Published in final edited form as:

Ann N Y Acad Sci. 2012 August ; 1265: 80–90. doi:10.1111/j.1749-6632.2012.06598.x.

Challenges to Deep Brain Stimulation: A Pragmatic Response to Ethical, Fiscal and Regulatory Concerns

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Part I

i. Pragmatics

In 1938, the American pragmatist philosopher, John Dewey, wrote in an essay, “Common Sense and Scientific Inquiry” of the adaptive response of humankind to scientific developments. He wrote that, “Inventions of new agencies and instruments create new ends; they create new consequences which stir men to form new purposes.” [1] It is an observation that has direct relevance to the evolution and maturation of deep brain stimulation (DBS) as the field imagines new applications but worries about fiscal and regulatory barriers that threaten this promising advance.

In the spirit of Dewey’s Pragmatism, and in response to the early success of deep brain stimulation, we offer some “common sense” strategies to sustain the work, addressing the need to do so in a fiscally workable, ethically transparent and scientifically informed manner. After delineating major threats to this burgeoning field, we will suggest “new agencies,” in both the legislative and regulatory spheres that might remediate these challenges.

We will recommend revisions to 1) the Bayh-Dole Act of 1980 that governs intellectual property exchange resulting from federally funded research [2] and 2) the AAMC recommendations concerning the management of conflicts of interest when scientists with an intellectual property interest participate in clinical research [3] in tandem with 3) modifications to the Food and Drug Administration’s (FDA’s) Pre-market Approval (PMA) Process for new devices. [4,5] The later regulatory recommendations will build upon the Institute of Medicine’s (IOM’s) recent analysis of the FDA’s 510(k) approval process for Class II devices. In that report experts critiqued the 510(k) pathway to market as too reliant

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Disclosures:

An earlier version of this paper was presented by Dr. Fins at the XIX Dynamical Neuroscience Satellite Symposium: Deep Brain Stimulation in Mental Illness, Neurological Disorders and Cognitive Impairment in Washington, D.C. on November 11, 2011.

upon predicate device approval. [6] We will generalize the IOM's recommendations to DBS devices which are Class III devices, building upon an earlier argument made by one of us (JJF) and colleagues about the limitations of analogic reasoning when it came to device approval by looking to predicates.[5]

Throughout this analysis, we will be guided by an ethical framework that views this work as science in the service of humanity. The goal is discovery and the elucidation of basic structure and function so that human suffering from neuropsychiatric disease, infirmities of psychiatric and/or neurological origin or etiology, can be ameliorated and treated. A related, but intertwined goal, is that of distributive justice. Given the historic marginalization of individuals with neuropsychiatric disorders,[7] the fruits of discovery should be accessible to those in need in a fair and just manner. [8,9,10]

ii. Problematics

Dewey's method of inquiry begins with the recognition of the *problematic situation*, those issues and questions that need to be made explicit in order to be subject to deeper analysis and critical reflection.[11] In the realm of DBS policy, the problematic situation is deeply rooted in the relationship between industry, investigators and the academy. [4] DBS devices, used for both investigative and clinical work, are instruments that cannot be produced casually. Manufacture requires stringent regulatory oversight and necessitates high capitalization costs. This makes investigators wholly dependent upon industry for their tools of the trade [11] and necessitates collaboration with industry.

This relationship is further complicated by a paucity of device manufacturers and near monopolistic practices which create a power imbalance which can threaten access to devices. [4, 12] More nefariously, industry can favor high volume users of devices by denying other investigators "rights of reference," technical information about their devices which is necessary to obtain FDA approval for an investigational device exemption (IDE). [12]

This dynamic between the academy and industry is further enmeshed by the provisions of the Bayh-Dole Act of 1980. [2] Under Bayh-Dole, federally funded research that results in intellectual property is ceded to the investigator's institution which could then negotiate with a commercial interest to bring the innovation to market and more expeditiously into clinical practice. All of this is for the good, save for the fact that with this exchange of intellectual property the ideas of investigators become commodified early in the course of discovery. [2,12] What had once been a scientific hypothesis is now something with market value.

