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February 5, 2018

Scott Gottlieb, MD, Commissioner
Food and Drug Administration (FDA)
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: Review of Existing Center for Devices and Radiological Health Regulatory and Information Collection Requirements

Dear Dr. Gottlieb,

The American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) appreciate the opportunity to provide our recommendations to assist the agency in its effort to identify existing regulations and related paperwork requirements that could be modified, repealed, or replaced, consistent with the law, to achieve meaningful burden reduction while allowing it to satisfy its public health mission and fulfill statutory obligations. Neurosurgery has a long history of collaboration with the Food and Drug Administration (FDA), as our specialty, highly dependent on medical technology, is one of rapid innovation. We are, therefore, eager to share our views on ways to enhance efficiency in bringing lifesaving improvements to our patients.

Physician Directed Use of Medical Products

The AANS and CNS have been active for many years on the issue of preserving physician-directed — referred to as "off-label" — use of FDA approved products. On Nov. 9, 2016, organized neurosurgery presented its views at an FDA public hearing on off-label promotion issues, held as part of a comprehensive review of FDA regulations and policies governing firms' communications about unapproved uses of approved/cleared medical products. In March 2017, the AANS and CNS joined the Alliance of Specialty Medicine in updating its Statement on Physician Directed Use. Included in the updated document is the recommendation that the FDA add language to drug and device labels to highlight the fact that, after marketing approval, additional scientifically valid data may become available to justify new uses, dosages, or contraindications and physicians should consider this information when prescribing the product. The goal of adding the language is to destigmatize the concept of off-label use and foster appropriate communication with patients. The updated Alliance statement was included in the FDA's docket of materials on the issue. These documents are in the public record at the FDA and are attached.

We note the ruling from *Amarin Pharma, Inc. v. FDA*, finalized in 2016, in which US District Court Judge Paul A. Engelmayer held that speech promoting the off-label use of Amarin's Vascepa might not form the basis of a prosecution for misbranding. As such, we hope that the FDA will revise its 2014 guidance on off-label promotion to preserve access to truthful scientific information from manufacturers.

Simplification for Investigator-sponsored IDE Projects

Neurological surgery is a specialty that is continuously innovating, and the AANS and CNS are committed to helping our neurosurgeon inventors bring their ideas to the FDA. We appreciate the efforts

of the FDA's Center for Devices and Radiological Health's (CDRH) division directors to educate neurosurgeons on the device approval process. Neurosurgeons and their academic centers can perform research and develop innovative products and tools for better patient care but, at times, they may feel left out of the process and daunted by regulatory hurdles, which can discourage neurosurgeons from bringing their inventions to the FDA. Improving this process is especially crucial for those devices intended for use in smaller patient populations — devices which may result in significant improvements in patient care, but, by virtue of the small target population size, are not sufficiently profitable to garner industry investment. To address the issues above, we recommend that the agency simplify the rules for investigator-sponsored Investigational Device Exemption (IDE) submissions. Smaller studies (i.e., those with fewer than 15 or 20 subjects) could enter a special category for exploration with fewer administrative requirements. Notably, eliminating the need for a Right of Reference letter, while indemnifying the manufacturer, would be very helpful and would significantly expedite the early phase of research that can then direct subsequent larger scale work. We have attached an article titled, "Barriers to Investigator-initiated Deep Brain Stimulation and Device Research," for your consideration.

Conflict of Interest Paperwork

The AANS and CNS are dedicated to actively engaging with the FDA to provide neurosurgical expertise on medical products and to foster innovation and patient safety. These activities include:

- Recommending neurosurgeon experts to serve on FDA advisory panels,
- Inviting FDA staff to national neurosurgical meetings;
- Providing input on FDA guidance documents; and
- Giving testimony at panel meetings.

In addition, the AANS and CNS are official partners with the FDA and the agency's Network of Experts program, which provides rapid clinical assistance to FDA reviewers.

Unfortunately, burdensome conflict-of-interest paperwork for advisory panel and other special government employee (SGE) participation makes it extremely difficult for neurosurgeons who are involved in cutting-edge research to participate. We support the agency's ability to grant waivers for conflicts-of-interest to ensure that the most experienced neurosurgical experts are available to help assess neurological devices under review by the FDA.

To remedy this problem, we urge the agency to consider simplifying and streamlining the paperwork requirements for physician reviewers. Even for neurosurgeons who meet the FDA conflict-of-interest requirements, the stacks of forms to complete can be off-putting. Many of our best neurosurgeon volunteers with prior service have refused to continue to participate because they must resubmit burdensome paperwork, most of which had already been provided to the FDA in the recent past. If an individual has not been called for service for twelve months, they must complete the same reams of paperwork that an individual who is new to FDA service must complete. Not infrequently the paperwork takes longer to complete than the number of hours the individual will spend assisting the FDA. Neurosurgeons have consistently been generous with their volunteer time and are eager to provide their expertise; however, they find being asked to duplicate paperwork frustrating and prohibitive. We recommend that the agency devises a system that would only require updating, not reproducing, the existing paperwork. One action the FDA could take for those individuals with past service, would be to pre-populate forms and ask only that any changes or new information be provided.

Use of Registry Data

The neurosurgery-led NeuroPoint Alliance (NPA) has worked closely with the FDA and other societies on several important initiatives to explore "real world" data sources and alternatives to costly and time-consuming randomized controlled trials. As the agency moves forward to examine its existing and

pending regulatory activity, we urge you to consider more timely and innovative ways to assess clinical efficacy and safety to bring potentially life-saving medical products to patients. The Society of NeuroInterventional Surgery (SNIS) and the AANS/CNS Cerebrovascular Section have agreed to use a single registry for neurovascular surgical procedures, run by the NPA, and are working with the FDA to use the data to evaluate acute thrombectomy devices. We support the agency's use of this registry as part of its coordinated registry network for Devices Used for Acute Ischemic Stroke Intervention (DAISI). We remain convinced that this registry is precisely the kind of collaborative effort that will lead to better care, and ultimately outcomes, for our patients. In addition to the registry for acute thrombectomy devices, the NPA has formed the Spine Quality Outcomes Database (SQOD) — developed in collaboration with the American Academy of Physical Medicine and Rehabilitation (AAPM&R) — and is working with the FDA to use the database for device evaluation and post-market surveillance. We urge you to foster a regulatory environment that supports and encourages the use of physician-led, specialty society registry data.

