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# Conflicts of Interest in Deep Brain Stimulation Research and the Ethics of Transparency

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## ABSTRACT

In this article we will draw on experiences from our own research on deep brain stimulation of the central thalamus in the minimally conscious state. We describe ethical challenges faced in clinical research involving medical devices and offer several cautionary notes about its funding and the interplay of market forces and scientific inquiry and suggest some reforms.

## INTRODUCTION

Deep brain stimulation (DBS) is an emerging field rich in discovery and innovation that is focused on developing therapies for neglected populations and exploring mechanisms of disease and injury. Clinical research in DBS presents a unique nexus of science and commerce in which market forces influence the contours of discovery, a small cadre of investigators is dependent upon an even smaller number of manufacturers for its tools of inquiry, and conflicts of interest complicate research.<sup>1</sup> Importantly, the field of DBS research is occurring within a historical context of legacies of past abuse from the psychosurgery era,<sup>2</sup> and what emerges is a confluence of forces that compel careful ethical reflection.

DBS has seen explosive growth in its application since its advent in the mid-1980s as an evolving treatment for Parkinson's disease and essential tremor (a progressive condition causing rhythmic trembling)<sup>3</sup> and more recently investigated as a therapy for obsessive-compulsive disorder,<sup>4</sup> depression,<sup>5</sup> and disorders of consciousness,<sup>6</sup> along with more established uses in the diagnosis and treatment of epilepsy and pain disorders.<sup>7</sup>

In this article we will draw upon our experiences from the broader vantage point of participants<sup>8</sup> and observers of this dynamic field.<sup>9</sup> Our own research focuses on studying DBS of the central thalamus in the minimally conscious state (MCS),<sup>10</sup> a disorder of consciousness that is functionally above the vegetative state in which patients are conscious — in contrast to the vegetative state.<sup>11</sup>

Our experience highlights the many ethical challenges faced in clinical research involving medical devices and offers several cautionary notes about its funding and the interplay of market forces and scientific

inquiry. We suggest some reforms of current practice that we believe are necessary to sustain this important area of medical research, both scientifically and normatively.

### **BEYOND BIOLOGICAL REDUCTIONISM: FINDING FUNDING**

Until recently DBS was on the margins of medicine and scientific investigation. A small number of investigators worked diligently to bring new treatments to patients with oft-neglected neuropsychiatric disorders — and they did so struggling to obtain funding.<sup>12</sup>

At a time in the history of medicine when reductionism reigned, and the gene was king, attempting to modulate the body's most complicated biological system was out of scientific step, if not out of fashion. To this discordance of interests add the technical and ethical complexity of placing electrodes into a living brain and government funding patterns that often saw the work as applied and clinical, and not basic or even translational science. It was too easy to view DBS as applied or therapeutic work. Although placing an electrode in a subject would constitute a clinical trial, these interventions also often clarified the basic mechanisms of disease, injury, and recovery at the level of systems and molecular biology. Many of these findings could not, in principle, be obtained from animal models, and thus they were basic science observations that were uniquely derived from DBS studies.

Although these devices became probative of new knowledge, mainstream funding sources did not see DBS as constituting basic or pioneering research. Much of this work was excluded from National Institutes of Health (NIH) funding through the R01 mechanism — a competitive project-based grant award made to a specific investigator or investigators — designed for basic studies of mechanisms of disease. A series of early applications by one of us (NDS) to the NIH in the late 1990s, to pursue the clinical and basic aspects of this work, did not receive funding for the respective reasons that the clinical effort "might be futile" and that the basic scientific questions were pitched at an intermediate level of observation that would not help elucidate the fundamental contribution of cells in the thalamus to cognitive functions. While current reforms aimed at encouraging and supporting "translational" research goals have greatly improved the likelihood of proposals at this intermediate level of inquiry, it is reasonable to assume that this work would remain unfunded by the NIH if current initiatives in translational research had not occurred.

Our team did receive a small planning grant from the National Institutes of Neurological Diseases and Stroke (NINDS) because of the efforts of a very forward-looking program officer. After two rounds of trying to obtain a grant to pay for the actual surgical costs, however, the program officer told us not to bother reapplying until we had preliminary data for two or three patients. We utilized this grant money to develop our team and advance the work, but its level of funding was insufficient for what would be required for a clinical trial, given the cost of devices, surgical implantation, and medical follow up, not to mention the added costs of clinical assessment, data storage and analysis, and the efforts of investigators. Moreover, the planning grant request for application (RFA) stipulated that no monies could go to surgical costs. We encountered a similar experience when attempting to raise private foundation funds. Although private foundations were interested in the work, the potential legal liability of underwriting the grant for these purposes was judged too high to support the actual clinical work. In the aggregate, these sustained efforts to obtain funding evolved over a more than six-year period before the initiation of actual human subject DBS research with electrodes.