While this commodification of an idea can enable the work to proceed, the monetarization of a hypothesis can generate a conflict of interest. The exchange can place the investigator into a conflicted situation in which he or she becomes ineligible to do early scientific work when his/her expertise is most essential to experimental success. The American Association of Academic Medical Center (AAMC), for example has offered up the notion of a "rebuttable presumption" with respect to conflicts of interest. Under this framework, investigators who have a significant conflict-of-interest are presumed *not to* be allowed to do clinical studies

unless the presumption against them has been reversed or rebutted by an institutional conflicts of interest committee. [3]

An investigator found to have a disqualifying conflict of interest could theoretically be precluded from doing clinical trials. This is particularly unfortunate -- and shortsighted -- because disqualifying an inventor because of a putative conflict of interest deprives a study or a trial of the individual best positioned to achieve early phase success. This is particularly true in the realm of DBS where the success of a device requires both the skills of the inventor and an interdisciplinary team. [13,14]

Beyond maximizing the likelihood of success of costly clinical trials, the exclusion of the neuroscientists, engineers and clinicians who have brought a device, method or target forward as intellectual property deprives those best situated to make salient scientific observations that might inform the next important hypothesis. Even in a clinical trial designed to assess efficacy of a device, the possibility of new discovery exists.

At this early juncture, it is probably safe to say that every trial, properly configured, is also an opportunity to learn something about basic mechanisms that could have resonance for iterative diagnostic or therapeutic work. Even in the rather settled realm of Parkinson's disease the debate over mechanism of action persists, [15] so the notion of a solely clinical trial is a fiction. Each venture of an electrode into a human brain, a barrier that the *Lancet* once described as the breach of a "penumbra of sacrilege," [16] should be seen as an opportunity as much as an obligation to learn something new.

NIMH director, Thomas Insel, emphasized the importance of physiologic and mechanistic understanding of brain disease and pathology when he opined on the need to supplement theoretical schema with *biological* data. He observed that, "“Despite the importance of wiring diagrams, [they] like the original genome maps, are necessary but not sufficient for understanding how the brain works.”[17] What is needed, in our view, is experimental data from complex biological systems, like the neural circuitry of depression or disorders of consciousness, that can optimally be elucidated through the diagnostic, therapeutic and investigative applications of DBS.

But this plurality of investigative potential -- or as one of us has written (JJF) -- this mosaicism of the device as both probative in basic and/or therapeutic in clinical practice, [18] is hindered by the regulatory practices of the FDA which are structured to view these devices for their clinical application, often at the exclusion of its investigative role. This practice, rooted in the FDA's historic mission to protect the public health, [19] has had the unintended consequence of making discovery research with the devices challenging, if not nearly impossible, especially when the objective is the discernment of biological mechanism, as much as the discovery of a new clinical diagnostic or therapeutic approach.

iii. Beyond Humanitarian Exemptions

The significance of these concordant challenges became readily apparent with the FDA's approval of an Humanitarian Device Exemption (HDE) for the "treatment" of the Obsessive Compulsive Disorder (OCD). [5] HDE's are granted for "orphan" diseases which affect less

than 4,000 cases per year which might not otherwise be the beneficiaries of novel interventions without the waiver of approval fees for the usual premarket approval application. [20, 21] These fees are waived in exchanged for steep discounts on the cost of the device and the on-going audit of revenues to demonstrate that they do not exceed the costs of research, development, fabrication and dissemination of the device.[22]

In early 2011, one of us (JJF and colleagues) argued in *Health Affairs* that the HDE for OCD was misplaced. [5] Although we countered the demographic eligibility of OCD based on disease prevalence, our main argument was scientific. We argued that the use of an established device for a new indication in a *new* target necessitated the use of the more rigorous IDE PMA process. IDEs require both efficacy and safety data before they are approved for market. The less rigorous HDE process need not demonstrate efficacy which generally requires a properly powered clinical trial.

