is also necessary and involves collecting post-clearance data efficiently on new 510(k) devices so that regulators can better understand when safety warnings need to be updated or, in a worst-case scenario, when devices need to be withdrawn from the market. Although the FDA requires manufacturers and hospitals to **report serious device-related injuries**, underreporting of these adverse events is widely recognized.⁷ Underreporting might be due to ambiguities in whether an injury was related to the device (or other etiologies).⁸

In addition to device adverse event reporting systems—the primary one being the FDA’s Manufacturer and User Facility Device Experience Database—creation of national registries for devices can promote more systematic oversight by enabling more rigorous evaluation of the real-world evidence of the benefits and risks of 510(k) devices. The European Union is in the process of creating a database across member countries to aid in device safety and effectiveness surveillance.⁹ To establish and maintain useful registries requires funds, although costs can be manageable; indeed, some well-regarded registries have been established by nonprofit institutions, including professional societies like the American College of Cardiology.¹⁰ However, if private registries are found to increase the price of devices and impede equitable access, public funding through a small tax on each device can be considered. Building registries for 510(k)-cleared devices should give hospital purchasing committees more confidence when considering purchasing these devices in bulk.

Informed Consent

Patients should also be better educated about the advantages and disadvantages of 510(k)-cleared devices. Adequate informed consent requires that patients have a full understanding of the known risks and benefits of both the device in question and alternatives. However, since many of these risks and benefits might be unknown initially, patients’ comprehension of the limitations of 510(k) clearance would help them make an informed decision among treatment options. The fact that some risks and benefits of the device might be initially unknown is a risk in and of itself, one that patients themselves must be fully informed of and willing to incur. In particular, patients must understand that collection of safety data may be ongoing. Unless clinicians explain that evidence of the cleared device’s safety and effectiveness is lacking, patients cannot make an accurate assessment of the benefits and risks of the proposed device vis-à-vis alternatives. Failure to do so could thus undermine collaborative decision making, leaving a crucial part of the decision solely in the clinician’s hands. Clinicians should

engage in **shared decision making** to understand the patient's personal risk tolerance and ability to comprehend the implications of what is and is not known about the device's effectiveness and safety—to do otherwise and make a decision based on what they believe is in the patient's best interest would disrespect the patient's autonomy.

Distribution of 510(k) Devices

As with the introduction of other new technologies, there is a need to ensure that 510(k)-cleared devices are used in accordance with the ethical principle of justice. Here, a tension arises. On one hand, there is a need to ensure that these devices are disseminated equitably to patients even in rural hospitals or resource-poor settings. On the other hand, given the uncertain safety profile of these devices, there is a need to ensure that these devices will not be used disproportionately in potentially vulnerable patient populations—such as patients of color—without adequate informed consent.

Ensuring that all patients have equitable access to new devices should not come at the expense of the principles of beneficence and nonmaleficence. Clinicians need to assess individual risk profiles for these devices, which involves careful assessment of whether the patient will benefit more from this device than other well-established devices and of any circumstances that might increase the patient's risk of harm from using the device. Such assessments are particularly important in order to avoid undue burden or harm to members of vulnerable patient populations. For example, caution should be taken in implanting 510(k)-cleared devices in patients who might not have access to affordable health care if a serious adverse event occurs.

Conclusion

The process of 510(k) clearance for devices raises multiple questions about benefit-risk analysis, optimizing patient safety, clinical decision making, and distribution of 510(k)-cleared devices. Policymakers are currently debating whether the 510(k) process needs to be updated or even replaced. For example, safety issues led a national expert panel to recommend the elimination and replacement of the 510(k) clearance pathway in 2011.⁴ The panel concluded that a device's substantial equivalence to a predicate device did not ensure a similar benefit-risk profile and that this pathway also did not encourage meaningful innovation. Without any assurance of either safety or innovation, the panel believed that 510(k) clearance did not advance the FDA's mission of protecting public health.⁴

While that debate continues, physicians and patients need better **guidance** about decision making related to currently available 510(k)-cleared devices. In this case, the hospital purchasing committee should avoid bulk purchasing of the device in question and encourage clinicians to discuss relevant information about 510(k) clearance with patients who might benefit from the device. In the future, when questions remain about the use of these devices in patients, clinicians and health care organizations should ensure that uncertainties are discussed with patients, restrict financial relationships that could cause conflicts of interest, and follow patients closely after the device is implanted to help inform the FDA about the safety of the device, if or when issues arise.

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Editor's Note

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

What Do Clinicians and Organizations Owe Patients With Recalled Implanted Devices or Materials?

Michele A. Manahan, MD, MBA

Abstract

Placement of prosthetic breast implants for augmentation or reconstruction is common. Two specific safety concerns are considered in this article: breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) and complexes of symptoms known as breast implant illness. In response to a case involving a patient with concerns about BIA-ALCL, this commentary notes that triage, counseling, and treatment are guided in practice by available data in the literature. The commentary also discusses ethical considerations regarding breast implants and related illnesses.

Case

As of January 2020, 733 cases of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) had been reported to the US Food and Drug Administration (FDA), with a large majority of those cases involving textured breast implants manufactured by one company.¹ In response, the FDA requested that the company voluntarily withdraw its textured breast implants and tissue expanders from the market.^{2,3} The company sent Urgent Medical Device Recall letters to US customer surgeons, instructing them to return all unused products to a third-party recall provider, and sent notification letters to patients.^{2,3}

Dr W is a plastic surgeon who has implanted textured breast implants in patients, but not those manufactured by the company in question. Dr W's retired practice partner and friend, Dr X, did implant this company's textured breast implants in patients, many of whom still live locally. Stimulated by local news coverage of the textured breast implant recall, hundreds of her own and Dr X's patients have been calling to request appointments to discuss the risks and benefits of implant removal and replacement and whether they require increased monitoring.

Commentary

Implantation of devices in the breast for augmentation or **reconstruction** is common, and concerns have been raised over time regarding safety. Currently, BIA-ALCL⁴ and complexes of symptoms termed *breast implant illness* (BII) are being most prominently

considered¹ in hopes that available data will guide triage, counseling, and treatment. The case highlights ethical issues related to triage, patient education, patient satisfaction and management, and balancing patients' financial worries and fears, which are considered in this article as best addressed through shared decision making among physicians, patients, and caregivers.

Triage

Understanding patients' psychological as well as physical reactions to the risk of breast implant-associated illnesses like BIA-ALCL and BII will affect triage. The intensity or severity of patients' concerns, symptoms, or signs, as well as the resources of the practice, will all inform how surgeons prioritize new and returning patients' needs. Severe clinical presentations or extreme psychological distress (eg, intrusive thoughts, mood changes, sleep disruption) warrant urgent response and appropriate management. Physicians and clinic staff members should also be prepared to field calls from patients whose implants were not recalled but who are concerned and seeking information.

Well-informed surgeons will be aware of the clinical issues and prepare office staff to respond appropriately and responsively to potential patient misconceptions.⁵ Advanced preparation of all team members with whom patients communicate can affect patients' experiences of device recalls. Much of the impetus for advanced preparation has arisen beyond clinical spaces—for example, on social media sites where patients get information of varying quality about BIA-ALCL and BII.⁵ Regardless of information and knowledge gaps between patients and physicians, physicians should validate patients' concerns.⁶

Patient Education

When the patient and physician begin discussing clinical implications of recalled breast implants, the nature of a recall, symptoms and signs, risks and benefits of and alternatives to explantation, limitations of present knowledge, and financial considerations must be carefully considered.

Recall. A good discussion starting point is the recall, which, in this case and in actual recalls, does not apply at present to breast implants that have already been implanted.^{2,3,7} While insufficiently reassuring to some patients, **accurate information** from physicians should remain a priority.

Symptoms and signs. Plastic surgeons likely will also carefully discuss the nature of symptoms and signs that may be associated with implants. These discussions may include not only rare events but also more common, less media-publicized phenomena like appearance changes over time, chest discomfort, and implant firmness. Physician counseling regarding warning signs and **symptoms of complications** could help patients to be vigilant about their health. Moreover, validation of patients' own health concerns could strengthen patient-clinician relationships. Building trust could also encourage patients to seek care about their future concerns, regardless of whether they are presently predictable.⁸

Risks and benefits. Explantation of breast implants, as with any surgical procedure, carries potential risks that must be balanced with proposed and hoped-for benefits. In addition to surgical risk, explantation of breast implants has implications for chest aesthetics. Clinicians should thoroughly describe potential postexplantation appearance changes to help patients understand that their breasts' appearance might be

suboptimal and present them with potential solutions. Techniques to address native breast or chest soft tissue changes postexplantation include no management, tissue rearrangement, and autologous augmentation. Some authors propose algorithms to guide application of these strategies.^{9,10,11} Patients must understand each of these choices, and physicians must be prepared for variable patient reactions to postexplantation management.^{12,13,14,15} Sharing knowledge of patient-reported outcomes in different clinical scenarios might help patients make decisions; however, the absence of consensus recommendations can be expected to add to the burden of the patients' decision making.

Limitations of present knowledge. Discussing what is not known with patients, including the nascent literature guiding practice decisions, remains essential. For example, estimates of BIA-ALCL risk vary tenfold.¹⁶ Many barriers exist to clinicians obtaining accurate information about the incidence and risk of BIA-ALCL.¹⁷ The existence of other difficult-to-define-and-treat conditions associated with breast implants, such as BII, further complicates patient-physician conversations.¹⁸ Debates remain about other technical aspects of explantation in asymptomatic patients, such as management of the capsule (the internal tissue surrounding the implant).¹⁹ However, while strong scientific evidence unequivocally supporting certain interventions (eg, en bloc capsulectomy for conditions other than BIA-ALCL) is lacking, social media connections among patients are driving treatments, especially surgery.^{5,6} Patients should understand that current counseling cannot incorporate future discoveries or fully address all possible outcomes. As such, patients' trusting relationships with their physicians will hopefully lead patients to return for further assessment and treatment as their circumstances change over time.

Insurance. Financial considerations affect decision making in many ways. Counseling about financial responsibility for complications associated with breast implants has long-standing roots in plastic surgery, since this challenge long predates recognition of BIA-ALCL. Patients who have undergone procedures without insurance coverage, like aesthetic breast augmentation, might find that insurers do not cover subsequent costs related to a recall. Vieira et al suggest that appropriate plastic surgery care can be considered independently of insurers' decisions.²⁰

In sum, education about a recall can enhance patients' sense of ownership about seeking further consultation aside from routine monitoring and can help patients develop actionable plans and a sense of agency if they need to respond to explantation complications. Patients should be invited to engage their physicians in standard clinical follow-up and in additional appointments as needed. Patient education can also build trust by demonstrating physician concern, knowledge, and interest in patients' concerns.

Patient Satisfaction

Consideration of the entire patient remains essential to patient satisfaction.⁹ And it does seem that surgical management of breast implant concerns through explantation is associated with patient satisfaction.²¹ Lee et al reported that, in their sample of 50 patients with explantation due to BII symptoms, none would reconsider breast implants.²² Of 345 BII Facebook support group posts examined by Tang et al, none expressed explantation regret.⁶ In Slavin and Goldwyn's words: "Satisfying the needs in these patients emphasizes the importance and necessity of the surgeon taking the time to understand what the patient wants,"²³ which remains as true today as when these words were written to address a prior surge in breast implant safety concerns.^{13,23}

Multidisciplinary Management

When diagnosed with life-altering or life-threatening conditions, patients deserve timely access to appropriate care. National Comprehensive Cancer Network guidelines exist to guide diagnosis and management of BIA-ALCL, for which multidisciplinary management is recommended.²⁴ **Multidisciplinary involvement** can benefit patients with breast implant concerns, even when BIA-ALCL is not the likely diagnosis. Ongoing health monitoring and surveillance, including routine breast cancer surveillance, can be managed by nonsurgical clinicians and coordination of care beyond the perioperative period.

Shared Decision Making

Specific communication strategies useful in decision sharing with patients after a recall are modeled here in an extension of the case.

Patient Z calls Dr W's office to arrange an urgent follow-up with Dr X. Upon hearing of Dr X's retirement, she begins to cry, relating to the receptionist that she has been so worried since hearing of the implant recall yesterday that she hasn't felt like eating and spent the night awake, worrying that she is going to need more surgery. The receptionist reassures the patient that Dr W has heard about the recall and has instructed the staff to make sure that Patient Z, and others like her, can be added to the schedule for an urgent appointment.

When Dr W and Patient Z meet, Patient Z appears distraught and begins the conversation by explaining that she feels lost and alone. Dr W explains that many patients are experiencing similar reactions to the news. Dr W suggests that Patient Z allow her to share her knowledge to help Patient Z decide on the next steps related to the implants. After a thorough discussion of the topics elucidated above, Dr W helps the asymptomatic Patient Z understand her choices. Dr W suggests that the patient consider the options for a period of time before making a decision, since Patient Z had been happy with her results until learning of the recall and is asymptomatic and the recall does not require removal of existing implants. Dr W reminds Patient Z that she can continue to work with her health care team to monitor the situation and stay up-to-date as knowledge evolves. Patient Z plans to talk to her family members and schedules another appointment to further discuss potential surgery when they can be present also.

Respect, education, and shared decision making can be empowering for patients concerned about breast implants, especially in the case of a recall. Physicians can promote patient satisfaction by optimizing the quality of the care they offer patients, expressing respect for patients, and cultivating ongoing awareness of clinical practice changes.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

What Should Physician-Researchers Tell Patient-Subjects About Their Relationships With Industry?

Jeffrey R. Botkin, MD, MPH

Abstract

An investigator's personal financial interest in technology under investigation or in the company sponsoring the research is a clear conflict of interest (COI). Such financial relationships are common, and ethical questions rightly emerge about COIs' capacity to compromise an investigator's approaches to research. This commentary on a case suggests that COI disclosure is appropriate during the process of facilitating patient-subjects' informed consent because it promotes informed decision making and motivates transparency. But COI disclosures are not always efficacious, nor are they sufficient to address the problem of research bias. This commentary argues that mitigation or elimination of COIs is a more effective strategy than disclosure.

Case

Dr M is a senior resident physician conducting research on a vagal nerve stimulator (VNS) with supervision from the attending physician and principal investigator, Dr A. The VNS was initially approved as a device for a specific indication and application by the US Food and Drug Administration (FDA) following clinical trials. Anecdotal reports from subjects in those clinical trials suggest that VNS might also be helpful for another indication, so the device's manufacturer, Company K, suggested that a novel off-label application of the VNS be investigated by Drs M and A. This new clinical trial is federally funded and also supported financially by Company K. Dr A has received numerous research grants, dinners, and speakers' fees from Company K.

Dr M asks Dr A about the nature and scope of what they need to disclose to subjects during informed consent in order to comply with the Physician Payments Sunshine Act. This law requires manufacturers to report all payments to physicians and for physicians to either confirm or dispute and correct the data within 60 days of it being posted.¹

"Nothing," responds Dr A to Dr M. "That law applies to manufacturers, not to physicians and patients."

"Well, that's true, but if you were going to enroll in our study, wouldn't you want to know?" Dr M continues.

“I guess I’m not sure what exactly you think patients should be told,” says Dr A. “I mean, how much detail is necessary? In the VNS world, there are a limited number of experts, folks like us, to research new technologies like this device. We have financial ties to these companies because if we don’t, we help these companies for free. So, of course, we have financial ties to these companies. And, of course, we can’t recuse ourselves from decisions affected by ties to these companies because we are the ones best positioned to try to help these subjects, and we are the ones with the expertise needed to take good care of patients who can benefit from new VNS devices. So, Dr M, I do see your concern. I see what you’re saying about disclosure. But when you have limited time with patients, it’s hard to clarify everyone’s interests. I try just to keep things simple when I talk with patients, and I try to keep the focus on what’s at stake for them. If you can think of a better, clearer way for us to be as transparent as we can with our patient-subjects, we can talk about your ideas, but I’ve been doing this for a long time, and this is the best I’ve come up with. Does that help, Dr M?”