Conclusion

The AANS and CNS have a deep respect for the professionalism, expertise, dedication and hard work of the men and women at the FDA. We know that many of them feel as challenged as we do about the bureaucracy. FDA processes have a profound impact on neurosurgeons and our patients, as our innovative and technology-dependent specialty requires sophisticated drugs, devices and tools to provide the highest quality care possible. Regulatory relief is necessary, and revisions to FDA processes should be carefully examined and reassessed to ensure they meet the dual challenge of fostering innovation while also protecting patient safety. As such, we appreciate the opportunity to share our recommendations to decrease the regulatory burden for medical device innovation and ensure safe patient access to new and improved medical technology. We continue to stand ready to assist the FDA with neurosurgical expertise and appreciate our collaborative and collegial partnership with the agency.

Thank you for considering our comments.

Sincerely,

Alex B. Valadka, MD, President
American Association of Neurological Surgeons

Ashwini D. Sharan, MD, President
Congress of Neurological Surgeons

Enclosures: AANS/CNS FDA Off-Label Hearing Testimony (11/9/16)
Alliance of Specialty Medicine "Physician Directed Applications Position Statement" (3/17)
Article: "Barriers to Investigator-initiated Deep Brain Stimulation and Device Research"

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American Association of Neurological Surgeons

CNS

Statement

of the

American Association of Neurological Surgeons
Congress of Neurological Surgeons

before the

Food and Drugs Administration

Public Hearing

on the Subject of

Manufacturer Communications of
Physician-Directed Uses of Approved Medical Products

November 9, 2016

My name is William Welch. I am a neurosurgeon practicing at the University of Pennsylvania Medical Center, and I am here today on behalf of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. I have been a member of the AANS/CNS Committee on Drugs and Devices for over 15 years and currently serve as its vice chair. I appreciate the opportunity to participate in today's public hearing to address issues surrounding communications regarding physician-directed — sometimes called off-label — use of FDA-approved medical products. We support the dissemination of scientifically valid information between healthcare professionals and manufacturers and urge the FDA to allow industry to provide physicians with access to such clinical information when asked.

In its notice of this hearing, the FDA posed questions about how clinicians might assess off-label communications, possible consequences of these communications, and ways they should be regulated. Organized neurosurgery, along with our colleagues in the Alliance of Specialty Medicine — from whom you will hear tomorrow — believe physicians have the ability to assess and interpret clinical data appropriately. This is an essential competency for physicians and we consider the source of all information used in shared decision-making with our patients, assuring their appropriate informed consent regarding the risks and benefits of treatment.

Physician directed use of FDA-approved drugs and devices is a central part of the practice of medicine. Of course, in a perfect world, we may all prefer to have randomized control trial data for every drug and device for each indication, but the cost and the rarity of some diseases make this impractical and often impossible. The refinement of the use of FDA-approved drugs and devices is a rational process. Scientific evaluation of a product necessarily must be limited to the questions asked, and variables examined. This results in narrow FDA marketing "approval." Once approved for sale and marketing, however, use of that product expands into areas of real-world clinical experience. As experience is gained by the medical community, physicians publish and discuss their findings on how the device performed, including its observed risks and benefits. Its use is then modified appropriately. If the manufacturer has data on uses of a drug or device that has been developed following approval, this is valuable additional information for physicians. Feedback to the manufacturers from the physician community may be useful as well and lead to future improvements of their products. Communication is a two-way street.

There are many examples of how this expansion of product indications benefits patients, relieves suffering and saves lives. In cancer care, for instance, many chemotherapy agents are approved for narrow "on-label" uses for a particular indication, but are quickly extrapolated to related cancers that have limited treatment options. In the area of spine disease, the use of screws to stabilize the back of the cervical spine was not FDA "approved" but over the years had become a medical standard as one of the best ways to securely stabilize the spine. We commend the FDA for recent efforts to classify many screws used in the spine. Off-label or physician-directed expansion is particularly important in pediatrics where few devices go through FDA clearance due to the expense, legal risk and difficulty of setting up valid studies with relatively limited numbers of potential patients. Without the application of products in off-label uses, advancement in the care of children would halt.

Neurosurgery is a very clinically diverse and device dependent specialty, and those devices hold great hope for improvement in the quality of life and reduction of pain for many patients. Neurostimulators are showing great promise for uses outside of the initially labeled indication — treating patients with secondary dystonia, essential tremor, and many conditions causing pain or dysfunction. New uses for endoscopic embolization devices are being developed, treating potentially debilitating or fatal cerebrovascular conditions. In addition to device development, the uses of drugs with other label indications have been found effective for serious nerve pain. The ability to share information about these hopeful new applications that were not part of the original label for a drug or device is beneficial and should be encouraged.

The expansion of use from the narrow on-label approval by the FDA to more broad off-label or physician-directed applications, then, is a standard part of medical practice and the advancement of patient care. As I have mentioned, in many cases, new applications are found that dramatically improve care and save lives in off-label or physician-directed ways that increasingly deviate from the original FDA approval. In those cases, best medical evidence leads to products that may have their primary use in off-label or physician-directed applications. Such refinement in patient care could not occur if government bodies, such as the FDA, regulated how professional judgment is exercised. The evaluation of evidence — including clinical trials, observational studies and registry data — is essential to improvement in patient care. Including manufacturers in this process is useful. As they and practitioners become aware of new indications, dosages, and complications about the use of a product after the label is created, sharing the information is of benefit to individual patients in particular and public health in general.