We estimate that the cost of implanting our first subject and institutional care for the subject was in excess of \$300,000. Although there would be economies of scale and efforts to find more cost-effective methodologies to follow, the costs of this work required support of either a large, multi-year NIH grant or equivalent support from industry.

Without some support, from somewhere, any scientific work would atrophy, cease, and die. Investigators will lose the opportunity to pursue work in which they are already highly emotionally and intellectually invested, and, of course, if the work ultimately produces positive results, subjects would suffer for want of potential progress. At the time (circa 1998 to 2002), only the Medtronic corporation had human DBS tech-

nologies and investments in early stage clinical trials. Through the Cornell Research Foundation, one of us (NDS) attempted to establish support for a small pilot clinical study with Medtronic. The corporation had supported a large, multi-center trial of DBS in the posterior intralaminar nuclei for vegetative state patients in the 1980s and there was a disinclination to pursue an MCS study. The earlier study of vegetative state (which had included Terri Schiavo) had negative results.<sup>13</sup>

To meet the funding gap presented by the lack of NIH or industry support, Weill Cornell Medical College and the Cleveland Clinic jointly established a new company, IntElect Medical Inc., built, in part, around the intellectual properties related to Cornell patents (NDS is a listed inventor), outlining the rationale and methods for intralaminar stimulation of the thalamus to improve cognitive function in patients with neurological disease. This was not an easy decision, due to concerns regarding potential conflicts of interest and time commitments, as well as a vague sense of a potential taint of collaborative work with industry. Despite these misgivings, this step proved essential to sustaining the work.<sup>14</sup>

It should be noted that while there was no interest from Medtronic in supporting the study with the MCS patient population, there was interest (and an offer that did not include a sponsored research component) to simply secure the intellectual properties from Cornell to hold the "blocking rights," to limit other companies from pursuing these same technologies, *while not developing a plan or financial assistance to pursue the specific intellectual property further*. Cornell University and the inventors saw this as antithetical to goals of academic scholarship, open inquiry, and university patents, which aim to operationalize the translation of ideas into existing technologies in the current marketplace. In retrospect, we can now recognize how close we came, at that early juncture, to falling prey to market forces that may have forestalled the work.

## **THE BAYH-DOLE ACT AND THE TRANSFER OF INTELLECTUAL PROPERTY**

The shift toward industry funding has its roots in the landmark Bayh-Dole Act of 1980, which stipulated that the intellectual property (IP) rights of research conducted with federal funding reverts to funded institutions and investigators so that they might work with industry to expedite the movement of ideas from the bench to bedside.<sup>15</sup>

It was hoped that by giving academics who had been funded by federal monies the patent rights to their inventions, partnerships could take root with industry and this alignment of incentives would speed the development of drugs and devices from scientific discovery.

The passage of Bayh-Dole was prompted by the slow migration of good ideas from the academy to clinical practice and the need to align incentives between university and corporate cultures. By ceding IP rights to funded universities, Bayh-Dole allowed the academy to negotiate with industry and basically sell its rights in exchange for ongoing funding of seminal and early stage work that otherwise might not occur, or might occur after undue delay. This process became a well orchestrated dance: industry would gain the security of IP rights, which could be commercialized, and academia would garner needed support.

Support is especially critical to work in DBS because of the huge capital costs associated with product development and the clinical use of the technology. A journalist who commented on the first modern application of this technology in Parkinson's disease by the French neurosurgeon Alim-Louis Benabid observed that his observations alone needed to be aligned with industry: "someone needed to develop Benabid's bright idea into a product."<sup>16</sup> But with industry funding comes the potential for conflicts of interest and the concern that the data will bear the mark of the funding source and its interests.

We reached the decision to develop the research with industry support because we appreciated that, without technology transfer, the work would not occur at all. We believed at that juncture that conflicts of interest could be managed, but that a failure to get this work done could not be remediated.<sup>17</sup> Our view of the potential conflict of interest with industry — and potential royalties, should the device work and be marketed — was that it could be balanced through mechanisms of conflict management and be subservient to the broader ethical principle of promoting access to a new class of interventions that might help a population in dire need of assistance. If the only way such a project could be undertaken was through a partnership through

industry, we felt it was justified, so long as the partnership was made transparent and the investigative team had truly exhausted other means of funding and was reflective about its motivations.<sup>18</sup> Again, we believed that if the motive was the pursuit of a new treatment or new knowledge that could be patient-centered, then the arrangement was justifiable. If it was motivated by greed, then it was a deviation from what we viewed as professional norms.