“Yes,” says Dr M. Dr M still wonders, however, what their patient-subjects should be told about Dr A’s relationships with Company K before enrolling them in the VNS trial.

Commentary

A conflict of interest (COI) in this case emerges because Dr A’s professional obligation to objectively conduct research conflicts with her personal interest in the device study generating favorable outcomes. The case asks us to consider what investigators should disclose to patient-subjects during informed consent. Related questions beyond the scope of this article also include whether and which information investigators should disclose to their institutions, sponsors, and journal publishers and readers. In what follows, I argue that investigators, in the case and in general, should **disclose their financial interests** to patient-subjects during informed consent but that medicine, as a profession, should not consider disclosure sufficient for addressing COIs.

Key Considerations About COIs

It’s helpful first to examine key decisions that COIs can influence and then consider some evidence about whether COIs lead to research bias.

Decisions, designs. COIs tend to work through subtle influences on decision making rather than by prompting investigators, say, to deliberately design a biased trial or falsify or fabricate data. But the prospect of money and Dr A’s prior commitments to the company could unconsciously influence many decisions about the trial that favor positive findings for the device. For example, trial design elements that can result in bias include use of a weak comparator drug, inadequate blinding, and poor follow-up.²

Evidence. Important to note is the absence of strong evidence that investigators’ personal financial interests commonly lead to research bias. Industry sponsorship does not necessarily create COIs, since funding tends to go to investigators’ institutions and might cover a portion of their salary but usually does not augment their income. Yet, it can create COIs when investigators have personal financial interests (ie, stock, speakers fees, royalties) in sponsors’ success. Evidence does show that industry sponsorship is associated with favorable outcomes.³ While notable from an ethics standpoint, this finding does not imply that investigators’ stakes are the most worrisome sources of bias, since industry roles in study design, data analysis, and data reporting can affect research outcomes. Meta-analyses show that, specifically, investigators’ stock ownership⁴ and industry roles⁵ in studies are associated with favorable outcomes. We

also know that companies court experts with lucrative payments to be advisors and speakers.^{6,7,8} While direct links between investigators' financial interests and study bias is difficult to establish in individual cases, identifying, managing, or eliminating COIs in biomedical research remains a priority for journals and all who are concerned with integrity in research.^{8,9}

Disclosure Requirements

Disclosure to subjects of investigators' financial interests is not required by federal regulations that govern human subjects research and protection. Public Health Service (PHS) regulations encourage consideration of whether to disclose investigator financial interests to participants, but such disclosures are not required.¹⁰ Most academic health centers (AHCs) in the United States have adopted PHS policy about COIs, which requires investigators' disclosure of "significant financial interest[s]" (ie, speaking and consulting fees, stocks exceeding \$5000 over 12 months) to their institutions¹¹—but does not require investigators' disclosure of industry ties to subjects—and states that identified COIs must be managed or eliminated.¹² PHS policy also does not stipulate how an institution should manage or eliminate an investigator's identified COIs. COIs are typically addressed by an institutional committee, officer, or institutional review board (IRB); common strategies for managing and eliminating identified COIs include, for example, COI disclosure in publications or requiring data to be analyzed by an investigator without COIs.

In the case, assuming her institution generally follows federal policy for PHS-funded research, Dr A should disclose **diners** and speaking fees to her institution if their value exceeds \$5000 cumulatively during the past 12 months, but she need not disclose grants from Company K to her institution because her institution would, presumably, already be aware of them. Her institution's IRB would determine whether and how Dr A must disclose dinner and fee information to subjects. This determination reflects the general consensus in the research ethics field that investigators should disclose to subjects relevant, significant **financial ties to industry**. The American Medical Association *Code of Medical Ethics* is in accord with this view, stating: "As part of the informed consent process, [investigators should] disclose to prospective participants the nature and source of funding and financial incentives offered to the investigators. This disclosure should be included in any written consent materials."¹³ Finally, an influential 2008 joint report on COIs by the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU)¹⁴ concurs, quoting an earlier AAMC task force report:

[T]he precise wording of disclosure in the consent form should be determined by the IRB, but should include an explanation of the fact that the financial interest in question has been reviewed by the COI committee, approved subject to committee oversight, and determined by both the committee and the IRB not to pose any additional significant risk to the welfare of research subjects or to the integrity of the research.¹⁵

Six Goals of Disclosure

Scholars have identified 6 goals of COI disclosures to research subjects.^{16,17}

1. *Enable subjects' informed consent and awareness of investigators' stakes.* Research subjects should make informed decisions about their participation in research. This requires awareness of the risks of participation—including factors that can increase risks—and possible benefits and awareness of factors that could threaten a study's integrity.

2. *Protect subjects' right to know about investigators' financial interests.* Some subjects want to know this information even if it is not critical to their decision about whether to participate in a study.^{18,19}
3. *Motivate trust.* Disclosure can help establish and maintain subjects' trust in investigators by promoting transparency. This can be key when, during research, subjects become ill or injured, or if they feel manipulated upon learning information they feel should have been revealed earlier.
4. *Minimize legal liability risk.* When, during research, subjects become ill, injured, or otherwise harmed, investigators' conduct prior to an adverse outcome can be important from a **risk management standpoint**.
5. *Deterrence.* Because disclosure can be uncomfortable for investigators, knowledge of an obligation to disclose could deter an investigator from pursuing financial relationships that could generate COIs.
6. *Minimizing risk of harm.* Disclosures might have a protective effect on subjects' welfare by reducing risk to which a subject is exposed over the course of a study.

Investigators' disclosure of financial interests might not always achieve or fully achieve these goals, but each suggests the importance of the role played by the ethical value of transparency and informed decision making for investigators and subjects.^{16,20}

Limits of Disclosure

It is unknown how many AHCs currently disclose investigator COIs to research subjects on a routine basis. In my own experience, disclosure to prospective subjects of investigators' financial interests typically happens during **informed consent**, and the nature of information disclosed varies. In interviews conducted with 23 IRB chairs from 2004 to 2005, 61% of interviewees supported COI disclosures to subjects in all circumstances.²¹ Of 120 respondents to a 2004 survey about their institution's policies, 48% noted disclosing financial ties to prospective subjects.²⁰ Since these studies were published, the roles of bias in clinical research and public scandals have brought attention and change to federal policy.^{22,23} In the case, an IRB would likely have required some disclosure if Dr A has a "significant financial interest," as defined by federal policy, in Company K. For example, if Dr A received more than \$5000 in dinners and speaking fees over the past year, an IRB would have likely required disclosure to patient-subjects.

Yet, as noted, it's important to acknowledge uncertainty about whether and to what extent COI disclosure to participants achieves the 6 goals articulated above. Lay people often have limited understanding of the information disclosed, its intended meaning, or what it could mean for them, and they remain uncertain about which questions to ask.^{17,18,19} In Weinfurt et al's study, several participants supposed that investigators with financial interests in research outcomes would conduct themselves more ethically and would do a better job.¹⁷ It's also possible that disclosure might exacerbate investigators' bias,²⁴ particularly if investigators feel that disclosure constitutes sufficient warning to others and absolves them of responsibility to avoid bias.²⁵

Recommendations

Concerns about the efficacy of disclosures should not lead us to forego them. Transparency is ethically appropriate, and disclosure promotes transparency between investigators and research participants. However, further research on the actual influence of disclosures on all stakeholders' decisions is important, and we must acknowledge the limitations of disclosure in mitigating COIs. The AAMC-AAU report¹⁴ and an Institute of Medicine report²⁶ both articulate standards for when investigators with

COIs should be able to conduct research, but whether AHCs commonly meet those standards remains unclear. Disclosures to participants are worthwhile, but greatly reducing or eliminating the conflicts to begin with is likely to be a much more effective strategy in reducing the risk of bias from an investigator's COIs.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

What Should Patients Be Told About Device Representatives' Roles at the Point of Surgical Care?

Jeffrey Bedard, MS

Abstract

Recent research has highlighted device representatives' roles in surgical cases. Additional review of cases based on actual events suggests that lack of training on the part of a surgeon and surgical team and lack of knowledge and training on the part of a representative can adversely affect a patient's clinical outcomes. While the necessity of surgical team training is acknowledged by health care organizations, organizations' policies about how to respond when surgeons or trainees refuse representatives' preoperative training remains unclear. Such a case is considered here with commentary that discusses a new model for technical support prior to, during, and after a patient's surgery.

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Case

Rep, a medical device representative for an orthopedic company, received a call from Dr N asking Rep to bring a specialized primary hip system and instrumentation for a patient with congenital dysplasia of the hip. Rep knew that Dr N had not previously worked with this implant, scheduled a time to meet Dr N and other resident physicians, and planned to perform a practice case using plastic foam pelvis and femur replicas. Upon arriving for the practice case, Dr N informed Rep that he did not need to perform the practice case. When Rep approached resident physicians working with Dr N and asked whether they would like to perform a practice case, they declined. Rep then tried to share with Dr N a training video illustrating the surgical technique, suggesting that Dr N review it over the weekend. Dr N declined and Rep agreed to be present for the case.

On the day of the case, Rep arrived in the operating room suite to find that the resident physicians had started the case. Dr N arrived and took over. Due to the unique shape of the acetabular cup Dr N wished to use, a specially designed reamer was needed for the cup. Dr N struggled with this reamer's assembly and use and the seating of the cup; Dr N requested fluoroscopy to visualize the cup's placement. After reviewing the fluoroscopy images, Dr N secured the cup. Dr N also encountered difficulty seating the

liner and asked Rep to verify that the liner was properly seated. Positioned beyond the sterile field, Rep was unable to see the liner. After struggling for 15 minutes to properly secure the acetabular liner, Dr N started the process of implanting the femoral prosthesis. The femoral component's unique design required Dr N to use special instruments to prepare the proximal femur for the prosthesis. Dr N struggled with the specialized instrumentation; to complete implantation of the femoral component, Rep held an illustration of the surgical technique and talked Dr N through each step. A trial reduction was completed, and the trial component was then replaced with the permanent femoral prosthesis.

Commentary

Interactions among device representatives and surgical care team members are often routine. Representatives are **regularly present during surgery** and often asked to respond to technical questions and facilitate smooth progress of a case. However, recent research suggests that there are times when device representatives' role exceeds the scope of their training or substitutes for surgeons' training or proficiency,¹ both of which pose significant risks for a surgical patient. The case above illuminates some questions about a device representative's role at the point of care.

A Device Representative's Role

Providing training resources and opportunities to a surgeon and surgical team members is a key responsibility of a device representative. Both the American College of Surgeons (ACS) and the American Medical Association (AMA) recognize the need for surgeons' assistance with devices and technologies^{2,3} and have developed guidelines for optimal patient outcomes. The ACS' "Revised Statement on Health Care Industry Representatives in the Operating Room" states: "The presence of the HCIR in the OR cannot substitute for preoperative training of the surgical team. The surgical team should have received training and demonstrated competence in the application of surgical devices and technologies used in the OR before the procedure."² And the AMA *Code of Medical Ethics* Opinion 10.6, "Industry Representatives in Clinical Settings," states: "Participation by industry representatives should not be allowed to substitute for training physicians to use devices and equipment safely themselves."³ It is reasonable to expect that a device representative, as a de facto surgical team member, should demonstrate the same ethical duty of care for the patient as everyone on a surgical team. However, that duty is realized through the representative's technical expertise in training the surgeon preparing for a procedure. Also ethically important is a representative's dependence on a surgeon for compensation; when this dependence compromises a representative's comfort with raising or capacity to **raise questions or concerns**—especially about a clinician's lack of training—manufacturer and institutional support can be key to keeping a patient safe.

Importance of Training Requirements

In the case, the rep provided training resources and opportunities to the surgical team: an opportunity to perform a practice case (or multiple cases, if so desired) using the implant instrumentation and training prosthesis on plastic bone replicas of the pelvis and femur, a video recording of a complete case, and a surgical technique illustration. The surgeon and surgical residents declined these resources. And Dr N's statement confirming that the rep would be present during the case certainly gives the impression that Dr N was planning to draw upon the rep's expertise, possibly as a substitute for Dr N's own training. While both the ACS and the AMA recognize that this kind of situation can occur, they offer no guidance about how to navigate it. To the best of my knowledge,

no health care organization provides guidance to representatives concerned about a surgeon's lack of training with a new technology. One health care industry representative's response to a survey conducted by me and my colleagues draws attention to this concern: "Our current medical environment does not allow for a 'sales rep' to question the ability of a surgeon regardless of patient outcome. There is no 'whistle blower law' in healthcare. The rep would lose their ability to call on the hospital and likely lose their job."¹

This case also suggests a possible disconnect between the device manufacturer's and the health care organization's **training requirements for new technology use**, especially at the point of care, and how those requirements are communicated. Collaboratively established training requirements could provide a mechanism by which device representatives could raise concerns about training adequacy and be supported by both the device's manufacturer and a health care organization, such that both could be held accountable for noncompliance. Training requirements should also clarify how someone might, even anonymously, report violations of training requirements, especially if someone feels that patient safety has been compromised.

Duty and Trust

Dr N's lack of preparation and training quickly became evident. His difficulty in assembling and using instrumentation and in recognizing when the acetabular cup was properly seated—which necessitated a fluoroscopy unit to visualize cup placement—added to the length of the patient's surgery. His difficulty seating the liner due to lack of familiarity with the components and how a properly seated liner should look also contributed to unnecessary delay of this patient's case and longer-than-necessary anesthesia. Finally, it should not have been necessary for the rep to hold up an illustration to talk Dr N through the femoral prosthesis implantation.

If the representative is not knowledgeable and well trained and a surgeon is untrained and lacking ability to implement critical steps safely, outcomes can be disastrous. In 2006, the Ohio Eighth District Court of Appeals upheld a \$1.75 million judgment against an Ohio neurosurgeon, a device representative, and the representative's employer.⁴ The representative had incorrectly informed the surgeon that the company's hydroxyapatite cement without mesh support was sufficient to cover a nearly 48 cm craniotomy cut when it was not. The representative also failed to inform the surgeon that drain placement would facilitate the patient's recovery. No drain was placed, the cement fractured, and, as a result, the patient endured 4 subsequent surgeries to repair the damage from fractured cement. The Ohio appeals court upheld the jury verdict finding both the representative and the manufacturer liable for negligence and negligent misrepresentation.

This case highlights a device or material manufacturer's duty to warn a learned intermediary. The representative noticed that the surgeon did not read the company's instructions about how to use hydroxyapatite cement without mesh support, failed to adequately guide the surgeon, and, as the manufacturer's agent, failed to execute a duty to adequately warn the surgeon about a prospective poor outcome for the patient. This case also decided that, though the intermediary, the neurosurgeon, was learned in surgery—presumably more so than the device representative—it does not follow that the device representative and manufacturer were not negligent.

The Ohio case sheds further light on the above case. Dr N's patients may rightfully assume that Dr N is well trained and owes patients a fiduciary duty to be technically competent. Placing a third party, such as a device representative, in a clinical decision-making role is a breach of Dr N's duty. Learning on the fly should be anathema for any physician, and a decision to postpone learning to the actual point of care damages patient-clinician relationships and violates trust.

Go Rep-less?

New models of providing support to those like the rep in the case above should also be considered. In 2014, a California academic health center (AHC) implemented a model of working with device innovators in which it acquired orthopedic implants directly from a manufacturer and trained one of its own surgical technicians to provide support.^{5,6} Although this AHC was looking to save on costs, other advantages to training its own surgical technicians include direct oversight of technicians as key members of a surgical care team who have a duty to the patient and are accountable, along with other team members, for providing a standard of care. Another benefit of a rep-less model is that an organization can establish its own rigorous training and continuing education programs to ensure all clinicians' technical proficiency, which could also improve clinical outcomes for patients undergoing implantation of new materials or devices.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.



