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PERSPECTIVE

Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation

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Abstract
The clinical promise of deep brain stimulation (DBS) for neuropsychiatric conditions is coupled with the potential for ethical conflicts of interest because the work is so heavily reliant upon collaborations between academia, industry and the clinic. To foster transparency and public trust, we offer ethical guidance for the management of conflicts of interest in the conduct of DBS research and practice so that this nascent field can better balance competing goods and engineer new and better strategies for the amelioration of human suffering. We also hope that our ethical analysis will be of relevance to those working with other related neuroprosthetic devices, such brain-computer interfaces and neural arrays, which naturally share many of the same concerns.

1. Preamble: rationale for ethical guidance

Deep brain stimulation (DBS) is a method used to reversibly modulate brain dysfunction. It has been systematically researched and developed for clinical application in neurology and psychiatry; indeed, it is the method of choice for various kinds of tremor and for intractable dopamine sensitive Parkinson's disease [1]. Its putative application for psychiatric disorders, such as treatment resistant obsessive–compulsive disorders [2, 3] and major depression [4–6], has come into investigative focus more recently. We believe that the application of DBS for psychiatric disorders has the potential to improve the condition of patients for whom conventional treatments have been ineffective.

This clinical promise is coupled with the potential for ethical conflicts of interest because the work is so heavily reliant upon collaborations between academia, industry and clinics [7]. This dynamic, coupled with the contentious antecedent history of psychosurgery [8, 9], increased government scrutiny, and remaining ethical and social challenges [10] makes transparency especially critical if public trust and confidence in this research is to be sustained.

To this end, we offer ethical guidance for the management of conflicts of interest in the conduct of DBS research and practice so that this nascent field can better balance competing goods, and engineer new and better strategies for the amelioration of human suffering. We also hope that our ethical analysis will be of relevance to those working with related neuroprosthetic devices, such as brain–computer interfaces and neural arrays, which would naturally share many of these same concerns.

Our concerns have come into focus through on-going deliberations as a multinational interdisciplinary group looking at ethical and policy issues related to DBS in neuropsychiatric disorders. Some of us are engaged in DBS research and others have been commentators on ethical and policy issues. Through these efforts, we have had to collaborate with industry and make judgments about the ethical propriety of these relationships. Collectively, we have learned that the process of editorial and institutional discernment about conflicts of interest can be arbitrary and idiosyncratic at best and sometimes ideological at worst. For example, in our efforts to publish our collective work—some of which has been critical of some relationships with corporate sponsors—we have encountered editorial or institutional resistance simply because of pre-existing relationships with industry. Indeed, some journals and organizations view these relationships as categorically disqualifying, despite the critical content of the argument, while others accept mere disclosure.

Because we believe that this work cannot go forward without interactions with industry, and because we think that the capricious management of these conflicts is problematic, we propose guidance on how investigators, their academic institutions and industry can negotiate and manage putative conflicts of interests. We believe that this effort to articulate a collective set of expectations will inform behaviors and lead to communal norms for the disclosure and management of conflicts, all to the benefit of science and society. We believe that investigators who bring their conflicts forward should not be viewed prejudically for these relationships but rather judged on the ethical justification of why corporate relationships might be necessary to pursue specific translational hypotheses [11].

Some might ask why we need such a document when organizations like the European Medicines Agency, the Association of American Medical Colleges, the US Institute of Medicine and the European Group on Ethics and Science and New Technologies to the European Commission (EGE)—whose deliberations we draw upon here—have all been promulgating recommendations [12–15]. While it can be argued that rules for the handling of conflicts of interest should be the same for all medical disciplines, we would assert that there are aspects of DBS for neuropsychiatric disorders that warrant, indeed necessitate, special guidance for the field.

Previously, some of us and other commentators drafted early ethics guidelines for DBS in psychiatric disorders and we believe that progress in the field necessitates further elaboration, refinement and additions [16–19]. We believe that there is a need for an updated statement related to DBS because of the complexity of device development and the invasive nature of implantation [20].