We took special pains to be overt in our relationship with industry, writing about the relationship and making that process itself a laboratory for scholarly work. We made a number of suggestions to make this arrangement just and transparent. To promote fairness, we proposed that the investigators and the institutions that were poised to benefit economically from commercialization of the intellectual property should divert some of those profits to charitable uses. Such uses might access to novel treatments or enhanced educational access to develop the work force to provide care to the study population. Some of the "profits" might, for example, provide care for the patient population that might have contributed to clinical trials or help underwrite research scholarships for worthy trainees.<sup>19</sup>

We also argued that investigators who had ties with industry should do more than simply disclose their relationships; they should also seek to justify them when submitting papers for peer review. Editors would thereby have to make judgments about sources of funding, levels of disclosure, and, ultimately, whether they were ethically justifiable and permissible. We called this process "disclose and justify."<sup>20</sup> Specifically, the process was to move beyond disclosure, which is necessary, but not sufficient in and of itself, and go on to explain why corporate sponsorship was necessary for the work and how the collaboration promoted access or some other patient-centered good. It is important to note that this would have constituted a prospective justification for the corporate relationship, and not a post hoc rationalization.<sup>21</sup> This approach was suggested as a less-judgmental alternative to the approaches of Association of Academic Medical Centers (AAMC), "rebuttable presumption," which held that investigators with industry ties were to be ineligible to conduct sponsored research until proven otherwise.<sup>22</sup>

## REFLECTIONS

From the experience of our clinical trial and the observation of other studies, which have generated some degree of notoriety, we now feel that "right behaviors" by individual investigators or investigative teams, while necessary to the preservation of integrity in research, are not, in isolation, sufficient.

Once a trial is considered "successful," putative or potential conflicts of interest become real and tangible. What was once a theoretical conflict can become actual once a project is monetized and equated with potential market value. This monetization leads to ethical distortions that require a higher degree of ethical scrutiny and systematic safeguards.

Ethical norms that may have sufficed within the academy to protect subjects and research integrity may no longer be sufficient once projects become the object of investors' interest. Scientific reports on the status of a work might suddenly take on the added import of their effect on stock prices or on the "valuation" of less-developed companies. Such reports, beyond conveying scientific information, might be hyped to satisfy investors and market interests, and become a kind of currency. An example is the reporting of a successful Phase I study that was designed to assess safety that is spun to prematurely convey hopes of a new therapy, a conclusion that can only be drawn from later stage studies.<sup>23</sup> This drive to patent ideas and quickly advance their application to market can distract investigators from more formative work, that in the longer term may prove to be scientifically more innovative.<sup>24</sup>

All of these influences on investigators and clinical trials are amplified by the limited number of device manufacturers and their close relationships with a very small cohort of capable investigators, as well as the wider (but still small in number) field of potential providers. Industry has been the nexus for epidemiological studies of practice patterns and the determination of who shall be included in study registries, which are based, presumably, on the volume of the devices that are used by particular surgeons or institutions.<sup>25</sup> Although we have just anecdotal claims about these links in the context of DBS, the relationships between the

makers of medical devices and surgeons has been the object of both criminal<sup>26</sup> and legislative inquiry.<sup>27</sup>

Device makers ultimately control decisions about which researchers may receive access to the use of their equipment, through the granting or withholding of *right of reference* letter (ROR), a large compilation of basic safety and materials studies on the device kept in a file at the Food and Drug Administration (FDA) in the U.S. Without the grant of an ROR, no study can begin. Given this, the medical device industry can determine who gets to do the most promising, interesting, or potentially lucrative work. For international corporations such constraints may be nearly global, as only a number of European countries are exempting this corporate sign-off policy. Anecdotal reports suggest that investigators or institutions that are high-volume purchasers have been given preferential access to devices and to opportunities to do the most exciting sponsored research. RORs for existing safe devices can be withheld from competitors. Such actions, if actual, undermine the requisite need for free inquiry that is necessary for the conduct of scientific research, and are economic constraints on the pursuit of knowledge.

### WHAT CAN INVESTIGATORS AND INDUSTRY DO?

Investigators need to be mindful of these conflicts and take a "step-back" position in the work so as to not promote the perception of biased results. That is, once they have done preliminary "proof of principle" work, in which their insights as inventors or pioneers are most needed,<sup>28</sup> they can then either cede the investigative role to another, or reconfigure their relationship with the ongoing research to limit direct control. This helps to dilute potential conflicts of interest and allows other, non-conflicted, investigators to validate and refine their initial findings.