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MEDICAL EDUCATION: PEER-REVIEWED ARTICLE

What Should the Public Know About Implantable Material and Device Innovation in the US?

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Abstract

Device innovation has potential to improve patient outcomes over time, yet prospective benefits must be considered in light of risks. At the macro level, designers and manufacturers of implantable devices and regulators must balance the need for assurance of devices' safety and effectiveness with industry and clinical investigational enthusiasm about innovation. At the micro level, clinician-investigators need to inform patient-subjects about a particular device's influence, for better or worse, on short- and long-term health goals.

To claim one AMA PRA Category 1 Credit™ for the CME activity associated with this article, you must do the following: (1) read this article in its entirety, (2) answer at least 80 percent of the quiz questions correctly, and (3) complete an evaluation. The quiz, evaluation, and form for claiming AMA PRA Category 1 Credit™ are available through the [AMA Ed Hub™](#).

Risk-Based Regulation

The US Food and Drug Administration (FDA) is the federal agency responsible for providing regulatory oversight of the manufacturing, sales, and distribution of medical devices in the United States. The FDA's mission includes both protecting public health by ensuring the safety and effectiveness of medical devices and "advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable."¹ When patients agree to have a device implanted, they expect that it will perform as designed and that it will not expose them to unreasonable risk. The FDA—via authority granted by the US Congress in the Federal Food, Drug, and Cosmetic Act of 1938,² the Medical Device Amendments of 1976,³ and subsequent acts⁴—is **responsible for ensuring** that device manufacturers have taken appropriate actions to meet these expectations.

Because the spectrum of devices ranges from low-risk toothbrushes, band-aids, and reading glasses to high-risk pacemakers, intraocular lenses, and artificial heart valves, the framers of the Medical Device Amendments created 3 classes of devices based on risk.

- Class I devices are the lowest risk and include the aforementioned household items, as well as surgical instruments and gloves; most do not require a premarket submission to the FDA.
- Class II devices are moderate risk and include many devices commonly encountered in health care (eg, electrocardiographs, sphygmomanometers, and other monitoring devices; x-ray and computed tomography imaging devices; syringes; and, as discussed below, some implanted devices). Most require FDA review and clearance of a premarket notification, commonly referred to as a 510(k), before they can be marketed.
- Class III devices are the highest risk or are novel devices that have not previously been classified and, prior to marketing, are subject to FDA review and approval of a premarket approval (PMA) application and inspection of the facility in which a device is manufactured. Most PMA submissions are for implants and novel diagnostic tests.

The concepts of safety and effectiveness as they pertain to medical devices must also be understood within the context of risk and benefit. FDA device regulations state:

There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.⁶

There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.⁷

What constitutes “clinically significant results” of the effectiveness of a device will vary with the patient population, the disease or condition for which it has been designed as an intervention, and the availability (or lack thereof) of alternative therapies. For example, when a disease or condition is life-threatening and alternatives are few, it may be appropriate to **accept a greater risk** to balance potential benefits. To be clear, safety is not the absence of risk but reflects a balance between prospective risks and benefits. That is, use of a device that results in adverse events in a small portion of a target population does not, in and of itself, mean the device is unsafe.

Moreover, the FDA requires only “reasonable assurance,” not a guarantee, of device safety and effectiveness. The framers of the Medical Device Amendments noted that this standard is “predicated upon the recognition that no regulatory mechanisms can guarantee that a product will never cause injury, or will always produce effective results.”⁸ An FDA decision to allow a device to be marketed reflects a balance between potential benefits that a device might offer a significant portion of a treated population against potential risks that might be experienced by some.

Implantable Device Regulation

Although the subset of implantable devices is generally regarded as high risk, each device presents a distinct **risk profile**. These risk profiles reflect the different conditions the devices are intended to treat (eg, coronary artery disease, diabetes, osteoarthritis), the different procedures required for implantation, and device characteristics (eg, whether the device is electrically powered; whether its function is physiological or

structural; whether it is permanent, removed after some duration, or resorbed over some duration; and whether it delivers a drug).

FDA regulations allow implants to be classified as class II (but not class I) if risks can be identified and appropriately mitigated to offer reasonable assurance of safety and effectiveness.⁹ For example, many orthopedic implants (eg, intramedullary fixation rods that are inserted into the bone canal of long bones for fixation of fractures,¹⁰ polymethylmethacrylate bone cement for fixing prosthetic implants to living bone,¹¹ and many ankle, hip, and knee prostheses¹²) are class II. Since these device types have well-understood risks, performance testing and animal data are generally sufficient to demonstrate performance of class II devices in accordance with established specifications, intended uses, and user needs.

Implantable devices that are high risk or less well understood are class III. These include cardiac pacemakers and heart valves, which are life-sustaining, and breast implants, dermal fillers for wrinkle reduction, and intraocular lenses, which are not life-sustaining. An FDA decision to classify devices as class III reflects the agency's determination that a higher degree of regulatory oversight is necessary to ensure the safety and effectiveness of these devices.

Regulatory Requirements

An FDA decision to classify a device as class III reflects its greater perceived risk or greater uncertainty about the information needed to determine reasonable assurance of safety and effectiveness. Devices in this class require a PMA submission¹³ that provides the clinical evidence necessary not only to demonstrate that the device will provide reasonable assurance of safety and effectiveness but also for users to understand its prospective risks and benefits. Furthermore, a PMA submission must describe how a device's manufacture will accord established quality practices, and a PMA submitter's manufacturing facilities must also pass FDA inspection.¹³

As mentioned, most class II devices require FDA review and clearance of a premarket notification, or 510(k). The **510(k) pathway** is sometimes incorrectly described as being a loophole or fast track. A device submitted through the 510(k) pathway must be found to be "substantially equivalent" to a legally marketed predicate device, but safety and effectiveness still underlie each 510(k) review and substantial equivalence determination.¹⁴ For implantable devices, a 510(k) submission includes the same bench and animal testing demonstrating that the materials are biocompatible and appropriate for the intended use as would be provided in a PMA submission, as well as the same electrical safety and software testing when needed. Most 510(k) submissions, however, do not require clinical testing (only 10% to 15% of 510(k) submissions include clinical data¹⁵), as many devices' performance can be fully evaluated using bench and animal studies and many class II devices already have a long history of safe use. For example, polypropylene sutures have been used since 1969,¹⁶ and their risks and benefits are well understood. Nevertheless, the FDA generally requires clinical studies for implantable devices with new designs or materials or for devices in which bench testing is insufficient to demonstrate performance.

In addition to following premarket submission requirements, all manufacturers of implantable devices must follow good manufacturing practices specified in the Quality System Regulation.¹⁷ The Quality System Regulation requires that specifications and controls be established for devices and that devices be designed to meet these

specifications (design controls); that devices be manufactured under a quality system; that finished devices meet these specifications; that devices be correctly installed, checked, and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed. The Quality System Regulation helps ensure that implantable devices are appropriately designed to meet user needs and intended uses and are consistently manufactured in accordance with established specifications.

Labeling

The Code of Federal Regulations requires device labels to include instructions, risk and benefit information, and other essential information for safe and effective use.¹⁸ Labeling is also important for risk mitigation and key to FDA review of PMA and 510(k) submissions. The FDA generally requires manufacturers of implantable devices, which are only for prescription use, to develop both physician- and patient-appropriate labeling. Physician labels are not supposed to substitute for professional judgment and should facilitate physicians' explanations to patients of why they recommend a particular device and its potential risks and benefits. Importantly, implantable devices' labels are not expected to include all possible adverse situations that could occur. Patient labels should educate patients about what to expect from the device, including potential risks and benefits. FDA guidance about patient labeling is intended to assist device manufacturers' preparation of labels that are readable at an eighth-grade level, define terms, summarize points, and promote understanding.¹⁹

Implantable devices available in the United States can save lives, restore lost function, and provide benefits to many patients. No implantable devices are risk free, and FDA device regulation helps ensure their safety and effectiveness.

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AMA CODE SAYS

AMA Code of Medical Ethics' Opinions Related to Implantable Devices

Robert Dinallo

Abstract

Many US patients will have an implantable device during their lives. The AMA Code of Medical Ethics offers guidance for weighing need for patient-subjects' safety against health care sector demand for innovation.

Role of the American Medical Association Code of Medical Ethics

Given that fewer than 1% of medical devices that enter the US market have undergone the 2 clinical trials required for pharmaceutical approval,^{1,2} resources such as the American Medical Association (AMA) Code of Medical Ethics are especially important in helping clinicians balance access to new devices against safety concerns. The AMA Code provides 2 opinions relevant to implantable devices—Opinion 1.2.9, “Use of Remote Sensing and Monitoring Devices,”³ and Opinion 7.1.2, “Informed Consent in Research.”⁴ Both affirm physicians' ethical obligations to disclose to patients whether a device has been rigorously tested and to support safety and effectiveness research on devices.

The AMA Code offers guidance to physicians on use of innovative and emerging therapies in Chapter 7, “Opinions on Research and Innovation,”⁵ and on implantable monitoring devices in Opinion 1.2.9.³ Both suggest the importance of maintaining patient-physician relationships and affirm physicians' ethical obligations to disclose to patients whether a novel therapy has been rigorously tested, to promote patient safety, and to improve quality of care.

Opinion 1.2.9 offers guidance relevant to a range of technologies and is especially relevant for devices with **remote monitoring capabilities**, which pose privacy risks. It states that physicians should “explain how the device(s) will be used in the patient's care and what will be expected of the patient in using the technology, and disclose any limitations, risks, or medical uncertainties associated with the device(s) and data transmission.”³ This guidance clarifies physicians' ethical obligation to disclose known risks. These devices can improve efficiency and quality of care and promote access, but they can also pose risks to the safety and confidentiality of patient information.³ As devices become more advanced and interconnected, **cybersecurity risks** must also be considered.⁶ Although no cyberattack leading to patient harm has been reported to date, the threat is real, has been demonstrated in research, and has been voiced by patients.⁶

Opinion 1.2.9 also states that physicians should support research into the safety and effectiveness of remote sensing and monitoring devices and advocate for **appropriate oversight**.³

Physicians searching for more ethics guidance on implantable devices can also consult chapter 7 of the *AMA Code*, which contains opinions on research, innovation, and uses of new technology.⁵ While these opinions do not reference implantable devices directly, their guidance can be applied to riskier implantable devices. Opinion 7.1.2 states that physicians should disclose “the nature of the experimental drug(s), device(s), or procedure(s) to be used in research.”⁴ Additionally, Opinion 7.1.1, “Physician Involvement in Research,” states that physicians should uphold rigorous scientific, ethical, and legal standards in conducting and disseminating research results.⁷

Conclusion

In short, physicians have ethical obligations to be honest with patients about the risks and purposes of implantable devices. The *AMA Code* affirms that conveying relevant information to patients is key to informed consent. Moreover, physicians should continue, through research and advocacy, to ensure that riskier devices are rigorously tested and comply with federal regulations.

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STATE OF THE ART AND SCIENCE: PEER-REVIEWED ARTICLE

What Should Cardiac Patients Know About Device Cybersecurity Prior to Implantation?

Emily P. Zeitler, MD, MHS and Daniel B. Kramer, MD, MPH

Abstract

Cardiac implantable electronic device (CIED) procedures require informed consent and, ideally, shared decision making to guide patients through their experiences as CIED recipients. The information that different patients need or want about cybersecurity risk varies. This article considers device cybersecurity risks in light of federal guidelines and suggests strategies for communicating these risks clearly during informed consent conversations and follow-up.

Introduction

Cardiac implantable electronic devices (CIEDs) reduce morbidity and mortality across a wide spectrum of cardiovascular conditions.¹ Devices such as permanent pacemakers, implantable cardioverter-defibrillators, and pulmonary artery pressure monitors for patients with heart failure store patient data and transmit it wirelessly to clinicians. Clinicians who implant these devices have legal and ethical obligations to obtain informed consent after outlining **risks and benefits** of surgical implantation to patients,² and they face policy mandates to engage in formal shared decision making with patients to align device-based therapy with patients' goals.³ Regulators charged with premarket evaluation of these devices and their postmarket surveillance, particularly the US Food and Drug Administration (FDA), communicate established risks through approved labeling when marketing authority is granted. Emerging safety concerns are addressed through tailored communications, advisories, or recalls.

While computing and data transmission functions of CIEDs necessarily entail selected cybersecurity risks,^{4,5} it remains unclear whether and in what way regulators ought to include this risk in initial and ongoing communications with clinicians and patients. Broad **disclosure of all potential risks** may needlessly worry patients and crowd out other information during time-pressured clinician encounters. Accordingly, there is genuine debate about whether patients need this information at all and, if so, at what level of detail.^{6,7} This approach would seem to align with the recognition that manufacturers communicate postmarket risks directly to clinicians but generally only indirectly to patients.⁸ Yet leaving disclosure decisions to clinicians alone likely stretches most physicians' expertise on technical cybersecurity details. Overly narrow communication about risks might be too paternalistic and fail to appropriately inform patients about essential aspects of their own treatment.

This article briefly characterizes current cybersecurity risks associated with CIED use and reviews recent FDA guidance on communicating cybersecurity vulnerabilities to patients. We then provide an ethical analysis of this FDA communication framework and suggest potential revisions that might help balance competing values and interests.

Potential Cybersecurity Risks of CIEDs

Unlike risks associated with implantation or longitudinal performance of CIEDs, **cybersecurity concerns** might seem abstract and difficult to quantify. The risks most familiar to both patients and clinicians are those related to privacy.² Data stored and transmitted by CIEDs monitor device function (eg, battery life, wire integrity) and patient status, such as detection of arrhythmias or changes in underlying disease in the case of heart failure. Data transmissions typically occur wirelessly through signals sent (either through radiofrequency telemetry or Bluetooth) from an implanted device to either a home monitor or a patient's smartphone, which then relays data to device manufacturers for storage on large servers. Data are then shared with clinical sites for monitoring of clinical and device status. Remote monitoring has been demonstrated to improve patient outcomes and health care utilization.^{9,10,11}

Much like other forms of patient data, patient information stored in these devices and transmitted wirelessly is encrypted and subject to privacy provisions of the Health Insurance Portability and Accountability Act (HIPAA).² Currently, data that are stored and transmitted by CIEDs are shared only with treating physicians and other health care professionals, patients, regulatory bodies, payers, and researchers in accordance with HIPAA regulations. Preimplantation counseling rarely, if ever, includes a discussion of risks related to privacy,¹² and limited data suggest that patients who consider these risks at all view them as acceptable in light of the clinical benefits of receiving a device for their specific condition.¹³

In addition to privacy concerns, which are not unique to CIEDs, implanted devices are at risk for direct interference with device function through malicious intrusion. Although, to the best of our knowledge, cases of actual patient harm have never been reported, it is theoretically possible to disrupt device function (eg, pacing therapy) through introduction of malware or direct interference that leverages the wireless communication through which devices are programmed clinically.¹⁴ This possibility was brought to wide public attention when former Vice President Dick Cheney, who had an implantable cardioverter-defibrillator during his time in office, noted in a *60 Minutes* interview in 2013 that the wireless telemetry on his device was deactivated, at his request, to reduce the possibility of malicious interference.¹⁵ The same idea of hacking a CIED was dramatized in the TV show *Homeland* in 2012,¹⁶ although the methods employed were not realistic.

Creative license notwithstanding, these types of cybersecurity concerns have potential for clinical impact and present clinicians with the dilemma of informing patients without creating panic or confusion. For example, in 2016, there were early reports of a possible cybersecurity threat related to remote monitoring of a particular manufacturer's pacemakers, but FDA communication on this issue was withheld until a software patch was available from the manufacturer, which downloaded automatically without patient engagement.⁵ Improving regulatory and clinical management of these circumstances is the primary motivation for recent, admirable engagement among the FDA, professional societies, and patient groups.