The stigma of off-label use can cause confusion and misunderstanding. Particularly for drugs and devices with long time use that differs from the labeling, we would urge the FDA to consider an expedited process to add the indications to the labeling or find another way to educate important stakeholders and dispel misinformation about physician-directed use. Some off-label uses have been in common practice and widely considered excellent medical care for decades, as was the case with some screws used in the spine for which the labeling was limited to other areas of the anatomy. We have joined the Alliance of Specialty Medicine in suggesting that one way to address these concerns would be to add a statement to drug and device labeling acknowledging that after FDA approval of a product, additional scientifically valid data may become available that would support new uses, dosages or other refinements. This would help to clarify physician-directed use for the public, payors and others. Specific language has been provided to the FDA by the Alliance and will be discussed tomorrow when Dr. Stulting speaks on behalf of the Alliance.

I have been privileged to interact with the FDA over the last 23 years — as a practicing neurosurgeon, a clinical investigator and a leader of the AANS/CNS Committee on Drugs and Devices. As such, I have stood before FDA panels as a physician innovator, as a representative of my medical specialty societies, and have, on occasion, reported device failures or malfunctions to the FDA. Based on my experiences, I have a deep respect for the dedication and intelligence of the men and women working at the FDA. Their purview is vast, they labor under a tremendously bureaucratic system, and, I believe, they are eager to foster open communication with practicing physicians and with industry to enhance patient care and reduce morbidity and mortality. As always, organized neurosurgery stands ready to continue to work with the agency to develop safe and effective drugs and devices and to improve scientific exchange for our patients.

Thank you.

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Alliance of Specialty Medicine

Sound Policy. Quality Care.

Physician-Directed Applications

A Position Statement of the Alliance of Specialty Medicine

Updated March 2017

Physician-Directed Applications

Physician-directed applications, also known as "off-label"[1] uses, are an integral component of the art and science of medical practice, particularly for specialty physicians. Using medical expertise and judgment, physicians may choose to use approved medical products such as prescription drugs, biologics, and devices, for uses not listed in the United States Food and Drug Administration (FDA) approved or cleared labeling, as appropriate.

Background

It is not uncommon for some off-label uses of medical products to become standard of care in the practice of medicine.[2] In fact, off-label uses of certain medical devices and drugs can be found in standard textbooks for medical subspecialties. In certain patient populations, such as children and cancer patients, off-label use of medical products is extensive when appropriate therapies have not been developed or evaluated for the populations or a clinical trial is not feasible (such as in the case of rare diseases). In these circumstances, physician-directed applications provide treatments that may not otherwise be available for some of the nation's youngest and most critically ill patients.

Physicians use the best available clinical evidence, judgment, and consideration of individual patient circumstances and preferences in treating and managing disease and injury. Good medical practice and the best interests of the patient require that physicians use legally-available drugs, biologics, and devices according to their best clinical expertise and judgment.

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[1] "Off-label" use for approved prescription drugs, biologics, and medical devices means any use that is not specified in the labeling approved by the FDA. For cleared medical devices, "off-label" means any use that is not included in the cleared "indications for use." Labeling is considered as any written material, which accompanies, supplements, or explains the product.

[2] Refer to specific specialty examples document at specialtydocs.org.

FDA Regulatory Principles and Labeling

The FDA has broad regulatory authority over the approval of pharmaceutical, medical device, and biologic products in the United States. Products may only be labeled, promoted, and advertised for the uses that the FDA has approved or cleared. Labeling of a medical product is negotiated between the FDA and the manufacturer to ensure that the labeling accurately reflects the safety and effectiveness data presented in the manufacturer's marketing application. Furthermore, a drug, device, or biologics manufacturer may choose, for economic reasons, not to pursue additional labeling for indications that may increase the cost of obtaining FDA approval or clearance. As a result, the label may not reflect changes in indications, contraindications, warnings, or dosage, supported by new data that become available after approval or clearance.

Practice of Medicine Exception

The Food and Drug Administration does not have the statutory authority to regulate the practice of medicine. In 1998, the US Supreme Court issued a judgment in *Buckman v. Henney* affirming physicians' right to use any FDA-approved therapies they believe are in the best interests of their patients. In addition, section 906 of the federal Food, Drug, and Cosmetic Act addresses the issue of the practice of medicine and states the following:

> *Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.*

Physicians may prescribe or administer any legally-marketed product for an off-label use within the practice of medicine.

Standards of Care

Standards of care change over time, and the emergence of new literature may alter treatment patterns. As a result, there are instances when the off-label use of medical products evolves to be recognized as a generally accepted medical standard. There are also instances in which the labeled uses of medical products are found to have contraindications and interactions that reduce their safety and efficacy. Specialty physicians are encouraged to notify the relevant agency or institution of adverse events related to the use of medical products.

Access to Available Information

To enhance patient care, physicians must have unrestricted access to truthful, non-misleading information about the benefits and risks of all therapies available for treatment, including

medically accepted alternative uses of approved prescription drugs, biologics, and/or devices. Manufacturers must be able to provide adequate directions for use of both approved and medically accepted alternative indications of approved medicines and treatments, along with adequate disclosures regarding risks and the limitations of scientific understanding.

Provided there is prominent disclosure that FDA does not approve such use, limitations on communications should only be related to patient risk based on factors including the approval status of the medicine, general medical acceptance of the treatment, and the level of scientific sophistication of the audience. Physicians have the ability to assess and interpret clinical data appropriately and consider the source of all information used in shared decision-making with patients.

Informed Consent

Informed consent is the process by which the treating health care provider discloses appropriate information to a competent patient so that the patient may make a voluntary choice to accept or refuse treatment.[3] Among other things, informed consent requires a discussion of reasonable alternatives to the proposed intervention, which may include a discussion of medically accepted alternative uses of approved prescription drugs, biologics, or devices.