Investigators can attempt to avoid positions of dual agency. Too often in the setting of a start-up company, an investigator who developed intellectual property or who conducts a novel operation is given a board seat or is designated as the chief science officer. These roles present complications for the investigator, because it is ethically inconsistent to be both a corporately funded investigator and the overseer of that research, either as a board member or corporate officer. A study of institutional academic-industry relationships that examined potentially conflict-laden activities of departmental chairs in allopathic medical schools — an exclusive group that is comparable to neurosurgeons engaged in DBS research — found that such interactions revealed a high degree of involvement in corporate governance and oversight: 7 percent served as an officer, 9 percent served as a founder, 11 percent served as a board member, and 27 percent served as a member of a scientific advisory board.<sup>29</sup> Yet, despite this degree of involvement at the corporate level, prohibitions for such activities are rather scant. A survey by Bernard Lo and colleagues of policies on conflicts of interest at the 10 medical schools receiving the largest amounts of NIH funding found that although all 10 schools required disclosure of corporate stock ownership, income, or options, only seven schools required disclosure of a "decision-making position," and only one prohibited investigators from having such a role with the company sponsoring research.<sup>30</sup> Our proposal would make this exception in Lo's study the norm for this area of research, given its unique characteristics.

In the setting of conflict, each party needs to understand its particular role and allow proper, transparent oversight. This is easier said than done, due to the unique and nearly monopolistic dynamics of the neuromodulation industry and its power to influence institutions and individuals. This dynamic is different than conflicts of interest in drug development, other research in neuroscience, or even investigative work involving other devices, because in DBS there is essentially one dominant manufacturer that has near total control of the market. Investigators have a limited choice of electrodes to insert in clinical trials, because the market is closed and dominated by one manufacturer. As an illustration, in our DBS in MCS trial<sup>31</sup> — *not* sponsored by Medtronic — we had, in essence, a single choice available to us for implantation under a new investigational device exemption (IDE) from the FDA: the standard Medtronic electrode, used to treat Parkinson's disease.

Industry holds such influence because these devices are inserted by a highly specialized group within the community of neurosurgery, the small cadre of functional neurosurgeons. According to the American

Association of Functional Neurosurgery, there are currently 12 such fellowship programs in the U.S.<sup>32</sup> As noted previously, many of the surgeons have close ties to industry.

Although the dominance of the medical device industry makes a call for reform more difficult — since investigators and their sponsoring institutions *currently are not equal partners with this industry* — it is essential that the status quo be altered. The muddling of roles can obscure responsibilities and facilitate self-serving transgressions, which is bad for investigators, universities, industry, shareholders, and future patients who may be disserved by fraudulent work or deprived of good interventions that were produced under an unwarranted shadow of suspicion.

Industry and start-up companies can be more vigilant about such conflicts of interest and ensure clear role sequestration, separating the activities of the investigator from the responsibilities of corporate governance. By that, we mean that we find that the roles of a funded investigator and a voting corporate officer or board member are ethically — and perhaps legally — incompatible. While we believe that investigators can serve appropriately on scientific advisory boards that do not make business decisions, service as a voting corporate officer seems, to us, to be incompatible with the investigator role and potentially distorting and self-serving. Although this has been found to be the practice of a small number of medical schools,<sup>33</sup> we believe that it is a practice that should — at the very least — warrant serious scrutiny, and, when found, careful oversight of potential conflicts of interest.

Finally, start-up companies that are spun off from universities need to have their own independent corporate board and corporate counsel. This is necessary to fulfill their fiduciary obligations if and when there is a conflict with the originating institution that seeded the start-up company and their interests diverge.

## SYSTEMIC REFORM

Although one might hope that this mix of medicine and the market might be remediated one trial at a time, through individual actions of investigators and their corporate sponsors, we have come to believe that there is a need for broader systemic reform. And here there are two varying choices.

One possibility is to take industry completely out of the mix. In our view, this would be a naïve, Fabian approach. To replace industry's intellectual and fiscal contributions to scientific research in general, and DBS work in particular, would be prohibitively expensive, if not impossible. There are no alternatives for companies that make the devices used for neuromodulation and that are developed to the sufficient degree of precision that they could be used under an FDA IDE.

A better choice should be to manage the relationship between the academy and industry a bit differently. We believe that many of the conflicts of interest that we have seen and can envision are the products of the premature entry of the market into the scientific process through the Bayh-Dole mechanism of intellectual property transfer, and that this process warrants reform.<sup>34</sup>

We are not the first to suggest that Bayh-Dole be revised,<sup>35</sup> but our suggestion is novel and specific to DBS for the aforementioned unique characteristics of this field, most notably the relationship between investigators and industry. The original formulation for reform was presented by one of us (JJF) as the plenary ethics address at the 38th Annual Neural Interface Conference sponsored by the NINDS and the NIH in June 2008, and further explained in print,<sup>36</sup> and is further elaborated upon here.