FDA Guidance

The FDA's public health mandate to provide reasonable assurance of safety and effectiveness for medical devices now includes evaluation of the cybersecurity features of implanted devices and strategies for communicating potential concerns. Accordingly, FDA guidance clarifies key definitions related to cybersecurity risks. *Vulnerabilities* refer to potential weaknesses within medical devices or systems that could potentially cause patient harm or impact safety or performance of connected devices or systems. *Threats* are events or circumstances with the potential to leverage vulnerabilities. *Exploits* are instances in which vulnerabilities are actually utilized, whether intentionally or accidentally, thereby compromising safety or performance. For example, in recent years there have been multiple advisories pertaining to identified cybersecurity vulnerabilities affecting various device manufacturer platforms, although actual exploits have not been reported.¹⁷

The FDA plays a central role in evaluating CIEDs for potential cybersecurity concerns not only through premarket evaluation but also through postmarket assessments and regulatory action.¹⁸ The real-life and theoretical risks of cybersecurity have led the FDA to issue guidance for CIED manufacturers on how to address cybersecurity issues when developing new devices¹⁹ and on postmarket cybersecurity activities, including controls or safeguards and monitoring vulnerabilities and controls' effectiveness.²⁰ FDA guidance provides transparency in regulatory decision making while setting standards for risk mitigation. Guidance documents are not legally binding but provide clarity to manufacturers and the public regarding current FDA thinking on specific regulatory topics.²¹ The FDA joins a chorus of other stakeholders who recognize the importance of cybersecurity vigilance for patient protection.²² Indeed, the FDA partners with other cybersecurity experts, including other federal agencies, academic groups, and nongovernment "white hat hackers" who proactively help to identify medical device vulnerabilities.²³

As part of this effort, the FDA has also sought to understand how best to communicate cybersecurity concerns to patients. Early results of these efforts indicate that patients prefer to be given control over how much information they receive related to cybersecurity vulnerabilities and that they wish to be informed as soon as the threat is identified, regardless of whether risk reduction measures are available.^{8,24} In October 2020, the FDA sought comments on a discussion paper written by the Patient Engagement Advisory Committee titled "Communicating Cybersecurity Vulnerabilities to Patients: Considerations for a Framework," which provided preliminary recommendations for best practices for presenting these unique risks to clinicians and patients.²⁵

Clear Disclosure Avoids Panic

The FDA's working framework on communicating cybersecurity risks to clinicians and patients implicitly draws on key ethical principles in coordinating responses to cybersecurity concerns. First, the framework admirably attempts to balance beneficence and nonmaleficence. A running theme is the need for the FDA and industry to inform clinicians and patients and to provide clear, accessible guidance on necessary steps for avoiding harm (for example, by communicating as clearly as possible whether patients have a specific action item, such as downloading a security patch).²⁵ Making the magnitude and likelihood of potential harm transparent is also emphasized, as the risk of vulnerabilities being exploited—at least for insulin pumps—is considered to be extremely small and outweighed by the benefits of the devices themselves.²⁶ Accurately

conveying the rarity of potential harms weighed against the much larger and more concrete clinical benefits might help patients avoid choosing to forgo devices that, on balance, substantially promote their well-being. Second, the FDA framework admirably addresses information transfer or access inequity by noting the need for translations, printed materials targeting modest levels of education, and multiple formats.²⁵

Despite these strengths, several specific aspects of communicating cybersecurity risks merit further consideration by the FDA and others. First, our practical experience with previous advisories suggests that most patients will only hear “pacemaker” or “implantable defibrillator” and tend not to absorb the details even of the brand of device affected, let alone a model name and number. Just as patients might not know their own device details, so health care proxies might not have that information readily accessible to them.

Second, even if the FDA’s own communications clearly identify the affected systems—and whether the cybersecurity risk applies to more than one class of device or vendor—clinics can still expect a large volume of **inquiries from patients** about whether their device is affected. The FDA can support clinics in answering patient queries through at least 2 different mechanisms. One would be to accelerate requirements for documenting the unique device identifier (UDI)—details about a specific device embedded in the device itself, such as type, model, and manufacturing lot—in patient records. This regulatory requirement for implantable devices has experienced delays in implementation, but the need to rapidly identify specific patient exposures to cybersecurity threats provides a motive for fully documenting UDIs. Another way for the FDA to support ambulatory clinics’ response to patient inquiries would be to use its platform and partnerships with professional societies to emphasize the importance of such clinics maintaining a structured database of all of their implanted CIEDs and following patients longitudinally. There are several third-party vendors who supply these systems,²⁷ which allow for rapid searches and identification of patients according to device type, serial number, and other parameters. Such systems are expensive, however, and might not be universally employed.

Third, the FDA’s framework points to an opportunity for clinicians, at the time of implantation, to be much more proactive in providing patients with their own device-specific information and emphasizing why it is critical to keep these data accessible. Doing so is within the scope of physicians’ traditional role in obtaining consent and advising patients of ongoing risks.

Finally, the FDA and professional societies can partner in engaging patients in remote monitoring and regular clinic follow-up by stressing that these activities promote cybersecurity protection. Presenting recommended follow-up and the use of remote monitoring as a strategy for forestalling cybersecurity concerns might motivate patients to undertake clinical care that might otherwise seem to be of low value.²⁸

Conclusion

With the overarching charge of protecting public health, medical device cybersecurity is part of the broader regulatory effort to balance making innovative devices available and ensuring their safe use. These pressures can be in conflict when limited data exist on a new device or device feature with significant promise of improving public health. Although patients have not traditionally been directly involved in regulatory decisions, they presume that medical device regulation prioritizes assurance of safety over other

factors.¹³ Continuing to engage patients in tailoring the FDA's approach to cybersecurity might help balance competing values underlying risk disclosure.

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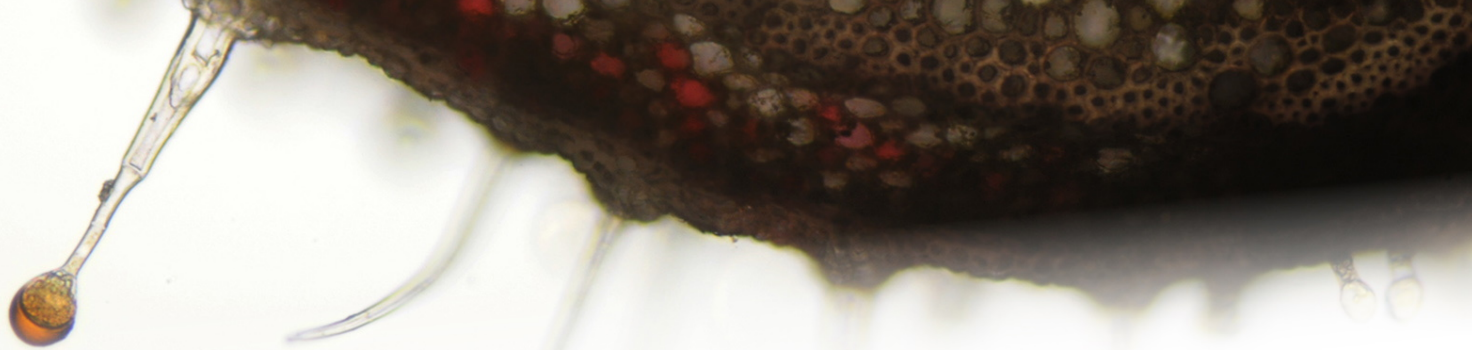
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HISTORY OF MEDICINE: PEER-REVIEWED ARTICLE

FDA Device Oversight From 1906 to the Present

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Abstract

This article examines the history of device oversight by the US Food and Drug Administration (FDA). Significant regulatory changes occurred in response to injuries caused by Dalkon Shield intrauterine devices. This article summarizes those changes as well as continued efforts by the FDA to strengthen device oversight and address areas of concern.

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Genesis of Device Oversight

The dramatic expansion of device use in health care demands that clinicians understand device regulation and its strengths and weaknesses as a key ethical and clinical responsibility. In 2018, the US Food and Drug Administration (FDA) approved more than 100 novel devices, a number that surpassed the prior year's record and represented a fourfold increase over 2009.¹ Medical product oversight began with a focus on food and medications during the early 20th century, spurred by public concern about the danger posed by common food additives, such as formaldehyde.² As a result, the Pure Food and Drug Act was signed into law in 1906,³ creating a federal entity that would become the FDA. The Federal Food, Drug, and Cosmetic Act of 1938 authorized product oversight by the FDA,⁴ but even with amendments⁵ in 1962 inspired by the tragic health consequences of sulfanilamide⁶ and thalidomide,⁷ the FDA did not regulate devices until 1976, when complications associated with the Dalkon Shield spurred new legislation.

Lessons From the Dalkon Shield

A contraceptive device inserted into a woman's uterus for pregnancy prevention, the Dalkon Shield was marketed to American women beginning in 1971 as a better alternative to contraceptive pills.⁸ Its use skyrocketed, with approximately 2.2 million devices implanted in American women by 1974.⁹ Due to limitations in regulatory requirements at that time, no federal oversight of the device's premarket assessment occurred.^{10,11} Postmarket research revealed a 4.7% pregnancy rate and a 6.3% rate of device expulsion (ie, displacement from its proper uterine position) in Dalkon Shield users—far higher than the rates touted by the manufacturer.¹² Furthermore, women who

became pregnant were at higher risk for complications, including septic pregnancy and maternal death.¹³ Despite reports of significant morbidity and mortality associated with use of the device, removal of the Dalkon Shield from the market was slow; voluntary recall was not issued until late May of 1974, months after the manufacturer became aware of hazards.¹⁴

The importance of pre- and postmarket device regulation and the dangers of decentralized regulatory authority were illuminated by the Dalkon Shield, leading to the passage of the Medical Device Amendments of 1976.¹⁵ These amendments assigned ultimate regulatory authority for devices to the FDA; established a 3-category, risk-based classification system for devices (I, II, III); and required postmarket adverse events reporting. Two regulatory pathways for devices were also established: premarket approval (PMA) and premarket notification, known as the 510(k) pathway. While most high-risk class III devices required PMA based on evaluation of their safety and effectiveness prior to use in clinical practice¹⁶ (similar to drugs^{17,18,19}), devices for which PMA was not required could utilize the 510(k) pathway,²⁰ discussed in more detail below.

Continued Framing of FDA Oversight

In 1982, the Center for Devices and Radiological Health (CDRH) was formed within the FDA to regulate devices and radiation-emitting products.²¹ The Safe Medical Devices Act (SMDA)²² of 1990 defined *substantial equivalence* to a predicate device (a device already on the market) as a standard for clearing devices utilizing the 510(k) pathway. A 510(k)-cleared device must (1) have the same intended use as a predicate device and (2) have the same technical characteristics or, if different, not raise questions about safety and effectiveness and demonstrate comparable safety and effectiveness to the predicate device through performance data submitted to the FDA.²⁰ In addition, the SMDA introduced postmarket surveillance requirements for manufacturers, mandated adverse event reporting for medical facilities, established penalties for violations, and granted the FDA recall authority.²² Three recall categories (I, II, III) based on health hazard risk were created, with class I considered the highest risk.²² Subsequent legislation included requirements to establish a unique device identification system and to include devices in the Sentinel System of postmarket safety surveillance.^{23,24,25}

As requirements became more stringent, however, concerns arose that regulation could stifle innovation and deprive patients of timely access to lifesaving devices.^{10,26} Subsequent legislation introduced a “least burdensome” approach to premarket review,²⁷ the De Novo program for novel low- to moderate-risk devices,²⁴ and reduction of the PMA cost burden for small business manufacturers.²⁸ More efficient and flexible approaches were outlined in 2016, with the 21st Century Cures Act²⁹ providing support for breakthrough devices and expanding criteria for humanitarian-use devices.

Pre- and Postmarket Oversight

Despite increased regulatory oversight by the FDA and expansion of device use in patient care, safety concerns can evolve over the lifespan of some devices. Recalls of cardioverter-defibrillator leads³⁰ and metal-on-metal hip implants,³¹ complications with urogynecologic surgical mesh³² and a permanent implantable contraceptive device,³³ anaplastic large cell lymphoma association with breast implants,³⁴ and potential mortality associated with paclitaxel-containing devices^{35,36} all reinforce the FDA’s critical ongoing role in public protection.

The 510(k) pathway, particularly the substantial equivalence standard, has faced criticism. For devices cleared or approved between 1992 and 2012, 510(k)-cleared devices were 11.5 times more likely to face recalls than devices approved through the more stringent PMA process.³⁷ The percentage of devices utilizing clinical evidence to support substantial equivalence on the basis of safety and effectiveness was 27% for otolaryngologic devices cleared between 1997 and 2016.³⁸ Additionally, manufacturers of just 16% of devices in a sample of 510(k)-implanted devices cleared from 2008 to 2012 offered publicly available documentation of scientific evidence used to establish substantial equivalence, despite FDA requirements to do so.³⁹

Furthermore, devices or materials have been cleared based on their substantial equivalence to predicates that were recalled due to adverse events, as was the case for 16% of surgical meshes cleared between 2013 and 2015.⁴⁰ A 2011 Institute of Medicine report concluded that, with some exceptions, “the 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices” but rather to assess substantial equivalence to predicate devices.¹⁷ Such concerns are clinically and ethically important, as premarket notification continues to be the primary regulatory pathway for many devices. In 2017, 3173 devices—82% of the total FDA-approved or cleared devices that year—entered the market via the 510(k) pathway.⁴¹

Postmarket surveillance, a combination of active and passive surveillance, has also faced criticism as being too narrowly focused or hampered by incomplete data. Although possible causal relationships between adverse events and a device have been successfully detected during postmarket surveillance, there is currently no comprehensive system for the FDA to field robust, reliable postmarket data.^{42,43}

Comparisons have been made between the safety and performance requirements for devices and drugs. **Drug approval** includes demonstration of “substantial evidence” of safety and efficacy through clinical trials.^{17,18,19} Moreover, for drugs, the FDA Sentinel Initiative^{25,44} utilizes well-coordinated, standardized database distribution and data collection structures with multiple partners and has been a robust part of FDA active postmarket surveillance.^{45,46}

Strengthening and Modernizing

Establishing a robust system of medical device postmarket surveillance and evaluation is a critical policy need that has been a major focus of the FDA, along with strengthening and modernizing premarket regulatory processes. This effort includes a focus on the 510(k) pathway, a unique device identification (UDI) system, use of real-world data (RWD) and real-world evidence (RWE), and, in collaboration with other stakeholders, the development of the National Evaluation System for Health Technology (NEST).⁴⁶

510(k) pathway. Throughout the last decade, the FDA has standardized device review procedures,⁴¹ introduced a “refuse-to-accept” policy based on submission completeness,⁴⁷ and added substantial equivalence documentation requirements for 510(k) clearance.⁴⁸ The FDA’s Safety and Performance Based Pathway offers manufacturers of well-understood device types an option to use FDA-identified performance criteria to demonstrate safety and effectiveness.^{49,50} To more fully address safety concerns stemming from use of recalled or high-risk predicates, nearly 1500 devices have been eliminated for use as predicates in 510(k) submissions since 2012.⁴¹ Use of the 510(k) pathway has also been curtailed for new high-risk devices,^{51,52} with no class III devices cleared for market via premarket notification in

2018.⁴¹ Recommendations have also been made that the Safety and Performance Based Pathway become mandatory for eligible devices, commonly recalled device types, and possibly all 510(k) devices.^{50,53}

UDI system. Development of a UDI system was prompted by the FDA's Unique Device Identification System Rule of 2013,⁵⁴ which required manufacturers to assign UDIs to devices. This requirement has facilitated development of a standard for electronic health record (EHR) documentation of device implants in patients,⁵⁵ adverse event reporting, and recall notification. UDI availability and use also supports improved aggregation of postmarket data from EHRs, payer claims, and **clinical registries**, enabling more robust postmarket surveillance.⁵⁶ A UDI implementation roadmap for implantable devices for health care organizations has been created,⁵⁷ and research has demonstrated successful UDI transmission via claims to payers.⁵⁸ One ongoing challenge is that, while moderate- and high-risk devices now have UDIs as mandated by the Unique Device Identification System Rule,⁵⁴ there is no requirement for UDI documentation during the course of clinical care, which is critical for broad UDI availability and use. Although some organizations are documenting UDIs without a mandate, policy updates will be required to advance broader applications.