The argument asserting the misapplication of the HDE to the use of DBS in OCD centered on the fact that while the device utilized for the intervention was one equivalent to that approved for Parkinson's Disease in rigorous clinical trials, the device was not known to be safe when applied to a new target. This argument by analogic reasoning was flawed because it was safety by virtue of the properties of the physical device and not the biology of the anatomic site. [5, 18]

And even there, the use of predicate device approval to assert its safety based on sequential predicate applications has not been without its own flaws as evidenced in *Medtronic, Inc. v. Lohr*. [23] In that landmark US Supreme Court case, the company defended itself against claims related to a defective cardiac stent by appeal to federal preemption of state law by virtue of the device's FDA 510(k) clearance. The Supreme Court rejected the defense noting that preemption was not a defense against negligence. Justice John Paul Stevens writing for the Court held:

The Lohrs' negligent design claims are not pre-empted. The FDA's "substantially equivalent" determination as well as its continuing authority to exclude a device from the market do not amount to a specific, federally enforceable design requirement that cannot be affected by state-law pressures such as those imposed here. Since the § 510(k) process is focused on equivalence, not safety, substantial equivalence determinations provide little protection to the public. Neither the statutory scheme nor legislative history suggests that the § 510(k) process was intended to do anything other than maintain the status quo, which included the possibility that a device's manufacturer would have to defend itself against state-law negligent design claims. [23]

Moreover, the FDA HDE approval [24] -- and marketing by the manufacturer [25] -- as a "treatment" [26] when only part of a safety profile had been satisfied and efficacy had not yet been demonstrated seemed a misnomer. Both safety and efficacy are necessary prerequisites for establishing a threshold for a vetted treatment. [27, 28] This representation was particularly problematic for potential recipients of the device as it led to a "therapeutic misconception," [29] the mistaken belief that an intervention that remained investigational

was an established therapy, potentially distorting how patients would view the risk-benefit ratio when providing their informed consent. [30]

The confusion about the status of whether an HDE status represented on-going research or clinical care was not limited to the patient. FDA regulations themselves embody the contradiction of work that seems to lie squarely between the investigative and therapeutic. Although Institutional Review Board oversight of an HDE is required under FDA policies, the IRB need not oversee the informed consent process because the FDA considers interventions carried out under an HDE, as a spokesperson put it as "...part of the practice of medicine." [31,32]

But, as he often did on the Court, [33] Justice Stevens got to the crux of the matter. He identified the problem of approval by the 510(k) process or the HDE mechanism which also relies upon predicate approvals. As he astutely put it, "Neither the statutory scheme nor legislative history suggests that the § 510(k) process was intended to do anything other than maintain the status quo ..."[23] If that is the case, the proper question to ask is why are such approval processes part and parcel of a regulatory schema designed to break out of the status quo and promote innovation?

Reliance on such mechanisms misses opportunities for discovery because the HDE process cannot generate aggregate data or collect adverse events in a systematic and controlled way. So why was it utilized to sustain clinical trials in an area so poorly understood as the mechanisms underlying OCD? Part of it was fiscal.

Daniel Bernard, in a review of the humanitarian device exemption process, describes how Medtronic uses a predicate device like the Activa, used in Parkinsons disease to promote a "horizontal model" of device development. [34] He notes that, "...an undisclosed source at Medtronic claimed that it would have been too costly and time-consuming to obtain a premarket approval for their Humanitarian Device Exemption-approved Activa Deep Brain Stimulation devices....Medtronic saved 3 years, recovered \$10 million from the initial research and development costs, and established a good relationship with many physicians within the field." [34]

Not only are there negative monetary and chronological impacts in pursuing a PMA, the current Class III approval paradigm imposes significant fiscal and time penalties for subsequent device revisions as compared with devices cleared through the 510(k) process or approved by the HDE-exemption. As noted earlier, experience with the current version of a device provides the information used to design subsequent devices versions. Hence, the 510(k) and HDE pathways provide an easier mechanism for subsequent device improvements than does the PMA pathway. This severe discontinuity between the 510(k)/HDE pathways and the PMA pathway related to initial commercialization and subsequent device improvements create an aberrancy with profound clinical and scientific impacts.