Simply put, to keep market forces out of the mix until they are needed in the development of DBS methods and technology, it was suggested that intellectual property transfer should not occur until Phase II of development. Early toxicity trials of new ideas would be conducted without exchange of IP by any and all qualified investigators.<sup>37</sup> For each study approved by an institutional review board (IRB), investigators would have open access to currently available electrodes and stimulators without constraint.<sup>38</sup>

These devices would be supplied by industry to a federally organized clearinghouse that would provide immunization from potential liability.<sup>39</sup> We envision constructing legal immunity in a manner that would be comparable to that employed in the federal government's efforts to encourage the manufacture of childhood vaccines under the National Childhood Vaccine Injury Compensation of 1986.<sup>40</sup> This act utilizes a special,

no-fault court, the U.S. Court of Federal Claims, and special masters, to adjudicate claims and provide compensation that is reasonable and capped for unexpected injuries occurring when vaccines performed as intended. Every dose of vaccine is taxed to create funding for settlements.<sup>41</sup> A similar mechanism was employed in the SAFETY Act of 2002 to grant immunity to manufacturers that made vaccines and drugs to be employed against bioterrorism<sup>42</sup> and the H1NI influenza, utilizing the National Vaccine Injury Compensation Program.<sup>43</sup> The SAFETY Act of 2002 is more nuanced, providing degrees of liability coverage depending upon the demonstrated effectiveness of the technology.

If immunization against liability is made available to manufacturers, it would decrease the cost of entry into the field by start-up firms and provide a richer array of devices for implantation, which would provide scientific benefit, and be useful in easing monopolistic market stress. Investigators who participate in the process would be able to work without the distraction of commercializing their ideas, and then be able to turn over their product or hypothesis to other investigators who would seek to validate it in later stages of investigation. Companies supplying the devices, in turn, would have the benefit of choosing interventions that were most promising, thus avoiding an investment in a method or device early in Phase I, before it was validated. More critically, a clearinghouse would create a marketplace of ideas, in which all participants would have open access to each other's work as a condition of participation. While each investigator would retain the scholarly rights of his or her discovery and potential intellectual property rights, all participants — investigator or industrial partner — would have access to the work products posted at the conclusion of the early Phase I period. This information exchange, prior to the cloak of a proprietary period, would catalyze discovery and be beneficial to the community of investigators and investors constituting the marketplace of ideas — and yes, of commerce.

Finally, a federal clearinghouse would help ensure standardized ethical norms for all those who participated, avoiding idiosyncratic review by scattered IRBs. This has been the case both in the U.S. and abroad, where local boards, without the requisite expertise, have been called upon to make determinations about the ethical propriety and scientific legitimacy of a work, a point just made by the editors of *Nature Neuroscience*.<sup>44</sup> This can also be an added rationale for similar efforts in other countries, such as Canada, where payment for devices can occur as part of clinical care. A centralized clearinghouse would help avoid the therapeutic misconception that investigational devices and interventions are misunderstood to be therapy because of how they are reimbursed.

In addition to creating ethical and scientific norms for study enrollment, a clearinghouse could also lay the foundation for a prospective registry of all of the studies that originated there. The import of such a registry can not be overstated,<sup>45</sup> and was one of the recommendations made by the 1977 report on psychosurgery authored by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.<sup>46</sup> Registries of this sort would help the conduct of empirical studies on both the scientific outcomes and ethical processes related to research in the area, work that is currently very difficult to do because of the hegemony too often exerted by industry.

## CONCLUSION

Both industry and the academy would benefit from the restoration of public trust and the re-establishment of a scientific commons that would promote effective science for the relief of neuropsychiatric disorders. We continue to collaborate with industrial partners to pursue our research in DBS, but recognize the need for constant vigilance because the ethical challenges change as the work evolves. We hope this window on our experience in the conduct of DBS research illustrates an inductive process of moral reasoning in which a specific example, told in detail, can point to more general principles for the regulation of this line inquiry, and perhaps other fields of endeavour.

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## DISCLOSURES

IntElect Medical provided partial support for the clinical study described and considered here. N.D. Schiff is an inventor, through Cornell University, of the technology in that study, and is a paid consultant and advisor to IntElect, to which the technology has been licensed by Cornell, and in which Cornell has an equity interest. J.J. Fins is an unfunded co-investigator.

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