Physicians and medical institutions have varied practices for obtaining and documenting informed consent provided to patients that may or may not address off-label use. In some instances where an off-label use has come to be considered a standard of care in the clinical community and/or raises little risk of an adverse outcome, the use may not be discussed specifically with the patient. However, physicians should use their clinical judgment in determining the need to discuss specific off-label uses with patients and include information about such uses in informed consent materials when the off-label use could be a significant factor in the patient's decision about whether to undergo the procedure. If a patient has questions, the physician should also personally inform the patient that the product is being used in an off-label manner and discuss the benefit/risk profile for that use. This approach not only serves the patient's best interests, but might also help to limit the physician's liability risk.

Benefits and Risks of Physician-Directed Applications

Benefits and risks exist with off-label use. Benefits include the ability to provide care to patients who may not receive appropriate treatment or perhaps treatment at all without off-label use, such as many pediatric patients. Risks include the potential for limited effectiveness and unexpected side-effects from uses that have not been adequately studied for the specific indication or patient population.

It is well-established that physicians who use a product for an indication not in the approved or cleared labeling have the responsibility: (1) to be well informed about the product; (2) to base

[3] Appelbaum PS. Assessment of patient's competence to consent to treatment. *New England Journal of Medicine.* 2007; 357: 1834-1840.

its use on a firm scientific rationale and sound medical evidence; and (3) to maintain awareness of the product's uses and effects.

Conflicts of Interest

Current FDA labeling regulations have the practical effect of restricting the flow of information between industry and physicians. Such restrictions may overly hinder the free-flow of information between physicians that would be appropriate in educational and clinical settings.

Conflicts of interest should be disclosed in compliance with all state and federal laws and regulations. Specialty physicians engaging in compensated arrangements with industry should disclose their financial arrangements in medical education, policy, research, and professional activities. Physicians who are involved in product development and/or testing should disclose this role to patients. Physicians should avoid interactions and activities where discussions of off-label use could be considered promotional in nature.

Statement of Policy

The Alliance of Specialty Medicine maintains that a specialty physician may prescribe or administer any legally marketed product for an off-label use within the authorized practice of medicine where the physician exercises appropriate medical judgment and it is in the best interests of the patient. If specialty physicians use a product for an indication not in the approved or cleared labeling, they have the responsibility: (1) to be well informed about the product; (2) to base its use on a firm scientific rationale and sound medical evidence; and (3) to maintain awareness of the product's use and effects. Specialty physicians should appropriately counsel patients about the benefits and risks of the proposed treatment, and whether alternative treatments might be available. Specialty physicians are encouraged to notify the relevant agency or institution of adverse events related to the use of medical products.

Additionally, we believe it would be appropriate to add a paragraph to all drug and device labels including the following or similar language: "The indications, contraindications, warnings, cautions, and other information contained in this label are based on data generated by the clinical trial(s) used to obtain approval for marketing this product in the United States. After marketing approval, additional scientifically valid data may become available to justify new uses, dosages, contraindications, or other modifications of the information contained herein. Your physician will take this information into consideration when prescribing this product and can discuss it with you." This, or similar wording would empower physicians to utilize approved products for the benefit of their patients on the basis of current, scientifically valid data without the stigma and hampered professional communication created by existing restrictions on off-label discussions.

Barriers to investigator-initiated deep brain stimulation and device research

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ABSTRACT

The success of device-based research in the clinical neurosciences has overshadowed a critical and emerging problem in the biomedical research environment in the United States. Neuroprosthetic devices, such as deep brain stimulation (DBS), have been shown in humans to be promising technologies for scientific exploration of neural pathways and as powerful treatments. Large device companies have, over the past several decades, funded and developed major research programs. However, both the structure of clinical trial funding and the current regulation of device research threaten investigator-initiated efforts in neurologic disorders. The current atmosphere dissuades clinical investigators from pursuing formal and prospective research with novel devices or novel indications. We review our experience in conducting a federally funded, investigator-initiated, device-based clinical trial that utilized DBS for thalamic pain syndrome. We also explore barriers that clinical investigators face in conducting device-based clinical trials, particularly in early-stage studies or small disease populations. We discuss 5 specific areas for potential reform and integration: (1) alternative pathways for device approval; (2) eliminating right of reference requirements; (3) combining federal grant awards with regulatory approval; (4) consolidation of oversight for human subjects research; and (5) private insurance coverage for clinical trials. Careful reformulation of regulatory policy and funding mechanisms is critical for expanding investigator-initiated device research, which has great potential to benefit science, industry, and, most importantly, patients. *Neurology*® 2014;82:1465–1473

GLOSSARY

CMS = Centers for Medicare & Medicaid Services; **DBS** = deep brain stimulation; **FDA** = US Food and Drug Administration; **IDE** = investigational device exemption; **IRB** = institutional review board.

Over the past few decades, clinical investigation with neuroprosthetic devices has flourished, resulting in advances such as deep brain stimulation (DBS), neurostimulators for pain, and brain–machine interfaces.[1–3] DBS, for example, has been shown to be effective for Parkinson disease, tremor, dystonia, and obsessive-compulsive disorder in industry-funded double-blind randomized clinical trials.[4–7] However, these successes have overshadowed emerging problems in the field, particularly for industry-independent investigators.[8] Neuroprosthetic device research has developed in a financial and regulatory milieu that is perceived, in some cases, as antagonistic to clinical investigation, particularly to investigator-initiated research.[9,10] Scarce funding, expensive regulatory burdens, industry control of investigative devices, and public scrutiny over financial conflicts of interest have all contributed to barriers that must be overcome for a successful device-related clinical investigation.[11] These barriers have also been cited as contributing to a decline in the number of independent clinical investigators, especially in an environment of scarce research funding and added pressures for greater clinical productivity.[12,13]