As important as economic realities are, they come with an even higher cost -- the failure to appreciate that the development of therapeutic devices also represent the production of critical tools of discovery. Again we appreciate the mosaicism of these devices which

straddle the therapeutic and basic science divide. [18] They are both potentially therapeutic and probative instruments of discovery either by virtue of their novel design and/or their anatomic placement.

In an ideal world, clinical trials with these devices should garner more basic science funding because they advance our understanding of neural circuitry and/or utilize new engineering methods (micro-arrays) or materials (eg. nanotechnology) in pursuit of an innovative device. To rush them (or their applications) to market because there is a lack of basic science funding is misconstrue them only as putative therapies and then fall into the trap of regulating and financing them as such. This limits their investigational promise and truncates discovery before it is completed or has even commenced.

To go down this path is to have the fate of an HDE-approved device which has neither demonstrated clinical efficacy, in a market place which will demand this for funding, nor been in a position to generate hypothesis driven data. It is the worst of both worlds, neither sufficiently rigorous for the test of commerce or science. It is nothing more than a refuge to sustain work when resources are scarce and either the logistics or finances of an IDE based premarket approval are viewed as an even greater hurdle.

v. The Institute of Medicine Critique of the 510(k) Process

The aforementioned critique of the HDE process [5] gained additional credence when the Institute of Medicine released its July 29th 2011 report critiquing the 510(k) approval process with its emphasis on looking to predicate devices for substantial equivalence. [6] Although the 510(k) process was intended for Class II devices under the 510(k) section of the 1976 Medical Device Amendments, [35] as we have seen, the logic of analogic/predicate approval has been applied to Class III devices under the guise of the HDE.

The IOM recommended the abolition of the 510(k) process for Class II devices noting device failures from prior equivalence approvals. [6] The report found that the process can neither assure safety nor efficacy, as Curfman and Redberg demonstrate in a *New England Journal of Medicine* editorial in which they welcome the Report as “insightful, judicious and long overdue” and recount how the 510(k) process has failed to ensure the public health. [36]

The IOM did not outline an alternative to the 510(k) process but did delineate criteria for a substitute. [6] Their recommendation calls for an integrated and longitudinal process to monitor the safety and efficacy of devices over their entire life span. This would include post-market surveillance. Assessments would be risk-based, predictable, and based upon sound science with the process itself evaluated for its impact on medical innovation. While the IOM report did not address the PMA process, it is notable that there have also been high visibility failures of devices approved through that process. [36] It is logical to assume that the criteria suggested in the IOM report for the process that should replace the 510(k)-clearance pathway for Class II devices would have at least equivalent, if not more stringent, applicability to Class III devices approved through the PMA process.

If adopted, the IOM recommendations would be staggering. They would necessitate a revamping of a regulatory schema that has been in place for decades [the 510(k) process] and have collateral impact on the HDE process. If device approval by equivalence criteria was no longer suitable for a Class II device, then it should no longer be acceptable for a Class III device -- like a deep brain stimulator -- under an HDE.

Part II

As we reflect upon the aforementioned problematic situations, we see that the field is ripe for creative inquiry to meet these challenges. Although there is no guarantee that 510(k) recommendations from the IOM will be adopted, given industry opposition and the objections of Jeff Shruen, director of FDA's Center for Devices and Radiological Health, [37] the fact that such a sweeping recommendation could be advanced is testament to a system that needs reform and revision.