RWD and RWE. Use of RWD and RWE in regulatory decision making and **postmarket surveillance** of devices has been an ongoing FDA priority, prompting the FDA to issue guidance⁵⁹ and convene an expert workshop in 2017.⁶⁰ Expanded UDI utilization would support the FDA's focus on RWD, which includes patient characteristics and health outcomes from multiple sources (EHRs, claims databases, and clinical registries).⁶¹ Use and analysis of RWD from clinical trials and observational studies can be used to generate RWE, the clinical information needed to determine device use risks and benefits.⁶¹ One historical limitation of RWD and RWE, however, has been data quality and analysis validity; both are current foci of the NEST Coordinating Center (NESTcc),⁶² the FDA's RWE program,⁶³ and collaborative efforts.⁶⁴

NESTcc. Establishing a national evaluation system for health technology was included in the CDRH's *2016-17 Strategic Priorities*.⁶⁵ NESTcc is a public-private organization consisting of multiple partners (health systems, academia, payers, registries, and research networks).⁶⁶ NESTcc is advancing the use of RWD and RWE in research projects,^{67,68,69} with the goal of informing device evaluation and regulation.⁷⁰

Conclusion

As the Dalkon Shield case illuminates, patient harm has been a driver of change in device oversight and regulation. This historical overview has summarized key strengths and weaknesses of the federal legislative response, which has attempted to protect patient safety while fostering innovation. Ongoing efforts by the FDA to strengthen and modernize pre- and postmarket regulatory processes aim to advance device safety and enhance patient outcomes.

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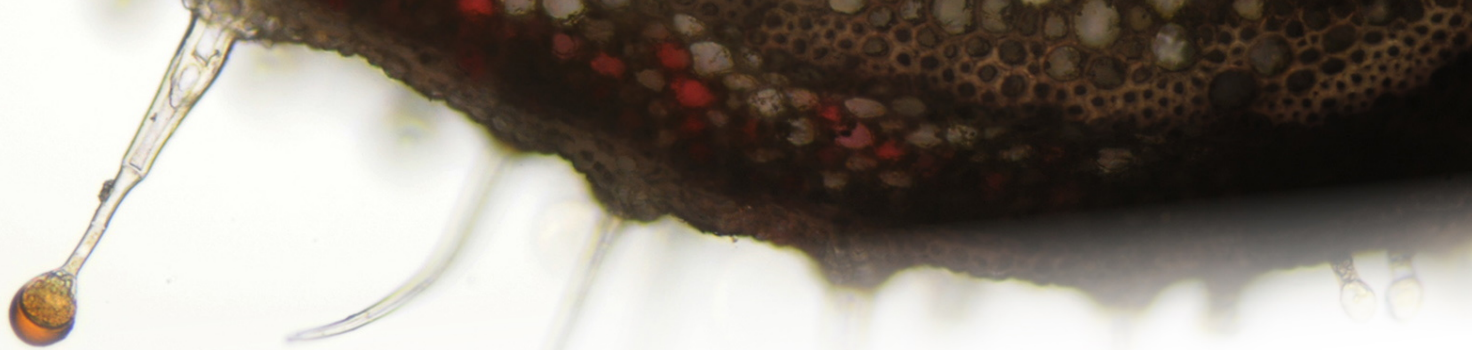
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Dr Wilson had stock options in Vitreos Health purchased in 2019 and has received grant funding for the BUILD project (2015-2019) from the Food and Drug Administration, Johnson and Johnson, and Medtronic; for the UDI2Claims project (2018-2019) from the Patient-Centered Outcomes Research Institute; and for Characterizing UDI Adoption and Use: A Mixed Methods Approach (2020-present) from NESTcc. She also consulted for Mass General Brigham in 2020. Anna Pisac purchased stock options in Kaleido Biosciences.

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HISTORY OF MEDICINE

How Pseudoscience Generated US Material and Device Regulations

Jorie Braunold, MLIS

Abstract

The images in the American Medical Association's Historic Health Fraud and Alternative Medicine Collection include quack devices from the early 20th century, which gave rise to regulatory and professional oversight.

Quackery

Use and even surgical implantation of regulated devices is common in 21st century health care. This is—perhaps ironically—one good outcome of unregulated, pseudoscience-based “medical” devices having been around for so long. The Industrial Revolution of the early to mid-19th century and applications of scientific method to medicine in the early 1900s, combined with the absence of regulations, led to the proliferation of contraptions and so-called miracle cure production, **advertising**, and use. Despite court-ordered injunctions against their use, many quack devices had devoted adherents.¹ Evidence—or its lack—doesn't always carry the weight it should, and this is still the case today.^{2,3}

Responses to Pseudoscientific Devices

At least we now have regulatory oversight. The US Food and Drug Administration (FDA) was established by Congress in 1906.⁴ Also in response to dubious “health” intervention promotions, the American Medical Association (AMA) took a 2-pronged approach.

Public outreach. In 1906, the AMA began publishing regularly about quackery and health fraud in the *Journal of the American Medical Association (JAMA)*. *JAMA* articles' successes in public education led the AMA to establish a department devoted to combatting health fraud in 1913.⁵ An AMA director of the Department of Investigation traveled the United States to instruct radio, television, and in-person audiences about how to identify quackery and avoid its risks.

Curricular standardization. In 1908, the AMA's Council on Education worked with the Carnegie Foundation to standardize and certify what students learn in medical schools. One product of this joint effort was publication of the **Flexner Report** in 1910,⁶ which, among other things, sought—though imperfectly and unjustly⁷—to help members of the public distinguish well from poorly trained physicians.

Device Advertising

In the early 20th century, devices to which the AMA responded fell into roughly 6 categories. Three categories were based on then-new scientific concepts: radiation, radio and magnetic waves, and electricity. Three other categories were based on popular pseudoscience: phrenology, chromotherapy, and orgone therapy. The images shown and briefly described in the rest of this article represent only a tiny fraction of materials the AMA has collected and archived.

Radiation. Discovered by Pierre and Marie Curie in 1898,⁸ radium became well known as an all-purpose restorative tonic and was thought by some to treat a wide range of conditions. As early as 1923, a *JAMA* article warned of skin cancer risks,⁹ but after learning that radium's radiation inhibited growth of cancer, physicians used radium-based interstitial irradiation to treat patients with cancer from 1930 to 1950.¹⁰ Early adopters (not necessarily limited to cancer patients) likely suffered radium's iatrogenic toxicity from doses that were neither carefully regulated nor expertly monitored. Figures 1 to 3 are advertisements for devices that facilitated radioactivity consumption.

Figure 1. Rador Toilet Requisites pamphlet, Radium and Beauty Rador Company, circa 1918

Degnen's Radio-Active Solar Pad

This Company guarantees Degnen's Radio-Active Solar Pad to contain a definite quantity of actual Radium.



**RADIOGRAPH OF SECTION CUT FROM
DEGNEN'S RADIO-ACTIVE SOLAR PAD**

This Radiograph was taken by placing a key, upon an ordinary photographic plate in utter darkness and a section cut from our Radio-Active Solar Pad was placed upon it. After a number of hours the plate was developed, showing the Radiograph here produced.

This Radiograph differs from photographs in that it was taken in absolute darkness, whereas a photograph is taken by exposure to light. Neither a radiograph nor a photograph can be taken without light. Therefore, the necessary light to reproduce the radiograph was supplied by the pad itself. This light is easily discernible by the human eye by taking pad in a dark closet after having exposed the pad for a few minutes to sunlight or daylight.

What the Doctors Say About Degnen's Radio-Active Solar Pad

Extracts from letter written in answer to a request for an investigation of our Company by an Association of Physicians in Chicago. This report is certainly very gratifying to us.

Dr. T. E. C. _____
Chicago, Illinois.

My dear C. _____:

Your letter of December 12th, requesting me to make some inquiries for you in regard to the Radium Appliance Company of this city, and the appliances now on the market manufactured by them, came duly to hand. After careful investigation, I can report about as follows:

The Company is a closed California corporation with no stock for sale, five men comprising the same, all residents of this City and most of them identified with business interests here. They all seem to be men of good standing.

M. L. Degnen, the President, is a mineralogist and chemist. He has been experimenting for a number of years with radium in particular. The process by which these radium appliances are made is entirely his own.

You remember that Mrs. B. _____ secured a pad thru Dr. E. S. B. _____ soon after her operation, and she is still using it and gets great relief from its use. This Company's pads at a lower price appear to be a great improvement on mine, both in materials, construction, and, so far as I can tell, of as high or higher radium content. Mr. Degnen showed me the entire process by which they are built up step by step, as the various coats of minerals are applied, the actual radium salts by the Degnen process being dispersed thru the alkali mineral earths forming the base. His technique and methods are his own, of course, but they appear to be sound and rational. The ionization of the mass is uniform and the face of the pad shows the characteristic emanations by exposure in a darkened room.

I believe, Doctor, they are exactly as represented and a most valuable adjunct in the treatment of disease, and I give them my hearty endorsement. It is true that the company is a commercial one and manufactures these appliances to make money. Dr. C. in his letter explains this and hopes that the physicians may become enough interested to control the entire output which can be done after the doctors find what greater benefits can be derived from their use by themselves.

The atomic energy of matter as displayed in radium fairly amazes one. If this energy can be harnessed and applied to any part of the human body at will and is constantly acting, curative force, it is surely worth our time to investigate it even if a layman points out the way. This Company is receiving many letters from people wearing these pads for their ills, some of which I have read; all show their genuineness, and many of the reports in these letters are truly flattering.

In regard to Dr. C., I know him personally and you will see by the enclosed clipping from the Tribune how he stands in the East. He is also well acquainted with the New York, Pennsylvania and New Jersey men, and the letters, that I have seen show me that they value his professional opinion very highly; also he is the Medical man in the Radium Appliance Company and is endeavoring to keep the manufacture and sale of their appliances in the medical profession, as he believes radium is one of the greatest assets that a physician can have, and from his own personal experience and those of his friends who have tried radium, he is convinced of its efficacy. I have seen letters of inquiry

from Drs. A. and B. of Chicago, and also men from the East, who are writing for information, and many have used the pads and are ordering them for their patients.

As a physician, it strikes me that these appliances are worthy of further unbiased clinical observation and study.

Fraternally yours,
(Signed) M. A. B., M. D.
W. Pa.,

Dr. Wm. H. C.,
Penna.

My Dear Doctor:

Replying to your letter of the 24th, regarding the Radio-Active Pad, I am only too glad to be able to fully corroborate anything that Dr. C. may have said. He is a conscientious and truthful gentleman, and if I may be pardoned for diverging, an ethical physician as well. Were I to write you the things that some of my Pad wearers have told me occurred to them after wearing them a short time or longer time, I fear you would class me as a member of the Ananias family. However, to be brief, I have so far as I can observe, been cured of a malignant gastric ulcer.

My patients and friends whom I have prescribed the Pads for, one and all, assure me that they have been much improved by their use, and many tell me that nothing would induce them to part with them could they not replace them.

Some few had so slow a response that they have been discouraged in the start, but have been more enthusiastic later than some who have had immediate relief.

I wore mine 30 days, and discarded it as being N. G. The following week, being desperate, and without faith, something impelled me to again wear it, and from that time we have been inseparable. I'm 70, Class of 1872, and am in active practice.

With best wishes, I am,
Fraternally yours,
(Signed) J. A. B., M. D.

**INTERESTING EXTRACTS FROM
HEALTH MAGAZINE**

"A man is as old as his arteries." It is a well known fact that the primal cause of old age is the hardening of the walls of the arteries. Many of the world's foremost thinkers have realized this fact and have sought through years of patient study to cope with man's most relentless enemy—time.

Some months ago the writer of this article had his attention called to a Radio-Active Appliance, which had only been on the market for a short time, and which, from the statements of those who had used it, seemed a veritable fountain of youth and a panacea for nearly every malady.

Needless to say I was interested and, with a view of determining to my own satisfaction, investigated personally many of the cases under treatment. I found that several of those who were using the appliance were well advanced in years and that nearly every case brought under my observation, the results were, to say the least, remarkable.

People who have been suffering for years from rheumatism, gout and other ailments were either cured or well on the way to recovery.

These results were brought about by the patients wearing an appliance in the form of a pad charged with highly Radio-Active mineral elements, having the property of storing up and holding in suspension the life giving energy and rays from the sun. When applied to the body, the Pad immediately begins to discharge this energy into the system, sending the life-giving current through the blood and nervous system, causing a healthy circulation, overcoming sluggishness, throwing off impurities and restoring the issues and nerves to a normal condition.

While it has been long known that many complicated diseases that baffled medical science have yielded readily to the treatment of Radium and its emanations, yet the chief obstacle to Radium treatment has been the prohibitive high cost and the rarity of the element. The curative powers of Radium emanations have been demonstrated by many of the great physicians of London, Paris and New York. They however, have only been able to supply this treatment for a short time on account of the extremely small quantity of Radium at their disposal, which could only be centralized upon a very small portion of the anatomy, and that only at short intervals.

The Radio-Active Solar Pad seems to have overcome these difficulties and supplies a means of giving a constant flow of Radio-Active energy to any part of the body.

All that is required to keep the activity of the pad up to its full capacity is to place it in the sunlight or ordinary daylight when sunlight is not available. In this manner the rays of light and energy are absorbed and are then in turn distributed throughout the system by placing the pad in contact with the body.

E. B.

Radium Appliance Company,
346 Broadway Bldg.
Los Angeles, California.

Gentlemen: In my general practice, I have had occasion to prescribe my Radio-Active Appliances, particularly the Pad, and the results have been most gratifying. I also wish to thank you for the great benefit I have derived from the same in using it on myself. You are at liberty to refer to me at any time.

Most sincerely yours,
DR. A. R. H.

This is not a copy of our Money-Back Guarantee

The Manufacturers of
"Degnen's Radio-Active Pads"

Guarantee this appliance to be thoroughly tested as to workmanship and materials and to contain a sufficient quantity of natural radium elements to insure its radio-activity at full strength for one year.

Radium Appliance Company
Los Angeles, Calif.

This Guarantee attaches to Pad No. _____

Radium Appliance Co.,
Los Angeles, Calif.
Gentlemen:

In my haste to send your last "order" I failed to state that the change for the better that has come to me already, while wearing your Pad, is marvelous, indeed, when my advanced years are considered. Born Dec. 13th, 1869. In my 3 years of Army service I contracted chronic Entritis, and a Hemorrhoidal Tumor formed just above lower Anal Sphincter,—both pathological conditions giving me no end of discomfort all these 58 years,—yet the change for the better in my condition is so great that I feel like a new man.

Am complimented by all my friends on my greatly improved condition, and I tell them I feel even better than I appear.

Hope to prevail on my chronically ailing friends to follow my example, and "Buy a Pad."

Had you an office in Chicago or N. Y. City, 'twould save much time in obtaining them.

You are at liberty to publish any portion.