Rigorous investigator-initiated prospective study of neuroprosthetic devices often lags behind industry-sponsored studies. Most funding by federal agencies, such as the NIH, is directed toward basic mechanisms, novel drugs, and biologics.[14] Consequently, industry and the private

From the Departments of Neurosurgery (M.L.K., A.G.M.) and Psychiatry (D.M.) and the Center for Neurological Restoration (A.G.M.), Neurological Institute, and the Center for Clinical Research (J.B.), Cleveland Clinic, OH; MacLean Center for Clinical Medical Ethics (M.L.K.), Department of Medicine, The University of Chicago, IL; and the Departments of Neurology and Neurosurgery (M.S.O.), University of Florida Center for Movement Disorders and Neurorestoration, Gainesville.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

sector take a leading role in device-based investigations.[15] The result is a predominance of large-market device-based clinical trials. These studies benefit large patient populations, including those with advanced Parkinson disease, essential tremor, and dystonia, but neglect some rare or orphan disease populations. A recent report by the Institute of Medicine highlights a growing concern over the underuse and understudy of devices in these populations.[14] Few efforts have emerged to address these shortages, although some funding agencies have responded. The Department of Defense, for example, recently allocated more than $19 million to the development and expeditious delivery of medical products to wounded veterans.[16]

In this article, we outline critical issues facing investigator-initiated research in biomedical devices using a case study from our own experience. We present lessons learned regarding the conduct of a federally funded first-in-man research trial with an existing medical device.[17] Although these lessons emanate from a single case study, they likely have wide applicability to all investigator-initiated medical device research, especially early-phase research in small or large disease populations. Our goal is not to criticize our peers at the US Food and Drug Administration (FDA), institutional review board (IRB), and funding agencies. In fact, the peer review process was critically important for improving the work presented in the case study. Rather, we propose changes for reducing systemic barriers and improving device-related research for independent clinical investigators. The future of device innovation in the clinical neurosciences will rely on a diversity of ideas produced by both industry and academia, and the safety and efficacy standards of our federal and local regulatory bodies.

AN INNOVATIVE IDEA An investigator in a tertiary care center developed a hypothesis-driven project based on prior clinical and research experience. This investigator had participated in DBS trials and had amassed enough clinical and research experience to serve as a principal investigator.[7,18] He was challenged by existing patients to focus more attention on rare disorders and to seek better alternatives to disorders without effective therapies. One patient, in particular, had voiced frustration with the lack of progress in novel therapies for poststroke pain.

The research idea evolved from clinical experiences with patients with thalamic pain syndrome and from previous research focused on DBS placed in the ventral striatal and anterior capsular region.[6,7,18] Thalamic pain syndrome is often characterized by unrelenting burning pain that may be associated with allodynia or dysesthesias.[19] The severity of symptoms and the lack of adequate treatment options combine in many patients to make this syndrome particularly devastating.[20] Historically, surgical therapy has targeted the somatosensory pathways in the CNS. Outcomes have been measured using simple numerical or analog pain scales[21] and attempts at therapy with cortical and subcortical targets have been unsuccessful or tainted by placebo effects.[22]

Recently published theoretical and empirical work in the pain literature suggested that previous therapeutic objectives had targeted a neural pathway already destroyed by the disease process underlying central pain syndromes.[17] Rather than targeting a compromised somatosensory system, the investigator decided to use a modified approach that targeted affective neural pain pathways.[23] Previous collaborative work revealed that combined DBS of the ventral capsule and ventral striatal areas could modulate mood in patients with depression.[18] Additionally, modern DBS techniques facilitated safe and reversible modulation of these pathways while mitigating the risk of emotional and cognitive deficits associated with earlier lesional strategies.[24] Historical evidence suggested that some ablative procedures in similar neural networks were effective for anxiety disorders.[25] The investigator also reasoned that validated functional outcome measures such as the pain disability scale would avoid the pitfalls of the more traditional visual analog scale in this population.[26,27]

Funding and approval. Once a first draft of the proposal was written, several major concerns emerged. First, the prevalence of thalamic pain syndrome in the general population was low as compared to other chronic pain conditions.[28] Second, the cost for a device-related clinical trial was very high.[29] Third, industry would be unwilling to participate given the small size of the market and the low likelihood of a return on investment.[30] Finally, the expansion of DBS for depression and obsessive-compulsive disorder into chronic pain populations represented a significant paradigm shift for the field.[17]

Given these concerns, the investigator sought federal funding and secured a new NIH award that catered to higher risk research: the Director's New Innovator Award.[31] The investigator was fortunate

since few federal funding opportunities exist for high-risk device-based research and success rates are low for grants of this kind (table 1).[32] Once funding was obtained, the investigator contacted the Centers for Medicare & Medicaid Services (CMS), which approved reimbursement for patients in his trial, although some commercial insurers denied coverage (figure).

The investigator then submitted an investigational device exemption (IDE) application to the FDA for the use of DBS in the clinical trial (table 1). The FDA granted conditional approval within a month and final IDE approval took about 5 months (figure). During this period, the FDA proposed several revisions to the NIH-approved trial protocol, including 2 major changes: (1) redefining the endpoint of the trial to include the visual analog scale rather than exclusively the pain disability index; and (2) reducing the target enrollment from a power analysis of 34 patients to a "typical" 10 patients since this was a first-in-man study.[33]

Following NIH funding, the investigator also applied to the device manufacturer for a right of reference letter. The right of reference letter is an FDA requirement for investigators pursuing research with an existing device. It authorizes the FDA to reference the safety and regulatory binder for the product, which is provided by the manufacturer.[34] Device manufacturers must provide the FDA with confidential safety data and information on their devices. The FDA keeps the information protected and accesses the information for the purpose of reviewing potential device approval. The criteria by which manufacturers process outside requests for right of reference authorization are underreported. In our case, it took over 3 months to obtain this letter.