Perhaps more critically, unlike the chemicals that constitute the building blocks for drug development, deep brain stimulators and other neuroprosthetic devices—while therapeutic—are also the tools of inquiry used by investigators to secure new knowledge about mechanisms of disease [11]. These devices are probative and essential to scientific inquiry but are only available from industrial sources. This makes neuromodulation's reliance upon industry rather unique and—in our view—calls for this discrete effort [7].

Finally, in contrast to the pharmaceutical industry and drug development, the neuromodulation community and the device industry is constituted by a smaller number of manufacturers and a smaller number of investigators. These dynamics can exert monopolistic pressures on relationships between investigators and industrial sponsors [7, 21].

We undertake this offering knowing full well that the consensus we have reached as a group may not be fully reflective of the broader community of investigators and scholars engaged in neuromodulation research. This represents the opinions of our group and we acknowledge that there may be alternative perspectives. Nonetheless, we hope that this effort will be a touchstone for us to collectively move toward shared standards, norms and uniformity. We look forward to the comments of others and their constructive critique as we seek to achieve a consensus on these pressing concerns.

2. Ethical principles

Beneficence and distributive justice are the two over-arching ethical principles that motivate these guidelines for the management of conflicts of interest and investigative work in neuromodulation [22]. Beneficence, or the pursuit of the 'good', takes the form of innovation and scientific discovery that seeks to maximize benefits and minimize harms, that is, the avoidance of its corollary non-maleficience. Justice is achieved through the appropriate delivery of these benefits to a historically marginalized population that has suffered and remains in need. Collectively, these principles constrain the systemic conditions under which investigators should receive private sector funding and compel the avoidance of corrosive practices. Investigators should not be driven by self-interest when pursuing corporate support but rather motivated by a desire to pursue important scientific work to enhance access to novel interventions [7, 17].

At a more dyadic level of relationships between doctor and patient or investigator and subject, the aforementioned systemic factors create the context for individualized informed consent for patient care or participation in clinical research. Here, the autonomy or self-determination of the patient or subject or their legally authorized representative must

be defended against external forces that might inhibit the appropriate exercise of informed choice.

2.1. Sources of conflict

There are multiple sources of conflict of interest, including sources of funding, intellectual property exchange, and reimbursement specific to the conduct of DBS research and practice. For each of these areas, we will delineate the potential conflict and our assessment.

2.2. Recommendations

2.2.1. Funding. The cost of DBS research is high and its conduct may be dependent upon the provision of devices or funding by industry to investigators[9]. This can create reliance upon industry for access to needed devices and result in ensuing conflicts of interest. To mitigate these putative conflicts:

a. Investigators should, as a minimum, 'disclose and justify' why receipt of corporate funding is needed to sustain the work, promote access to scientific discovery and pursue the work safely and effectively [17]. This disclosure and justification should be done explicitly in the public square.
b. Investigators should seek to balance funding from corporate sources and other funders in order to dilute perceived and real conflicts [23].
c. Investigator conflicts of interests should be disclosed not only to subjects participating in research and institutions charged with regulatory oversight but also to their co-investigators who may not have similar financial involvements. Such conflicts should be disclosed to one's colleagues prospectively and early in the course of collaborative work.

2.2.2. Rights of reference. The provision of devices for the conduct of research requires industry to provide a right of reference (ROR) [24, 25]—permission to use pre-existing data about a device—for investigators to utilize an established device for a new indication or a novel target. For example, in the United States, this ROR—which includes device details and safety profile—is necessary to obtain subsequent regulatory approval (Food and Drug Administration investigational device exemption (IDE)) for any study of that device for a new indication or target. Manufacturers are under no obligation to share their RORs with investigators.

Given the potential of an ROR denial to preclude scientific discovery, device manufacturers should seek to maintain the scientific commons by liberally viewing requests for an ROR by qualified investigators. This perspective is consistent with the 'scientific commons' and the humanitarian goals of science to provide open access to innovative therapies and the tools of discovery [7, 17]. For these reasons, industry should not seek a competitive market advantage at critical stages of discovery.