As described above, the effective industry monopoly of DBS devices requires academic investigators to prematurely define and assign intellectual property to neurotechnology companies to be able to pursue studies. An additional issue is the significant cost borne by academic investigators to pursue an investigational device exemption for DBS probative studies. While the investigators are likely driven by scientific and clinical interests, these motivations are not necessarily shared by industry sponsors.

Given these forces, industrial sponsors may well be influenced by the perceived likelihood of the proposed study leading to new and significant markets for the technology. This dynamic may skew allocation of support and resources for clinician-investigators in spite of the quality of the proposed science. In addition, prior studies have shown that financial support from industry sponsors to investigators is detrimental to research credibility, which is important to the impact of the research [38] and ultimately return on investment. Therefore, by providing direct industrial support, the sponsor is decreasing the perceived value of the work itself.

i. Reform of Bayh Dole and Intellectual Property Exchange

To address these concerns and mitigate the negative influence of industry on the scientific development of the field, we will first suggest a reform of the Bayh-Dole Act as it relates to neuromodulation and the development and use of deep brain stimulators. As advanced previously by one of us (JJF), [4] in order to temper the premature entry of the market into the scientific process, a revised Bayh-Dole would delay the transfer of any intellectual property until phase II after a device or approach has demonstrated early efficacy in a phase I trial. This would occur through the establishment of a clearinghouse which would provide access to manufacturer supplied devices to qualified investigators pursuing IRB-approved research. Manufacturers that supplied devices would have access to the discoveries that emerged after this preliminary stage at which point an idea could be commodified and IP transferred from an institution to a corporate sponsor.

This change would mitigate conflicts of interest because commodification comes later in the process. And because industry would back a group of neuromodulation investigators rather

than individuals, all qualified scientists and investigators could compete together to produce the best results non-competitively with respect to industrial support. Because industry interests would be aligned with the greater group, and not individual investigators, corporate forces would champion the many and make rights of reference freely available to all who participated in the clearinghouse function.

Investigators would have access to devices for therapeutic and translational work and the best device available for a particular purpose. Participating manufacturers would have the advantage of choosing ideas that were most viable coming out of phase I, thus avoiding errant investments in projects that were destined to fail in early trials. These cost-savings to industry would be off-set by their donation of devices and the payment of user-fees to the clearinghouse organization (see below ii for details) through which IP is first secured for commercialization. A small percentage of royalties paid to academic institutions and inventors would also be diverted to the clearinghouse so as to underwrite this important work.

Companies that chose not to participate in support of these early phase trials would not have access to the fruits of discovery that emerged on the other end or, if they chose to later participate and bid on a device or an application, would have to pay a penalty fee.

Industry could reasonably object to liability concerns with the use of their devices in experimental work. This could be addressed by the provision of global liability insurance from the federal government to immunize device makers. The mechanism would be analogous to efforts to protect vaccine makers wary of vaccine liability. These fears were allayed by legislation such as the National Childhood Vaccine Injury Compensation of 1986, [39] the SAFETY Act of 2002 related to drugs and vaccines to counter bioterrorism, [40] and the National Vaccine Injury Compensation Program [41] for vaccines against H1NI influenza.

ii. Establishment of a Public-Private Partnership

The goal of this section of the paper is to outline and explore where, within the governmental or non-governmental organizational structure, to place the clearinghouse function for a public-private partnership (PPP) that would link industry, the academy and government.

The stakeholders for neuroscience endeavors include the academic investigators, federal agencies sponsoring related research such as the National Institutes of Health (NIH) and the National Science Foundation (NSF), the neurotechnology industry, and the principal regulatory body for medical devices, the Food and Drug Administration (FDA). These federal organizations have missions and prior investments that align with DBS discovery science, yet each face limitations that a PPP may aid in surmounting.