E. F., M. D.

Figure 2. Radio-Active Solar Pad advertisement, Radium Appliance Company, circa 1920

DEC 14 1918 16269

**Radium Preparations are
GUARANTEED**
(under \$5000 penalty)
to be prepared from the
purest pharmaceutical
ingredients to contain a
definite quantity of Actual
Natural Radium, and to
retain their Radio-activity
for at least 20 years

The Radium Coy

RADIUM CO. Ltd.
of London
235 Fifth Ave., New York
167 Oxford Street, London



**RADIUM
and
BEAUTY**

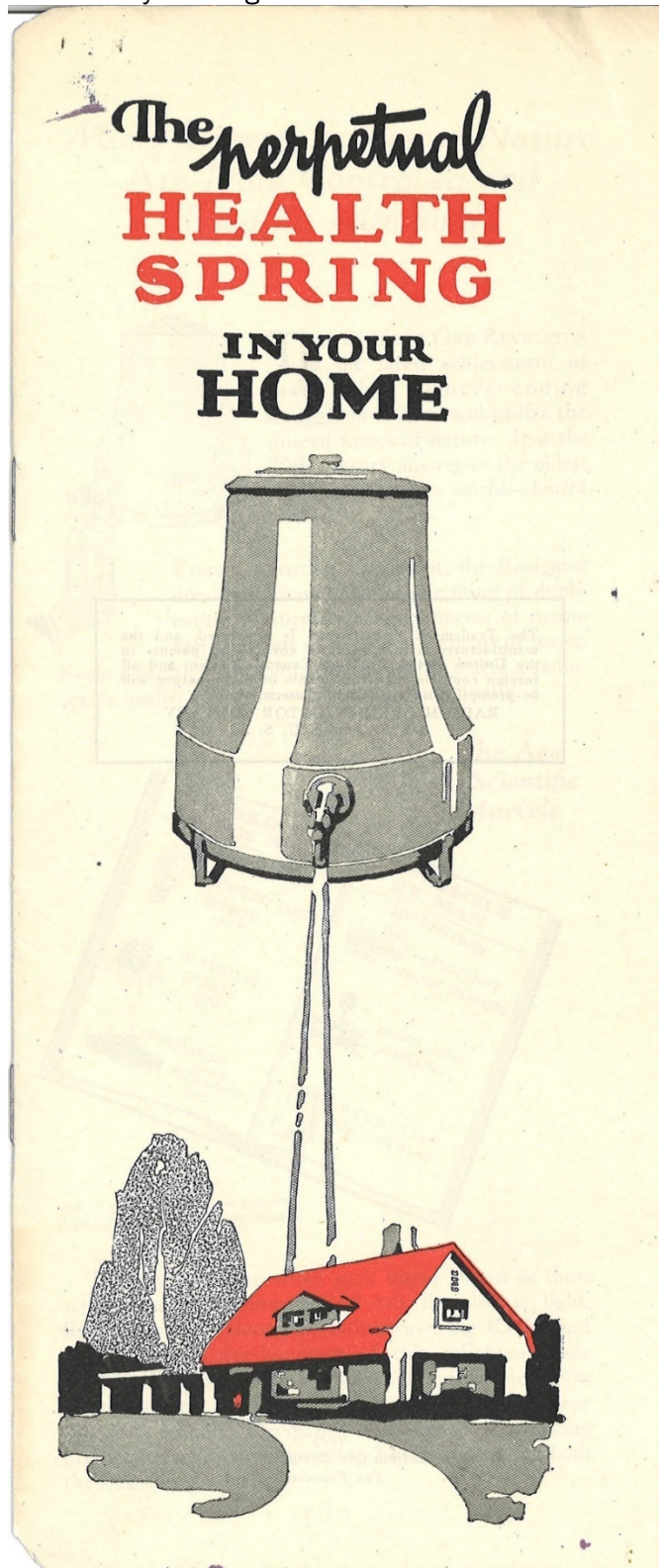
Radium
Toilet
Requisites

Arevision of the English
edition of "Radium...it's
Discovery and Powers"
by
C. ACEY
which is in its 120th
thousand in England

Figure 3. R. W. Thomas' Revigator, created circa 1925



Figure 4. Revigator's brochure, circa 1925. The brochure explained how the device "worked" by infusing water with radium.



Wave-based devices. Around 1916, use of the terms *magnetic waves*, *radio waves*, and *vibrations* was popularized based on the physician Albert Abrams' work.¹¹ Along with other individuals and companies that manufactured their own machines, Abrams told patients that, with a blood sample, one's illness could be diagnosed and cured using "wave" technology. The AMA tested Abrams' claims by sending a rooster's blood sample. The rooster was diagnosed remotely with a sinus infection and tooth decay, but other patients were diagnosed with multiple serious diseases. Abrams' quackery was exposed by *JAMA* in 1922,¹² and though Abrams died in 1924—and despite the AMA's and others' efforts—similar wave devices were advertised for remote or in-person use for many subsequent years, as shown in Figures 5 to 8.¹³

Figure 5. Drown Radio Display, created by Ruth B. Drown, circa 1940



Figure 6. Albert Abrams' Oscilloclast, created circa 1910 (reenactment photo circa 1965)

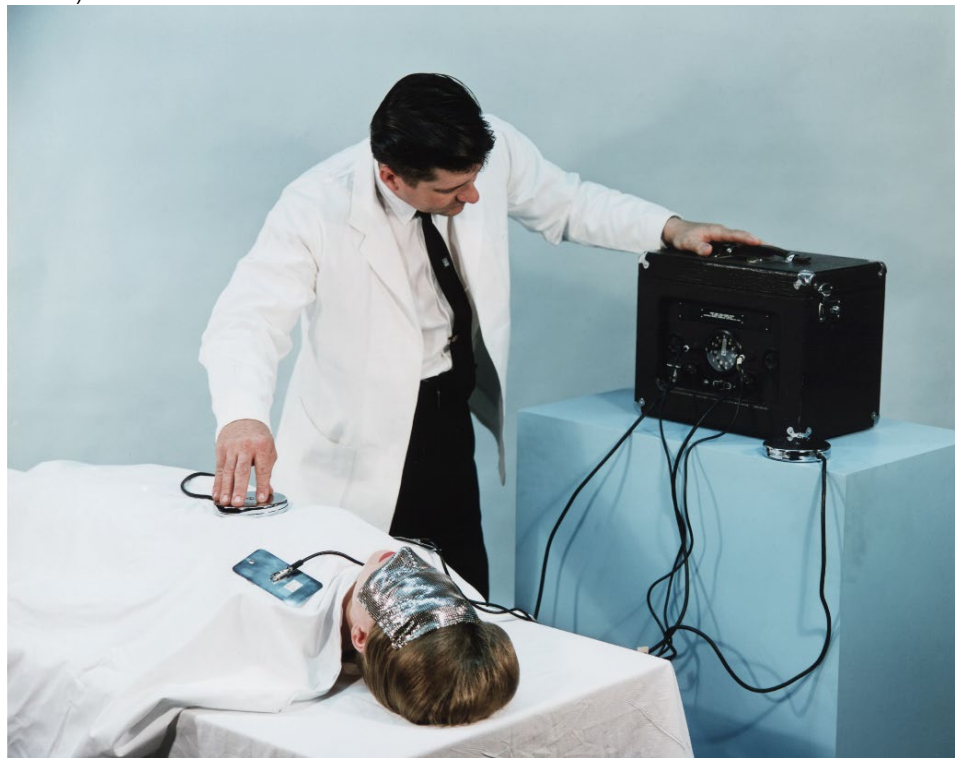


Figure 7. The Sonus Film O Sonic, circa 1950 (reenactment photo circa 1965). The device used song recordings to generate vibrations that were thought to be healing.

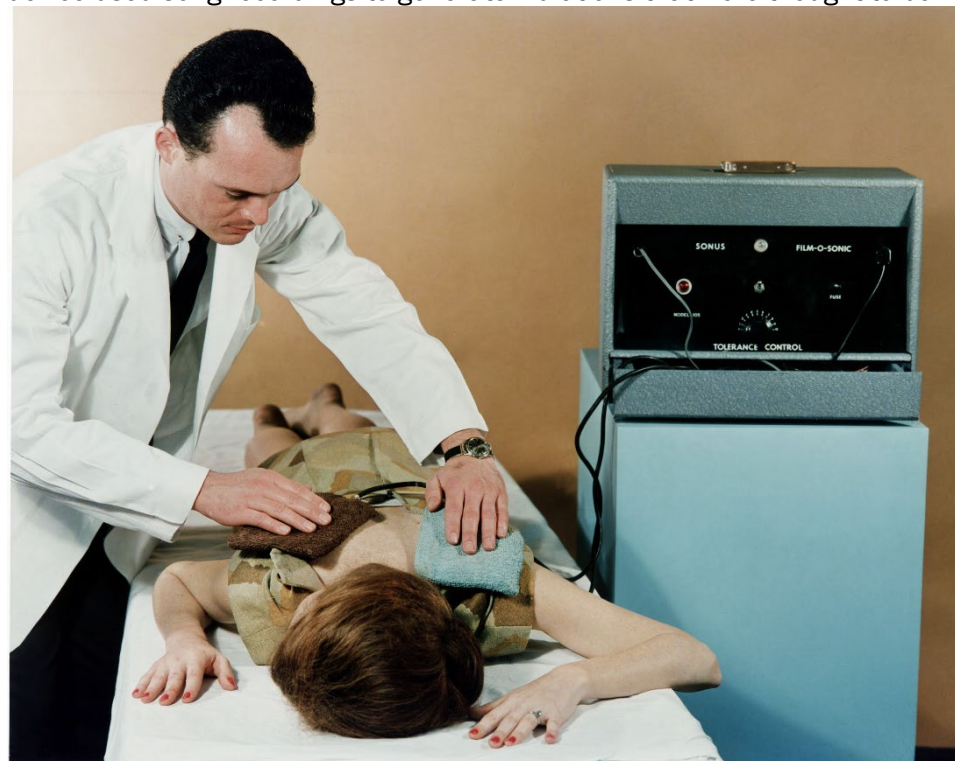
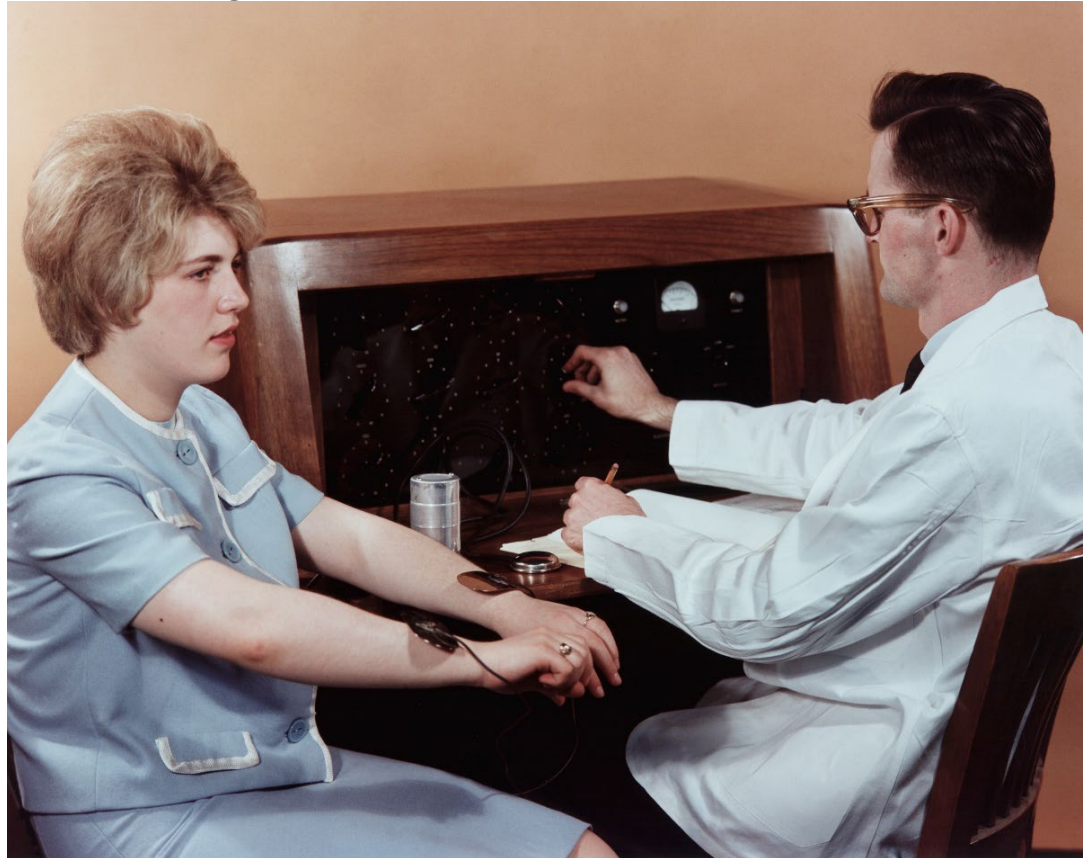
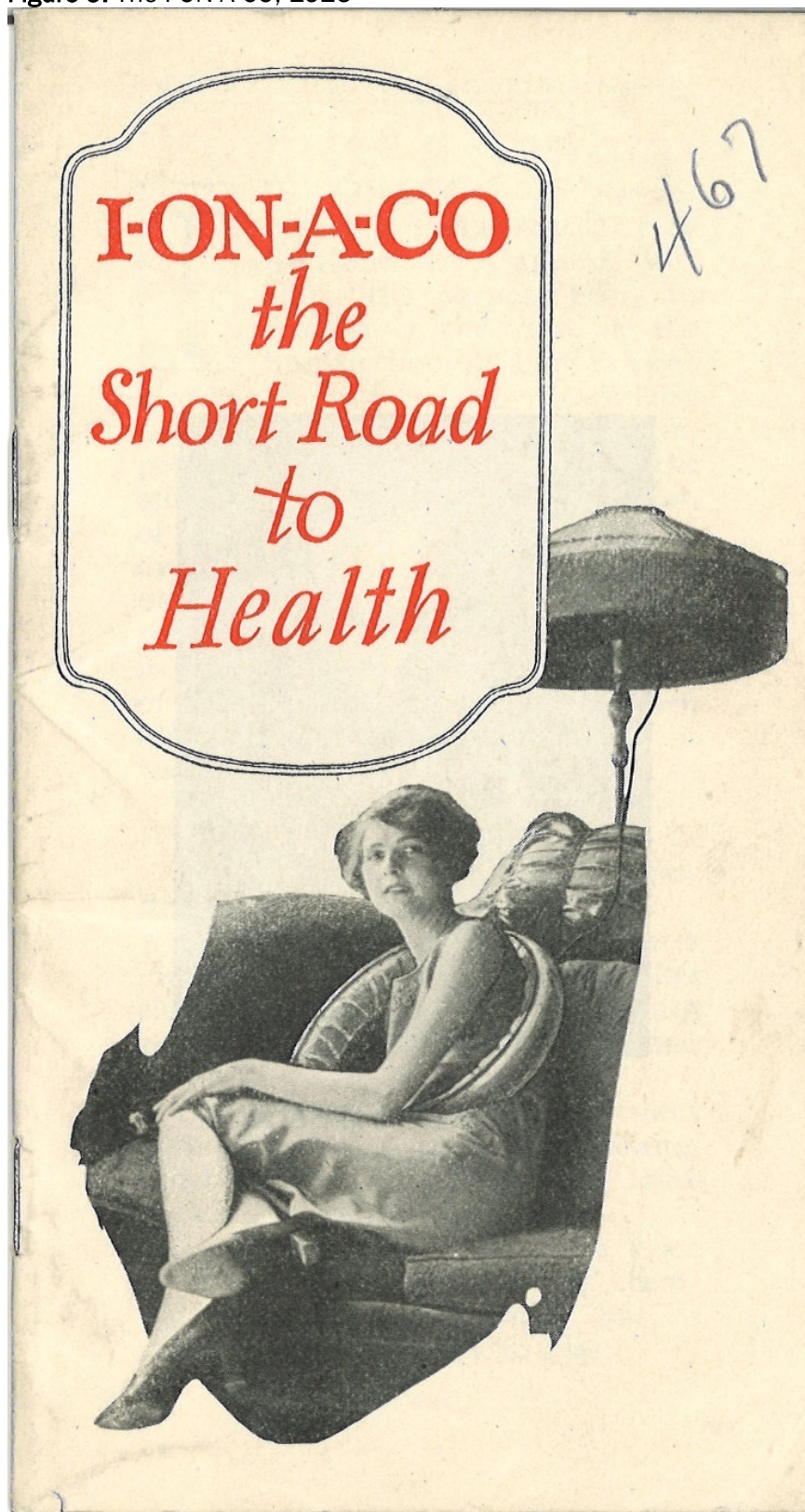


Figure 8. The Radioclast, circa 1920 (reenactment photo circa 1965). This was one of Albert Abrams' original inventions.



