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

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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 scales²¹ 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 co-authors 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 syndrome²⁸ 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 others¹¹ 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, Fins⁹ 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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