The investigator then submitted the protocol to the local IRB for approval. The IRB ruled that it could not approve the proposal until all changes had been submitted and reviewed by the FDA. Once approved by the FDA, the local IRB required additional minor changes to the protocol and informed consent. These changes had to be once again approved by the FDA. This back-and-forth review consumed several additional months and resulted in a prolonged delay in study enrollment. Moreover, the NIH award fell under enrollment restrictions until the IRB approved the protocol. When initial IRB approval was granted, the NIH then re-reviewed the original award and granted final approval 8 months after the initial award had been received (figure). Although no money had been spent on human research up to this point, the award was covering a percentage effort of the investigator's time, including 25% of the investigator's salary. Overall, the time elapsed from the initial NIH award to enrollment of the first subject extended beyond 1 year of the 5-year grant period (figure).

PROBLEMS: FUNDING, REGULATION, INSURANCE, AND BIAS

Although the experience presented in our case study is not uncommon for investigator-initiated device research, it is underreported. One of the coauthors of this article (M.S.O.) experienced 2 similar cases in his DBS center. Regulatory processes in device research have been criticized previously for increasing approval times.[15,35] A lack of systematic integration between the NIH, CMS, and the FDA has been cited as a potential reason for placing ineffective and sometimes harmful devices into the medical community.[15] However, little attention has been given to how approval times and regulatory disintegration affect investigator-initiated device research and the needs of orphan or rare disease populations. Several critical barriers may hinder or block successful investigator-initiated device-based clinical trials.

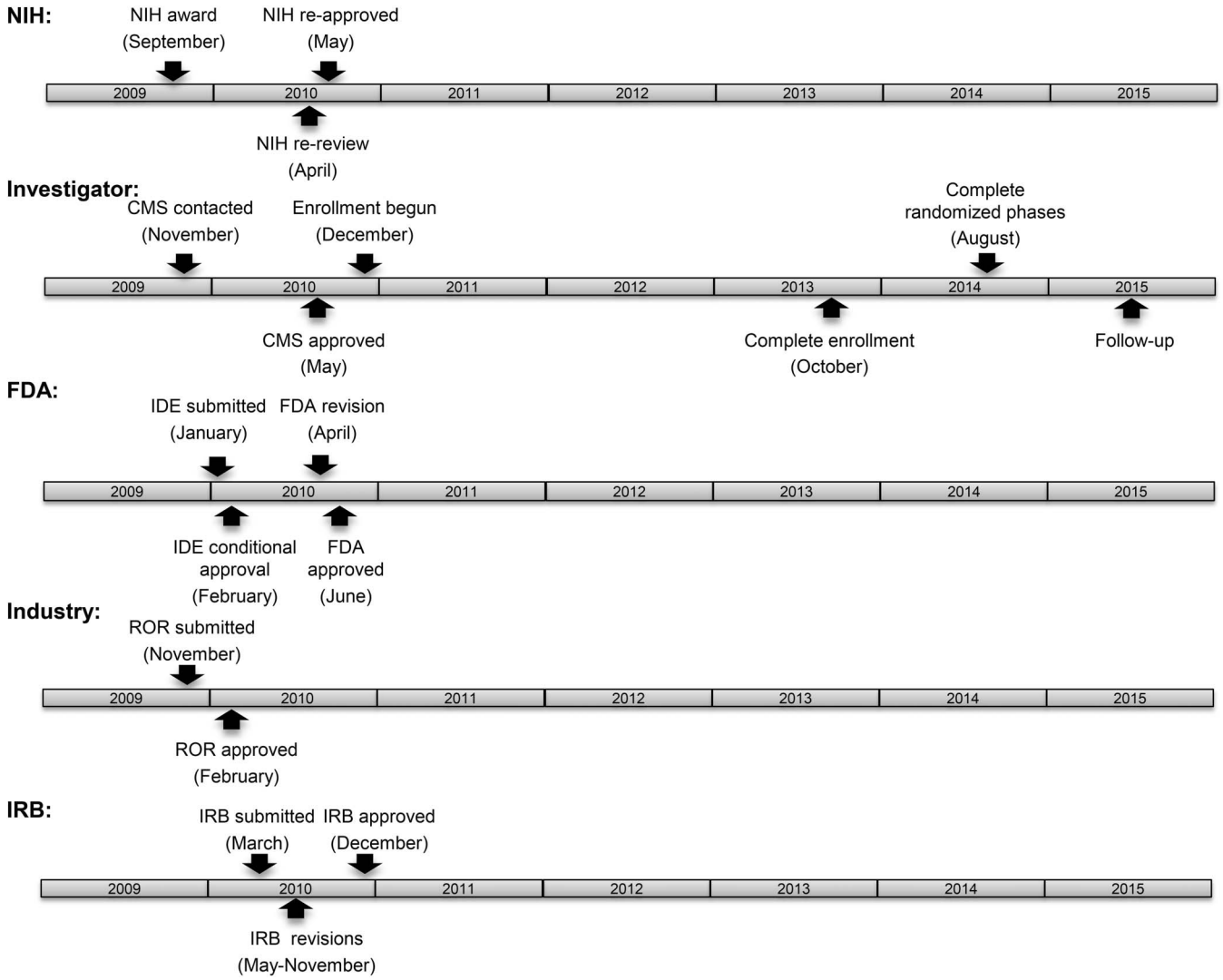
Funding. Most research in DBS is expensive and requires large funding support mechanisms. Three primary funding sources exist for studies of this kind: (1) private foundation/not-for-profit, (2) industry, and (3) governmental support (i.e., NIH).[36] In neuroscience research, private foundations provide less than 1% of the total research support,[37] and the