The NIH, which has the mission to conduct and support research that generates knowledge to reduce the burden of disease and injury, is partitioned into a confederacy of multiple institutes and centers with responsibility for organs, disciplines, and/or diseases. It is important to recognize that DBS discovery science does not neatly fit within the mission of a

single institute at the NIH. The main institutes within the NIH that have responsibility for neurological and mental health disorders are the National Institute for Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH). NINDS takes assignment of basic, translational, and clinical research aimed at neurological disorders and stroke, i.e. brain dysfunction, whereas NIMH supports research pertaining to mental health disorders, i.e. mind dysfunction. Consistent with the NIH-wide growth in clinical translational research and development, [42] the NINDS has been a leader in the development and implementation of a multi-pronged, cooperative agreement based translational research program primarily centered on pharmacological and biological therapeutics. [43]

More recently, NINDS in partnership with other institutes has implemented a similar program for neurotechnology development, acquisition of an IDE, and pilot clinical trials. [44] In addition, the National Institute for Biomedical Imaging and Bioengineering (NIBIB) aims to develop and accelerate the application of biomedical technologies, including those that are oriented towards the nervous system. The NIBIB is primary sponsor of the Human Connectome project which seeks to understand the functioning of brain networks by defining the structural connectivity of elements within the human brain. [45] The mission of the NSF, a long-term supporter of engineering and computational science programs, includes the promotion of progress in science and the advancement of the health, prosperity, and welfare of the nation. In partnership with the aforementioned NIH institutes, the NSF has sponsored the Collaborative Research in Computational Neuroscience program which aims to advance the understanding of nervous system structure and function, mechanisms underlying nervous system disorders, and computational neuroscience data sharing. [46] The FDA, which includes the Center for Radiological Health and Devices, has the mission of advancing the public health by helping to speed innovations that make treatments more effective and safer. In summary, the potential yield of DBS discovery science which offers insights in the circuitry and functional connectivity of the brain is entirely consistent with the missions and prior investments of a range of federal research sponsors.

With the increasing funding pressure faced by federal agencies charged with supporting research, there is substantial hesitancy in providing funding mechanisms that support research where the product is a new clinical indication for an approved medical device. Neurotechnology, in particular that which focuses on devices for therapeutic neurostimulation, had revenues exceeding \$7B in 2010. [47] Federal agencies, where priority for projects is driven by scientific peer-review dominated by academic scientists, maintain research and development portfolios that primarily emphasize knowledge generation. To fully engage potential federal agency sponsors, the product of DBS discovery science must lead to a more comprehensive --or probative-- understanding of the functional circuitry of the brain. In this context, the expertise of the investigators should extend beyond the clinician investigator to include disciplines such as computational neuroscience, imaging, and data visualization. In many instances, these partnerships have already self-assembled as a necessity for conducting hypothesis-driven DBS probative inquiry.

A PPP may provide added incentive for agency participation in the current challenging national fiscal climate. These agencies may be more likely to consider participating in a PPP

where potential cost-sharing could be realized by partnering with a neurotechnology industry. There may also be value for participation by the FDA. The FDA has established the Critical Path Initiative which aims to develop technology and harness information technology to evaluate and predict the safety, effectiveness, and manufacturability of medical products. Clearly, a more comprehensive understanding of functional circuitry of the brain may aid in predicting effectiveness, and perhaps safety, of neurostimulation paradigms.

An agency that is well-positioned to convene a PPP is the Foundation for the NIH (FNIH). The FNIH was established by Congress in 1990 as a 501(c)(3) public charity. Since it is a non-governmental entity, the FNIH is not bound by the policies and regulations to which the NIH as an agency of the U.S. government must adhere. As an independent non-profit organization, the FNIH can raise private funds and create public-private partnerships to support the mission of the NIH. [48] The FNIH has successfully implemented precompetitive consortia that partner multiple federal agencies, academia, the private sector, and non-governmental organizations for a range of topics including but not limited to osteoarthritis, neuroimaging for Alzheimer's Disease, and biomarkers for chronic disease. The PPP would provide a means of reducing the conflict of interest faced by academic investigators while enabling access to devices contributed by the private sector. The PPP would not have the explicit goal of generating intellectual property although mechanisms can be established within it to protect intellectual property generated by projects through confidentiality agreements. The scientific review, handled by the FNIH, would carry the imprimatur of the federal agencies known to support meritorious work, thus enhancing research credibility of the academic investigators and the value of the research itself.