Electricity. Nikola Tesla's and Thomas Edison's innovative electric devices of the late 1800s seemed like magic, and their novelty was exploited to suggest that electricity could cure ailments or control disease by magnetizing iron in a patient's blood. Gaylord Wilshire's I-ON-A-CO was a metal coil, which patients wore around their necks, enlivened by an electric current (see Figure 9).

Figure 9. The I-ON-A-CO, 1925



The AMA's Arthur J. Cramp called devices like the I-ON-A-CO "magic horse collar[s]"¹³ and issued warnings to the public by placing articles in widely read publications, such as *Popular Mechanics*, and organizing conferences with the FDA.¹ The Theronoid belt—a device similar to the I-ON-A-CO with a smaller coil and a bulb added to the belt to indicate when the belt was "working"—was introduced by a former employee of Wilshire's company, Philip Ilsey (see Figure 10).¹⁴

Figure 10. The Theronoid Belt, circa 1928 (reenactment photo circa 1965)



The Evans Vacuum Cap drew on a person's vanity as a cure for baldness and was sold by the Modern Vacuum Cap Company at the turn of the 20th century (see Figure 11).

Figure 11. Evans Vacuum Cap

Cosmopolitan Magazine

A Scientific Method of Growing Hair



It is a known fact that the blood conveys nourishment to all parts of the body. It is likewise known that exercise makes the blood circulate, and that where the blood does *not* circulate no nourishment is supplied.

The lack of proper circulation of blood in the scalp, due mainly to congestion produced by artificial causes, results in the starvation of the hair roots, and produces falling hair and baldness. Therefore the logical and only relief from baldness is in the restoration of the scalp to its normal condition, thus enabling the blood to resume its work or nourishing the hair roots. It was work along these logical lines that produced and perfected

THE EVANS VACUUM CAP.

The Evans Vacuum Cap provides the exercise which makes the blood circulate *in the scalp*. It gently draws the rich blood to the scalp and feeds the shrunken hair roots. This causes the hair to grow. It is the simple, common-sense principles of physical culture scientifically applied to the scalp.

Easy and Pleasant to Use.

The Evans Vacuum Cap is portable and can readily be attached to any ordinary straight back chair. Three or four minutes' use each morning and evening is all that is required. It leaves a pleasant tingling sensation for a few moments after use, indicating the presence of new life in the scalp.

Method of Testing.

You can tell by a few minutes' use of the Evans Vacuum Cap whether it is possible for you to cultivate a growth of hair on your head, and we will send you the apparatus to make the experiment, *without expense on your part*. If the Evans Vacuum Cap gives the scalp a healthy glow, the normal condition of the scalp can be restored, and a three or four minutes' use of the Cap each day thereafter will, within a reasonable time, develop a natural and permanent growth of hair. If, however, the scalp remains white and lifeless after the Cap is removed, there would be no use to give the appliance a further trial. The hair cannot be made to grow in such cases.

The Bank Guarantee.

We will send you, by prepaid express, an Evans Vacuum Cap, and will allow you ample time to prove its virtue. All we ask of you is to deposit the price of the Cap in the Jefferson Bank of St. Louis, where it will remain during the trial period, subject to your own order. If you do not cultivate a sufficient growth of hair to convince you that the method is effective, simply notify the bank and they will return your deposit in full. We have no agents, and no one is authorized to sell, offer for sale or receive money for an Evans Vacuum Cap. All Caps are sold under the bank's guarantee, and all money is sent direct to Jefferson Bank.

A sixteen-page illustrated book will be sent you free, on request.

EVANS VACUUM CAP CO. 1043 Fullerton Building, St. Louis

When you write, please mention the Cosmopolitan

Phrenology. Phrenology erroneously holds that measurements of bumps on a person's skull can determine that person's traits. Developed in the late 1700s and popularized in the 1800s, phrenology had been discredited as pseudoscience by the dawn of the 20th century,¹⁵ but it was still used to promote devices through the 1930s. One such device, the Psychograph, created by Henry C. Lavery, was installed not only in malls and cinemas as entertainment, but also in physicians' offices in the early 20th century (see Figure 12).¹⁶

Figure 12. The Psychograph Phrenology Machine, early 20th century (reenactment photo circa 1990)



The AMA's efforts to professionalize medicine and to articulate to members of the public the differences between science-based medicine and pseudoscience-based quackery was one reason phrenology lost adherents, but many other quack devices remained.

Chromotherapy. Chromotherapy began with a scientifically sound kernel of truth: “light is energy, and the phenomenon of color is a product of the interaction of energy and matter.”¹⁷ Dinshah P. Ghadiali popularized these properties to promote his Spectrochrome, erroneously suggesting that illness or injury could be remedied by colors and light (see Figure 13). Violet rays, via wand, were applied to a patient’s body (see Figure 14). *JAMA* continued publishing refutations of chromotherapy until 1958,¹⁸ when the FDA facilitated a permanent injunction against Ghadiali’s institute.¹⁹

Figure 13. Spectrochrome, circa 1930s. Although it looks like there is a Star of David on it, this symbol, created by Ghadiali, actually represents chemical elements in attuned color waves.²⁰



Figure 14. Spectrochrome with wand, circa 1940 (reenactment photo circa 1990)



Orgone. Wilhelm Reich conceived of orgone as similar to chi or life force but drew on Freudian ideas about sex to suggest that traumatic experiences block energy flow in a person's body, causing ill health, and that orgasms promote wellness.²¹ Christopher Turner writes: "[I]n the ideological confusion of the postwar period ... Reich's ideas landed on fertile ground."²¹ Orgone energy, which a conical hat would trap, was thought to dissipate like heat from the top of one's head, and orgone devices were promoted as pulling orgone energy from the atmosphere and radiating it to a user. AMA investigations encouraged the FDA to bring Reich to court, resulting in a ruling that stopped the sale of Reich's machines in 1954.²¹

Figure 15. Orgon Cone Hat, circa 1950 (reenactment photo circa 1965)



Figure 16. Orgone energy box created by Wilhelm Reich, circa 1950 (reenactment photo circa 1990)



Conclusion

While the shine may have worn off some of these inventions (though some are still used), there is no shortage of new pseudoscientific devices being marketed. The internet, of course, has given rise to a whole new class of hucksters and frauds, and the rise of conspiracy theories, along with the Covid-19 pandemic, has certainly not helped. We now have a great variety of governmental and nongovernmental bodies dedicated to fighting the scourge of misinformation, although it remains to be seen how effective they will ultimately be.

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ART OF MEDICINE

Recovery

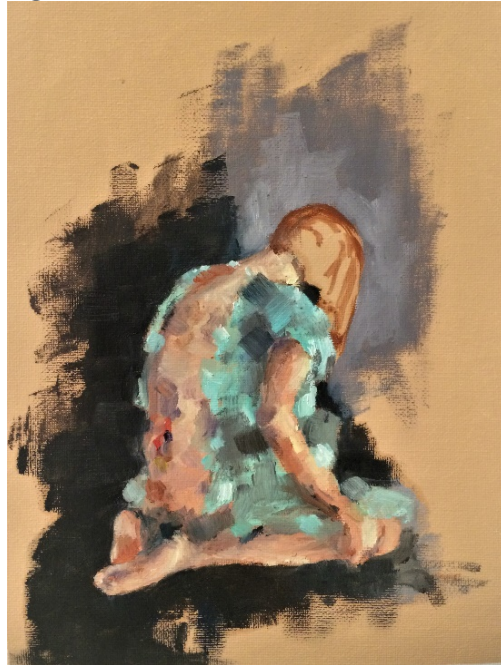
Tatiana Patrone, PhD

Abstract

This series of 5 color oil on canvas sketches includes a sequence of images and explores, from a first-person perspective, a patient's postoperative recovery experiences.

Five color oil on canvas sketches explore my recovery from spinal surgery on April 1, 2020. As a patient-philosopher-artist, I considered my recovery in these sketches with an aim of being present in moments of recovery and capturing, day by day, my own postoperative experiences. Another aim was eventually to share my experiences with other patients trying to meet the **demands of recovery** and feeling fragile, vulnerable, and uncertain. Recovery is not an event but a process and, indeed, a pursuit.

Figure 1. Untitled 1, from the series *Recovery*



Media

Oil on canvas, 8" x 11".

This first oil sketch of the series was done at home 2 weeks after my spinal surgery. At this stage of my recovery, I was unable to move or sit; the position of the “subject” in the painting aims to capture the *feeling* of convalescing rather than the actual positioning of my body. (It would be weeks before I would be able to sit in this position.) Addressing recovery through painting was—for me—a way to cope with the new reality of convalescing and with recovery as an entirely new experience. My goal was to do this painting and others in one sitting—to be “in the moment,” as it were. Addressing the **feeling of vulnerability** and uncertainty through art was a way to make sense of what my body was going through—and it became a way to regain control over my story and experiences. It was also a way to transform my postoperative bodily experiences into something aesthetically appealing rather than repulsive.

Figure 2. Scar, from the series *Recovery*



Media
Oil on canvas, 8" x 11".

After completing the first painting, it became clear to me that addressing recovery through art could be both therapeutic and emotionally taxing. By capturing my recovery visually, I felt like I was responding to my feelings of **hopelessness and pain**. For this second work in the series, I chose to work on an “observed abstraction” representing the scar on my back some 2 weeks after surgery. The pallet is true to reality (with colorful bruising, for instance), but the image itself is not a literal color depiction of my skin. Abstract painting presented its own challenges in composition and brush strokes but allowed me to step away from a literal depiction of my body and to be open to a new aesthetic way of engaging with my recovery.

Figure 3. *I.V.*, from the series *Recovery*



Media
Oil on canvas, 8" x 11".

The third painting of the series was done during week 3 of my recovery. Painted from memory, it is based on my experience of trying to sit up for the first time at the hospital, being careful not to remove the intravenous (IV) line from my arm. The turquoise color of the hospital gown became emblematic for me—almost a symbol of pain and disorientation. Sitting at the edge of my bed from time to time was all I was allowed to do during the first postoperative 48 hours, and my gaze would follow, over and over, the outlines of my arm. This painting is a window onto my world that had shrunk to small, close objects, such as my arm, the IV, or my gown.

Figure 4. *Walker*, from the series *Recovery*



Media
Oil on canvas, 8" x 11".

Much like the prior painting, this one was done from memory while I continued to recover at home. It captures another of my common “gazing spots”—my feet. During this time, sitting was allowed but walking wasn’t, and I would stare at my feet and think about walking as a future goal.

Figure 5. Untitled 2, from the series *Recovery*



Media
Oil on canvas, 8" x 11".

The final image of the series depicts my internal emotional exhaustion during the first days after surgery. A focal point is my hospital-issued red socks. For safety, patients in red socks were not allowed to move unassisted since they could not rely on their legs during the first 48 postoperative hours. Patients in yellow socks were allowed to walk unassisted. However well-intended, red socks remind me of immobility, of the compromised basic capacity to navigate space freely, of the psychological challenge of recovery.

My surgery was ultimately successful, and, in July 2020, I sailed on my 25-foot boat across Lake Ontario to Toronto and back, a goal that had motivated me during 3 months of physical therapy. For 2 weeks after surgery, however, any goal involving movement was aspirational; it was not a given that I would be able to walk well, that nerves in my leg would regenerate well, or that I would resume my normal life. Focusing on painting was a way to create meaning and to make sense of recovery. In retrospect, I can say that turning pain into art was the way to go—I cannot imagine this recovery without these creations.

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VIEWPOINT: PEER-REVIEWED ARTICLE

Who, If Not the FDA, Should Regulate Implantable Brain-Computer Interface Devices?

Charles E. Binkley, MD, Michael S. Politz, MA, and Brian P. Green, PhD

Abstract

Implantable brain-computer interface (BCI) and other devices with potential for both therapeutic purposes and human enhancement are being rapidly developed. The distinction between therapeutic and enhancement uses of these devices is not well defined. While the US Food and Drug Administration (FDA) rightly determines what is safe and effective, this article argues that the FDA should not make subjective, value-laden assessments about risks and benefits when it comes to approval of BCIs for therapy and enhancement. This article also argues that determining BCIs' benefits to society requires deliberations on values that the FDA is neither accustomed to making nor qualified to make. Given the inadequacy of the FDA's safe-and-effective standard to judge devices spanning the spectrum of therapy to enhancement, this article argues that BCI regulation should not be overseen by the FDA.

To claim one AMA PRA Category 1 Credit™ for the CME activity associated with this article, you must do the following: (1) read this article in its entirety, (2) answer at least 80 percent of the quiz questions correctly, and (3) complete an evaluation. The quiz, evaluation, and form for claiming AMA PRA Category 1 Credit™ are available through the [AMA Ed Hub™](#).

Brain-Computer Interface Devices

A “working brain-to-machine interface”¹ (BCI) designed for both therapeutic and human enhancement^{4,2} purposes might be easily dismissed as one billionaire's pet project, but many similar devices are being developed.^{3,4} A facile approach to **brain-computer interface devices**, which we refer to here as *spectrum use devices*, might attempt to fit them into the current US Food and Drug Administration (FDA) safe-and-effective regulatory framework for approving devices.⁵ However, we argue that this approach is not sufficient and that, given BCIs' potential influence on individuals and society, the nature of what is safe and effective and the balance between risk and benefit require special consideration.

BCIs that are currently being developed are claimed to serve therapeutic ends and thus are subject to FDA regulation.⁵ However, the **line between therapy and enhancement** for BCIs is difficult to draw precisely. Therapeutic devices function to correct or compensate for some disease state, thereby restoring one to “normality” or the standard species-

typical form.^{6,7,8,9,10} However, devices implanted for therapeutic purposes might also enhance individuals beyond the limits of what would be considered normal. A device intended to correct cognitive impairment associated with dementia, for example, may result in above-average cognition.¹¹ BCIs' blurring of the distinction between therapy and enhancement is further complicated by different perspectives on what is normal and abnormal. For instance, would an IQ below the mean be considered "abnormal" and thus justify implanting a BCI intended to correct a cognitive "deficit"? Almost anyone could then claim therapeutic intent aimed at improving some perceived or real deficiency not only in cognition but also in sensation or motor function. Conversely, for people in the deaf community who do not adhere to the "deficit model" of disability,^{6,12} cochlear implants are enhancement rather than therapeutic devices.^{6,13} Thus, any BCI will have some therapeutic claim, however thin. At the same time, any BCI could also be **considered an enhancement device**. It is in part this lack of distinction between therapy and enhancement that makes the FDA unqualified to regulate this class of spectrum-use device.

Regulating Safety and Effectiveness, Risk, and Benefit

While BCIs raise multiple ethical concerns, such as how to define personhood, respect for autonomy, and adequacy of informed consent, not all ethical issues justifiably form the basis of government regulation.^{6,14} The FDA's standard for evaluating and approving implantable devices is whether a device is safe and effective.⁵ As a result, the FDA largely focuses on assessment of engineering technology.^{15,16} Four integral features have been identified that help the FDA to regulate approval of implantable devices: materials choices, device design and functionality, risk factors, and implantation procedure.¹⁵ The more similar a proposed device is to an already approved device with respect to these 4 categories, the more likely the device is to receive FDA approval.¹⁵ For BCIs, the approval process entails evaluating the safety of surgical implantation, explantation, and function. Complications such as infections, scarring, probe damage to brain tissue, cerebral edema, and bleeding would be some of the typical outcomes used by the FDA to assess safety.^{8,15} In terms of efficacy, therapeutic devices are evaluated in large part based on whether or not they demonstrate consistency between manufacturers' claims and measured outcomes. For BCIs with potential for cognitive enhancement, efficacy can be assessed by the extent of improvement in cognitive function as it is measured by commonly used assessment instruments.¹⁷

It is well within the FDA's purview to assess devices, including spectrum-use BCIs, strictly along the lines of what is safe and effective. However, implicit in considerations of safety and efficacy is also an assessment of risk and benefit. This assessment involves a value judgment not only about a device's absolute level of risk and benefit but also about what is the right balance between the two. The FDA is not qualified to make these kinds of value judgments about spectrum-use BCIs, however.