Table 1 Controlled trial approval process for existing biomedical devices

Regulatory step	Requirements	Success rate	Time	Alternatives
NIH	Grant	5.7%[a]	1 year	Private or industry
FDA	IDE	25%[b]	<1 year	Humanitarian device exemption or "off-label" use
IRB	Committee approval	Variable[c]	Months	None
Industry	Right of reference letter	Unknown	Months	None

Abbreviations: FDA = US Food and Drug Administration; IDE = investigational device exemption; IRB = institutional review board.
[a] Success rate for NIH Common Fund DP2 award.[32]
[b] FDA's first review approval rate and timeline.[39]
[c] IRB variability.[56,57]

Figure Timeline of deep brain stimulation trial



CMS = Centers for Medicare & Medicaid Services; FDA = US Food and Drug Administration; IDE = investigational device exemption; IRB = institutional review board; ROR = right of reference letter.

budget for DBS trials is beyond the capacity of most private foundations.[29] Funding sources for DBS trials, even very small ones, are generally limited to industry, government, and occasionally a partnership between the two.

According to recent data by Dorsey et al.,[37] industry funds 58% of all neuroscience research. This figure is likely much larger in device-based research areas such as DBS, where companies hold proprietary rights on the use of their devices in research.[9] In addition, regulatory management requires full-time personnel, which can be overly expensive for most independent investigators.[29] Industry has been a critical partner for most successful device-related trials in disorders like Parkinson disease and essential tremor. However, the small number of patients with medically refractive thalamic pain syndrome[28] and other rare diseases provides little market incentive for industry partnership. In our case study, federal funding was the best and perhaps only option.

NIH funding and insurance coverage. NIH grants have become exceedingly competitive over the past 2 decades, particularly for clinical researchers.[12,38] Moreover, these grants typically cover costs directly related to the trial, including the costs of enrollment and follow-up. Funding of clinical care, such as hospitalization, surgical implants, and, importantly, management of potential complications, requires insurance approval for an experimental indication. While industry-conducted research frequently covers all costs, including those related to research, clinical care, and follow-up, investigator-initiated research requires a patchwork of funding sources to launch and sustain a project. CMS may fund the clinical care associated with some IDEs, but

patients with private insurance are often excluded. If insurance coverage fails or expires, the clinical trial will collapse. In addition, insurance coverage for long-term follow-up issues such as battery replacement, hardware maintenance, and surgically related costs remains uncertain for many patients.

IDE approval and the right of reference letter. According to the last IDE memorandum from the FDA, approximately 25% of all IDE applications are approved on the first review, with an average final approval process time of approximately 242 days (i.e., 8 months) from receipt of the application.[39] Approval is often conditional, requiring further modification or an optional in-person hearing.[40] Large device companies can apply for IDE sponsorship as a corporation, dedicating sizeable teams of professionals to the design, writing, and management of an IDE. However, for investigator-initiated research, it is the individual and his or her academic institution, rather than a corporation, which assumes all risks and regulatory burdens.[41] In addition, obtaining a right of reference letter from the manufacturer represents a crucial sine qua non in device-based research efforts and has been the subject of several recent publications.[9,42,43] Industry can effectively terminate a project by exercising their right to refuse to provide such a letter or, alternatively, demanding fundamental changes to the protocol regardless of the NIH, FDA, or IRB review process.

Bias and the use of devices. Financial, regulatory, and insurance barriers to device-related research all contribute to the problem of bias in the medical device literature.[44,45] Innovative clinical practice is often criticized for a lack of evidence-based standards and in particular for a lack of randomized and controlled trials.[45,46] This lack of evidence is particularly true for less common disorders such as Tourette syndrome and central pain syndrome, which currently lack a large randomized controlled clinical trial. Observers note that a preponderance of case reports and uncontrolled case series makes much of the device-based literature susceptible to systemic errors.[45] These errors include the placebo effect, which has been reported to be higher in the chronic pain population.[22] Moreover, recent studies using spinal cord stimulation as treatment for failed back surgery syndrome reveal important discrepancies in results between independent investigator-initiated and industry-initiated clinical trials, making investigator-initiated trials essential.[47] DBS, in turn, is amenable to controlled trial designs, randomization, and even sham controls.[48,49] Several designs for sham-controlled DBS studies have been reported, including those for thalamic pain syndrome.[50,51]

However, there have been many publications of potential DBS applications in uncontrolled settings on topics ranging from alcohol dependency to memory enhancement.[52,53] Many of these indications have lacked follow-up controlled trials for validation and may not meet the rigorous, evidence-based approach to device approval as modeled by the CMS Coverage with Evidence Development Program. This DBS publication trend likely reflects the difficulties that clinician–scientists face in competing for NIH funding and for meeting the regulatory burdens imposed by IDE mechanisms, the IRB, and CMS.

A simpler, less formal, and commonly used route is employed by clinicians who implant devices "off-label" in small cohorts of patients, later reporting experiences in a retrospective experience design. This alternative route is quick, inexpensive, and potentially informative, although subject to several biases.[54] This approach does not allow for prospective, structured, and sham-controlled evaluation because the a priori intent is innovative clinical care rather than research. Without reform of the existing regulatory structure and process, it is difficult to envision how prospective investigator-initiated trials might be better incentivized.

Table 2 Proposed reforms to the approval process for biomedical device–based research

Action	Actor	Impact
Early feasibility study/mini-IDE pathway	FDA	Reduces approval time
Eliminate right of reference requirement	FDA	Promotes independent investigation
Joint NIH-FDA application	NIH and FDA	Preserves award dollars for investigation rather than regulation
Exempt/expedite local IRB review	NIH Scientific Review Group	Consolidates oversight of human subjects research
Extend private insurance coverage	Affordable Care Act	Mandates coverage of clinical trials

Abbreviations: FDA = US Food and Drug Administration; IDE = investigational device exemption; IRB = institutional review board.