iii. Caveats

Although we are advancing reform of the Bayh-Dole Act and the establishment of a PPP to house it within the auspices of the Foundation of the NIH Foundation (FNIH), we appreciate the implementation challenge as we seek to *delay* the exchange of IP in the context of device development and the science of neuromodulation. While we think that this is good for this sector of science, our approach goes against a trend championed by the Obama Administration. In September 2011, the President signed into law the America Invents Act (AIA) which also replaces the traditional first to invent standard to the first who files for a patent. [49] To further complicate the matter, the White House recently announced plans to accelerate technology transfer and commercialization of federal research for growth industries. [50]

Taken together, the AIA and White House plans to accelerate tech transfer would likely speed the pursuit of a patent and favor those entities with the means to do so. This could further privilege large corporations which dominate the DBS market and heighten the monopolistic tensions and conflicts of interest described above. Given these trends outside neuromodulation, it might be best to view our proposals as pilots designed for research and development with this discrete field and not, as yet, a more generalizeable recommendation, although they might evolve to have broader applications for IP and innovation.

iii. Regulatory Reform: The Mini-IDE

While a PPP designed to address IP exchange and innovation would help to restore the scientific commons against market place dynamics, [2, 52] this intervention would only partially remediate the barriers to sound sciences outlined above. Regulatory reform is also necessary to address the challenges of mounting high cost, small volume clinical trials outside of the HDE or 510(k) process, with all their aforementioned liabilities.

To address this lacunae in the regulatory space, we propose that the FDA, working in tandem with partners at the proposed FNIH-PPP, consider the establishment of the mini-IDE. The mini-IDE would allow for hypothesis driven and randomized studies to take place over a longer period of time and over a number of sites in order to amortize costs for the overall study and for any individual site. It would be sustained, in part, by clinical revenue from device implantation and by corporate user-fees.

The mini-IDE might begin with the clearance by predicate standards of the 510(k) or HDE process when appropriate but would not end there. For those devices that do not have a clear predicate, the *de novo* 510(k) process could be invoked but in an optimized manner as suggested by the IOM report. Devices would first demonstrate safety by an analogic process but then be subject to protocol standards akin to the usual IDE process. New applications of predicate devices would be limited to standardized hypothesis driven protocols.

The mini-IDE would accrue patients through geographically dispersed institutions which were willing to abide by pre-determined standards and managed centrally at the FNIH-PPP. Devices under provisional licensure would only be available for use within either an IDE or a mini-IDE and only reimbursed by the Center for Medicare and Medicaid Studies (CMS) if within these structures. CMS would no longer approve reimbursement for HDE except under extraordinary circumstances, thus incentivizing the mini-IDE as a sounder alternative. However, CMS (and private payors as well) should extend reimbursement and payment to facilities and providers during the course of clinical trials under the mini-IDE (or *de novo* 510(k)) clinical trial, just as CMS currently supports the conduct of IND drug trials.

Centralized data storage and a study registry [53] could be supported by FNIH-PPP/This would allow for the collection of aggregate outcomes and adverse events data for scientific analysis as well monitoring by a data safety monitoring board (DSMB).

In a critically important contrast to a device approved by a 510(k) or HDE process, those covered by a mini-IDE would have a *contingent FDA licensure* which would be based upon reaching designated milestones. Before the granting of a contingent license a device would need to demonstrate safety. *De novo* devices first would do so in animal studies; followed by later human studies. Applications for established devices would demonstrate safety by predicate approvals as through the 510(k) or HDE process. Continued approval would be based on the accrual of data that demonstrates proof of principle and on-going safety in human clinical trials. These trials would be financed by clinical revenues for device implantation, as is currently the case in HDE and IDE trials, FNIH-PPP user fees and DBS IP royalties as well as grant funding from the usual foundations and extra-mural and intra-mural NIH sources.