Evaluating the benefit of BCIs involves an assessment of the extent to which a device can increase an individual's well-being and chance of living a good life.¹⁷ While the effectiveness of BCIs can be objectively measured, the value placed on that cognitive, sensory, or motor skill improvement will vary significantly among people.¹⁷ A patient with amyotrophic lateral sclerosis who **rejects the stigma of disability** may assign very little benefit to a BCI that improves their motor skills. In contrast, a young computer engineer may place high value on an improvement in cognitive function. Because what is good or beneficial to an individual is subjective and value laden, it is not justifiable for the FDA to base its approval of a device on any one specific notion of what is good or beneficial.^{14,18}

Similarly, individual assessment of risk is highly subjective and qualitative.¹⁷ Is there some absolute risk threshold above which a spectrum-use device should not be approved by the FDA? How would that threshold be determined, and would it take into account potential harm both to the individual and to society? Spectrum-use devices also have the potential to introduce risks that are difficult to quantify. For instance, it would be difficult to objectively measure the potential psychological impact of explanting an enhancement device or how individuals would cope with the transition from enhanced to unenhanced states.¹⁹ While these risks are important for the individual and for society to consider, because they are subjective and require value judgments, they are outside the scope of risks that the FDA can evaluate as part of the basis of device approval.

Just as the FDA has no basis for making isolated assessments of a spectrum-use device's risks and benefits, so it lacks a basis for measuring whether the device's benefits outweigh its risks. For strictly therapeutic devices, patients may be willing to "take a gamble" and accept a high level of risk for a therapy that confers minimal or no demonstrable benefit. In addition, patients may wrongly infer that an intervention is beneficial just because it was recommended by a health care practitioner, regardless of its actual measured benefit.¹⁷ Although ensuring that the benefit of a therapeutic device exceeds its risk is part of the FDA's role in protecting vulnerable patients,^{14,17} for spectrum-use devices for which assessments of risk and benefit are highly subjective, a more robust consideration for device approval is necessary than is afforded by the narrow categories used by the FDA.

Regulation Based on "Good" to Society

Finally, there are aspects of the enhancement of individuals that, at the level of society, have potentially very different effects than those of therapy for individuals, particularly aspects related to mental function. While therapeutic interventions upon individuals in the aggregate would not significantly affect society in unexpected ways, enhancement interventions might.²⁰ BCIs will not simply augment a single person; they present the potential for a bifurcation between "enhanced" and "standard" human beings. As of now, BCIs for human enhancement remain largely untested and their potential unknown, even at the individual level. How do we then judge (let alone legally enforce) the implementation of these devices at the societal level? The potential for social disruption introduced by BCIs for human enhancement would seem to call for government intervention. However, as already noted, judgments about their risks and benefits are not within the realm of competency of the FDA. Rather, it seems that some new governing body would be required to assess risks and benefits of spectrum-use BCIs. In addition to assessing safety and efficacy and risks and benefits, this governing body would need to have some conception of what "good" means for society, which is a difficult prospect in a pluralistic society like the United States.

Some regulations will be vital even if enhancement is allowed, eg, BCIs should be secure against "hacking." Previous presidentially appointed groups on bioethics have indicated this need already exists, but merely repurposing such a group would be too political and lack legitimacy: a new organization needs to be established that has in mind the good of society, not politicians. Needless to say, the establishment of such an organization will require much careful thought.

Conclusion

With devices like BCIs presenting the possibility of extensive and widespread human change, the current FDA safe-and-effective model of regulation is not robust enough to

do justice to the multifaceted issues posed by these devices. At both the individual and the societal level, BCIs represent a potential for change far surpassing mere therapeutic measures. In place of maintaining standards of health, living, and personhood, BCIs, representing a new wave of biotech, promise deviation from and augmentation of these standards. A new committee or regulatory body with humanistic aims, including the concerns of both individuals and society, ought to be legislated at the federal level in order to assist in regulating the nature, scope, and use of these devices.

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VIEWPOINT: PEER-REVIEWED ARTICLE

Is the FDA Failing Women?

Madris Kinard, MBA and Rita F. Redberg, MD, MSc

Abstract

Many devices in current use were marketed before the US Food and Drug Administration (FDA) began regulating devices in 1976. Thus, manufacturers of these devices were not required to demonstrate safety and effectiveness, which presents both clinical and ethical problem for patients, especially for women, as some of the most dangerous devices—such as implanted contraceptive devices—are used only in women. This article investigates whether and to what extent devices for women receive less rigorous scrutiny than devices for men. This article also suggests how the FDA Center for Devices and Radiological Health could more effectively ensure safety and effectiveness of devices that were marketed prior to 1976.

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Grandfathering and Intended Use in Women

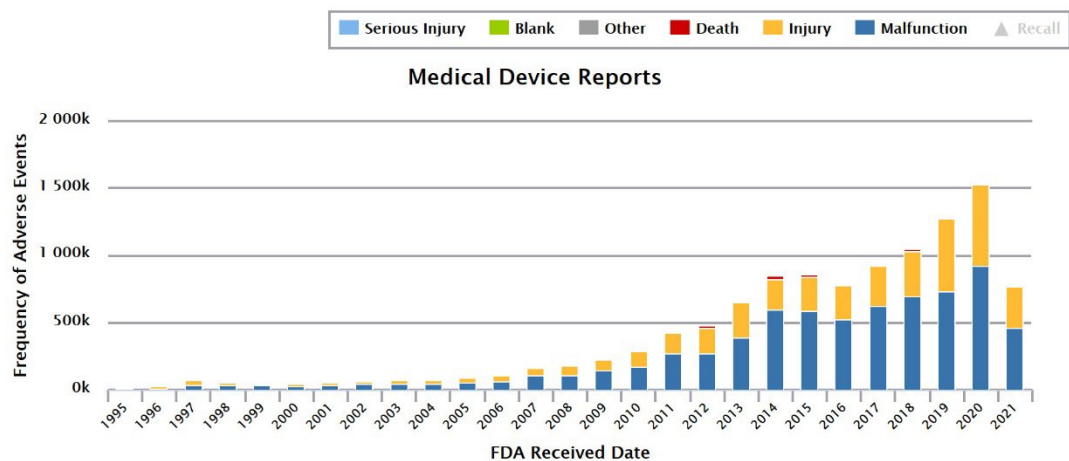
The Center for Devices and Radiological Health (CDRH) of the US Food and Drug Administration (FDA) began regulating devices in 1976 after it was discovered that use of the [Dalkon Shield](#) and other women's intrauterine contraceptive devices were linked to infertility.¹ Congress and the FDA weighed the competing goals of providing the public reasonable assurance of safety and effectiveness and avoiding overregulation.¹ Devices marketed prior to 1976 were grandfathered in with an amendment to the Food, Drug, and Cosmetic Act and were not required to establish safety and effectiveness.¹ Such devices included mesh used for hernia repair, breast implants, and electroshock therapy devices. Currently, approximately 1% of devices enter the market through a process that generally requires clinical data, known as premarket approval (PMA). Approximately 30% of the remaining 99% of devices are "cleared" through the 510(k) pathway, which requires only that a device be "substantially equivalent" to a "predicate" device already on the market, without any requirement to demonstrate safety and effectiveness.² Predicate devices, which can include those marketed before 1976,¹ might never have received any FDA review for safety and effectiveness. Recalled devices have served as predicate devices, which raises ethical concerns, and even when a device has gone through trials, most subjects were men.^{3,4,5,6} This article specifically examines devices

(ie, transcervical contraceptives, breast implants, vaginal meshes) intended for use in women. This article also suggests how the FDA Center for Devices and Radiological Health could more effectively ensure safety and effectiveness of devices that were marketed prior to 1976.

Postmarket Regulation

When a device fails a patient, it falls to the Division of Postmarket Surveillance at the FDA to identify patterns of problems with devices and then to formulate appropriate enforcement actions.⁷ These actions can vary from issuing or requiring issue of recalls, warning labels, or warning letters to manufacturers, organizations, or clinicians about safety concerns.^{8,9} The slow speed at which the FDA identifies patterns of harm has been under intense scrutiny, as the number of adverse events (AEs), ie, deaths, injuries, and malfunctions, reported to the FDA has doubled in the last 5 years—from 65 000 reports per month in 2016 to 115 000 reports per month in 2020 (see Figure).

Figure. Number of Adverse Event Reports for Medical Devices, 1995 Through May 2021^a



Abbreviation: FDA, Food and Drug Administration.

^a Data from Device Events™ database.¹⁰

The FDA’s current and most expeditious method of tracking problems with devices is via AE reporting by manufacturers and facilities, such as hospitals and laboratories. The Medical Device Reporting regulation requires a facility or manufacturer to self-report an adverse event within 30 days,¹¹ or within 5 days if the “reportable event necessitates remedial action to prevent unreasonable risk of substantial harm to the public health.”¹² When a facility contacts a device manufacturer to report a serious device-related concern, injury, or death, a manufacturer is mandated to file an AE report with the FDA.¹³ Of 11.4 million AE reports submitted to the FDA, most were reported from facilities via a manufacturer, 1.9 million were from physicians reported via a manufacturer; only 7291 were voluntarily submitted directly to CDRH by physicians.¹⁰

Sixteen Years on the Market

Attention to health problems caused by a transcervical contraceptive was generated by a popular film, *The Bleeding Edge*,¹⁴ and social media groups that encourage reporting AEs directly to the FDA rather than through a manufacturer. These groups recognized the need to directly report to the FDA when it was discovered that FDA AE reports were fewer in number than complaints submitted to manufacturers. For example, a social

media group devoted to problems with a permanent birth control device had 22 000 members when the FDA held a public meeting on hysteroscopic sterilization devices in September 2015. Members suspected that the number of their complaints to manufacturers exceeded the 6000 AE reports shown in the FDA's AE database at that time; Freedom of Information Act inquiries about FDA inspections of this device's manufacturer yielded 2 inspection reports 3 years apart, with a combined 32 000 complaints that had not been submitted to the FDA by the manufacturer as AE reports. The FDA did not act until more severe events (ie, device migration and uterine perforation) were reported directly to the agency by patients; the company settled the claims for \$1.6 billion.¹⁵

However, the FDA public meeting on hysteroscopic sterilization devices generated publicity. One US Congressman questioned the FDA about the device's safety.¹⁶ Physicians became more aware of links between the device and their patients' health, resulting in submission of another 5400 reports to the FDA with the reporter occupation designated as "physician."¹⁰ Although the FDA required a "black box" warning to be added to the device's packaging in February 2016 and ordered the manufacturer to conduct a new clinical study on risks,¹⁷ it did not mandate or recommend a recall, offering the reason that the agency did not want to limit patients' choices. After 16 years on the market, the manufacturer voluntarily withdrew the device from international commercial distribution in September 2017, citing "commercial reasons"¹⁸ and then domestically in December 2018,¹⁹ following release of *The Bleeding Edge*, which documented the trauma and dangers of this device in women.¹⁴ So, why is the FDA slow to ensure that women's devices are safe and effective?

Failing to Make AE Reports Public

Consider another example. Scrutiny of breast implant material in the late 1980s prompted a moratorium on **silicone breast implants** from 1992 to 2006,²⁰ yet lack of transparency about AE reports resulted in patients and physicians assuming, for 20 years, that newer breast implant materials were safer than those targeted by the moratorium. Again, because women harmed by breast implants spoke up, search for AE reports ensued. How could there be more than 100 000 members in breast implant social media support groups and so few AE reports?

Patient safety advocates began meeting with the FDA in 2015; in 2018, the agency revealed that the adverse event reports existed but were not made public, despite the mandatory reporting requirement. During a public meeting in 2019, the FDA disclosed receipt of more than 300 000 breast implant AE reports—more than 20 times the number made public.²¹ After this meeting, then-FDA Commissioner Scott Gottlieb promised release of all AE reports collected through "alternative summary reporting,"²² most of which were released in June 2019.²³

Only 54 400 of 5.8 million alternative summary reports made public by the FDA in June 2019 were for devices or materials marketed solely to men. Vaginal mesh AE reports have still not been released. It is not known how many of these reports exist, and I argue here that withholding them during pending legal cases is unethical, since members of the public—who have been or could be harmed by a device or material—need access to this data, which is intended by Congress to be publicly available. This data is critical for patients trying to exercise self-determination and to make informed decisions about whether and when to have a device or material implanted or about whether and how to respond to a past decision made without access to existing information that should have

been public and could have informed their risk-benefit analyses prior to surgical implantation. Sharing the actual number of AEs and their timeline is critical for public protection.

Lack of Enforcement and Compliance

In addition to reviewing AEs, CDRH monitors devices' postmarket safety and effectiveness. Although AEs are public, more than 1 million reports are made available per year in the Manufacturer and User Facility Device Experience Database, and the FDA does not release them in a format that is easy to review or understand. The FDA does not have resources to proactively identify device problems, and even when the agency orders postmarket surveillance studies, it can struggle to enforce manufacturers' compliance.²⁴

For example, postmarket surveillance studies of all major brands of breast implants were ordered by the FDA in 2006 and remain incomplete. The FDA updated the study parameters in 2013 and 2014 to allow for smaller studies, since the manufacturers struggled with enrollment and patient follow-up. Every 1 to 2 years, the CDRH sends warning letters to the breast implant manufacturers, who respond with requests for additional time to complete these studies. After each request, the FDA allows additional time, seemingly due to lack of resources or mechanisms for compliance enforcement. Despite warning that delay and noncompliance can compromise device marketing and distribution, no further enforcement (ie, production suspension, moratorium on sales, withdrawal from the market, or recall) has been enacted, rendering the requirement for postmarket surveillance meaningless.

Remaining Questions, Next Steps

Ethical and clinical questions about withdrawing a device from the market arise when no alternative exists: Are patients safer when a device of questionable or unknown safety and effectiveness is at least available rather than unavailable? Breast cancer survivors, for example, express concern about limited breast implant material options. Is a 2020 FDA-recommended black box warning for breast implants²⁵ best regarded, ethically and clinically, as promoting safety or as generating risk awareness that further limits an already narrow set of options? Even with a warning in place, a patient is not the one who actually removes packaging for an implant, so will she see the black box warning? Should she see it? How many adverse events should be regarded as too many? As Jeanne Lenzer noted: "The question is not whether a device ever causes harm but whether the benefits are expected to exceed the harm in a defined population."²⁶

The FDA plans to more proactively identify devices' risks, but these initiatives are years from implementation, as they require integrating health care organizations' electronic health records (EHRs) and must be adopted by clinicians and payers. The CDRH Health of Women Initiative, launched in December 2016,²⁷ for example, focuses on device performance across women's lifespans and includes tracking device use via claims payments systems by 2023 and future tracking of adverse events via EHRs—once the EHR vendors are in full compliance.

It is essential to make the mechanism for AE reporting user friendly and widely accessible and to ensure transparency of AE reporting, as well as enforce requirements for postmarket surveillance to protect women, as well as men, from having dangerous devices implanted without knowledge of potential harms and benefits.

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Conflict of Interest Disclosure

Ms Kinard is the owner of Device Events™, a cloud-based software service that uses publicly available US Food and Drug Administration (FDA) data, and worked for the FDA until 2014. She also participates in the American Hospital Association's Learning UDI Community, which collaborates with health care practitioners, medical device companies, and other third-party stakeholders to improve implementation of the FDA's unique device identification system. Ms Kinard and Dr Redberg reported receiving grants from Arnold Ventures.

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