WHAT CAN BE IMPROVED IN THE INVESTIGATOR-INITIATED DEVICE TRIAL PROCESS?

Solutions to the problem of investigator-initiated device research must acknowledge the realities of funding limitations and complex regulatory requirements while preserving the unique role that clinical investigators play. We propose 5 specific areas for reform (table 2): (1) alternative pathways for device approval; (2) eliminating right of reference requirements; (3) combining federal grant awards with regulatory approval; (4) consolidation of oversight for human subjects research; and (5) private insurance coverage for clinical trials.

Proposals for reform thus far have emphasized changes in funding mechanisms and in specific

FDA regulatory processes. Fins and others[11] have argued for a reconfiguration of funding agencies at the NIH, National Institute for Biomedical Imaging and Bioengineering, and the National Science Foundation, all in an effort to promote interdisciplinary collaboration in device-based research projects. Establishing a "mini-IDE" pathway for academic-based research within the FDA would allow investigators to pursue clinical investigation under reduced regulatory burden.[11] To meet these needs, the FDA has recently implemented an Early Feasibility Study pathway to facilitate clinical trials in small populations.[55] This pathway has yet to be tested in DBS research.

The right of reference requirement may be as undesirable for industry as it is for independent investigators. Reviewing right of reference requests is an additional regulatory role for device companies and is a distraction from their core mission of selling safe and effective devices. A high volume of DBS proposals, for example, would likely slow the right of reference approval process and require increasing corporate resources for scientific and regulatory purposes rather than for product development and commercial purposes. To this end, Fins[9] has argued for reform of the Bayh-Dole Act of 1980, including delaying the transfer of intellectual property rights until phase 2 trials, establishing a national "clearinghouse" for DBS devices to bypass right of reference access issues, and providing global liability protection for participating device companies.

Perhaps even more important to the clinical investigator is the need to consolidate funding and regulatory processes. Investigator-sponsored NIH awards could be coupled to regulatory approval from the FDA so that award dollars and time are spent on the investigation and not on regulatory requirements. This coupling could be accomplished via a joint NIH–FDA application process for DBS and other device-based investigations. A similar recommendation has been made in a recent Institute of Medicine report.[14] A joint application might also allow for the inclusion of functional endpoints in device-based clinical trials, such as the pain disability index, which better approximates clinically meaningful rehabilitation outcomes.

Additionally, the IRB or ethics committee might also be centralized or combined when possible. NIH awards undergoing review by the NIH Scientific Review Group could exempt or expedite local IRB review since award approval already requires a review of human subjects protections under NIH Peer Review regulations (42 CFR 52 h). Some IRBs also require preapproval from an internal review committee prior to full IRB consideration, which further adds to the approval process. NIH approval of a study protocol could function to replace this IRB preapproval requirement. Consolidation of oversight over human subjects research protections would likely increase efficiency and reduce conflicting regulatory requirements.[56] In fact, variability in the IRB approval process has been associated with increased cost in clinical investigations.[57]

Insurance access to experimental studies and follow-up care for biomedical devices pose an equally important challenge. Costs related to hospitalization, the device, and potential medical complications are normally all shouldered by the device manufacturer in industry-funded studies. Investigator-sponsored studies, however, lack these financial resources, and despite certain federal provisions for Medicare coverage of clinical trial participants, a significant share of participants with private insurance remain without a guarantee of coverage.[58] However, beginning January 1, 2014, a provision in the 2010 Affordable Care Act will mandate insurance coverage for clinical trials.[59] It remains to be seen, however, how this new provision will affect enrollment in clinical device trials, particularly when considering variations in implementation across states and the impact of private insurance exemptions.

Innovation and the clinical investigator. Innovative device-based clinical trials are associated with a steep learning curve and require attention to complex scientific and methodologic questions. This learning curve is even larger for higher-risk research in the clinical neurosciences. In our case study, the time and effort required by the principal investigator and his investigative team throughout the research process was exhausting. By the time the study was opened to enrollment, the team was already fatigued and, to some extent, demoralized by the serial delays, turns, and twists. Institutional support mechanisms for individual investigators have improved under the NIH roadmap and were utilized by the investigator in the case study.[60] One of the coauthors (J.B.) is the director of research operations for clinical research at the investigator's institution. The reforms of the NIH roadmap did not resolve the many unique challenges facing investigator-initiated device research discussed in this article.

Recently, many clinician–scientists have called for securing the future of clinical investigators and for promoting innovative medical care.[11–13] Yet regulatory obstacles, ethical concerns, economic realities, and career anxiety all threaten this goal. Without robust and thriving clinical investigator activity, academia-initiated clinical innovation is likely to suffer. The challenge is to make the tools of clinical investigation (i.e., medical devices) fully available and to improve funding, regulatory, and insurance coverage mechanisms for investigator-initiated device research.

DISCUSSION The rise of neuroprosthetic devices over recent decades illustrates the many successes and shortcomings present in the current biomedical research environment. DBS has emerged as a promising technology both for scientific exploration of neural pathways and for innovative therapeutics. The problematic structure of funding and regulation in device research threatens critical progress and may prevent future clinical investigators from sustained research careers. Careful reformulation of regulatory policy and funding mechanisms is needed to benefit science, industry, and patients.

AUTHOR CONTRIBUTIONS

Dr. Michael Kelly conceived and designed the work, analyzed the literature, wrote the paper, critically reviewed and revised the paper, and reviewed and approved the final manuscript. Dr. Donald Malone analyzed the literature, critically reviewed and revised the paper, and reviewed and approved the final manuscript. Dr. Michael Okun analyzed the literature, critically reviewed and revised the paper, and reviewed and approved the final manuscript. Joan Booth analyzed the literature, critically reviewed and revised the paper, and reviewed and approved the final manuscript. Dr. Andre Machado conceived and designed the work, analyzed the literature, critically reviewed and revised the paper, and reviewed and approved the final manuscript.

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