Once enough data has been collected, to approximate the demonstration of both safety and efficacy commensurate with a PMA via an IDE, the device would garner approval status equal to that of a device which traversed the more traditional PMA pathway. This approval would be supplemented by on-going life-time post-market surveillance of the device once it reached phase IV. In addition, the supplemental PMA process should be managed in a similar manner with initial conditional approval with provision of required data supporting safety and effectiveness a prerequisite for ongoing approval.

iv. In Praise of Contingent Licensure

The virtues of contingent and incremental licensure should be obvious to any interested observer, but if it is not, then the experience of the Wingspan vascular stent should make them obvious. The Wingspan device is a vascular stent designed to prevent stroke. As reported recently in the *New England Journal of Medicine*, [54] it was approved six years ago via an HDE, which according to a *New York Times* report “did not require solid evidence that it would prevent stroke.” [55] A subsequent randomized clinical trial however, utilizing an IDE, demonstrated however that medical management was safer and superior to an interventional one. It should be noted that the device is appropriately still available through the HDE pathway for patients who have failed medical management or in whom medical management is contraindicated. Thus, this is an example of how post-market surveillance could be used to modify the conditional approval on the basis of data collected in a rigorous manner; something that is impossible under the current HDE paradigm and not mandated for any 510(k)-cleared and most PMA-approved devices.

Because of the deficiencies of the regulatory system, this information only became available six years after the device was approved. Instead of learning of the liabilities of the original HDE approval through on-going data collection, as in the proposed mini-IDE process, the device was in clinical use under the HDE until IDE data determined that it should no longer be used. How this late-in-the-game IDE occurred points to mechanisms embedded within the proposed mini-IDE that will be central to its success: the alignment of good science with fiscal incentives. As in the proposed mini-IDE, CMS only reimbursed device use when it was inserted as a part of a designated clinical trial:

Finally, CMS played an important role in expediting the conduct of the SAMMPRIS trial. The FDA approved the Wingspan stent for clinical use under a humanitarian device exemption in 2005 and approved the use of the device for the SAMMPRIS trial under an investigational device exemption. However, CMS did not reimburse for the Wingspan device outside of its use in a randomized trial. Recruitment within the trial proceeded quite well. Similarly, CMS, despite lobbying by physicians and industry, reimbursed for carotid stenting in asymptomatic patients only if the stenting was performed within the context of a trial. This action facilitated recruitment into CREST. In contrast, endovascular devices for the treatment of acute stroke have been cleared by the FDA through the 510(k) pathway and reimbursed by CMS without demonstration of clinical benefit. Not surprisingly, the use of these devices in clinical practice is increasing, while recruitment into trials designed to show the clinical efficacy of the endovascular treatment in patients with acute stroke has lagged. [56]

III. Conclusion

We are not naive. The reform of Bayh-Dole, the establishment of an FNIH-PPP for DBS and the reform of FDA regulations for Class III devices will be a formidable challenge. Less daunting but still necessary is revision of the AAMC provisions that limit the involvement of the most knowledgeable scientists in the clinical investigations of novel devices. These challenges are real, but are no less so than the scientific, and therapeutic task, of understanding and manipulating the neural circuitry of the brain. If we can imagine such interventions in the human brain, we should surely be able to envision how to overcome societal barriers to meaningful and responsible progress.

Acknowledgments

Dr. Fins gratefully acknowledges the support of a Clinical and Translational Science Center (UL1)-Cooperative Agreement (CTSC) 1UL1 RR024996 to Weill Cornell Medical College and its Ethics Core for support as well as the support of the Buster Foundation and Jerold B. Katz Foundation.

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