2.2.3. Intellectual property rights. Intellectual property rights in DBS will generally be related to the conceptualization of a new application (new disease, target or method) and/or the development of a novel device. Under the US Bayh–Dole Act of 1980, investigators and their institutions receiving federal funding retain the intellectual property rights of their discoveries in order to negotiate applications with industry and accelerate the pace of innovation from bench to bedside [26]. This model of dissemination is being considered for the European context, as some commentators note that the EU suffers from weak intellectual property laws and poor performance with respect to bringing good ideas forward to market [27]. Beyond the need for harmonization with the EU, there are often inadequate incentives for academics to engage in innovation versus publication of conventional research and little infra-structural support for academics who try to patent their ideas. (See reference [27] for a comprehensive analysis of the European patent law, the Bayh–Dole Act and a country-by-country review of variance in IP practices.)

Despite its putative value within the United States and in the European context, the Bayh–Dole Act can also create challenges. When ideas gain potential market value and become commoditized, conflicts of interest can arise. They can occur between investigators and their home institutions as well as amongst institutional officials with differing priorities (e.g. between the Technology Transfer Office and the Conflicts Office). To manage these conflicts:

a. The exchange of intellectual property rights by an investigator to a corporate sponsor should be done transparently and include all institutional officials who regulate conflicts of interest, e.g. Conflict of Interest Panels, Institutional Review Boards, Technology Transfer Offices and Ethics Committees. This joint disclosure should ideally result in an institutional conflict of interest management plan.
b. Payments, royalties, fees and stock options should be determined based on prospectively determined and established institutional policy.
c. Corporate payments, royalties and fees should be designed to maximize the viability and sustainability of the scientific work [7, 17]. Institutions should aid their investigators in these negotiations to secure these objectives and avoid short-term settlements, which generate 'cash flow' but fail to catalyze longitudinal research programs.
d. Investigators pursuing the work who have putative conflicts of interest (including, but not limited to, intellectual property rights related to earlier discoveries) should be able to pursue their scientific work in order to elucidate mechanism of action and ensure the safety of early phase studies. Their involvement in such studies helps to ensure the safety of subjects and maximizes the likelihood of success at an early critical juncture in the maturation of the work [7]. Conflicted investigators

[9] By 'investigator' we refer to all those engaged in neuromodulation research, including device development, study of mechanisms of action, surgical implantation and outcomes assessment. Investigators in this interdisciplinary space will include an array of engineers (electrical, material, biomedical and others); physician–scientists from multiple specialty areas (neurology, neurosurgery, psychiatry and others); and other clinicians engaged in patient care and translational research.

should assume a step-back role—ceding the actual conduct of industry sponsored clinical studies to other un-conflicted qualified investigators—as soon as feasible in order to minimize the possibility generating data that might be open to critique because of a potential conflict of interest [21].

e. Conflicted investigators should feel free to pursue longitudinal research related to their discovery outside of industry sponsored pivotal trials. Contractual arrangements between investigators, the academy and industry should not preempt the investigator's academic freedom to pursue their scientific work.

f. Access to specialized DBS care that results from one's research should be an ethical principle embraced by all along the research continuum. Investigators, institutions and industry might consider what to do with some percentage of royalties garnered through the ownership of intellectual property earned, in part, through the participation of human subjects afflicted with a disease or malady under study. Collectively, they should seek to use their influence with industry to advocate for the underserved and work to ensure that the exclusivity granted by patents does not make products so prohibitively expensive that access is compromised. This might be achieved by directing a percentage of proceeds to a not-for-profit use underwriting surgeries on patients who would otherwise be unable to be treated, or for support of translational research [7, 17].

2.2.4. Consent. The relationship between respect for people and the origins of informed consent date to landmark judicial rulings in the 20th century addressed the right to self-dominion and considered necessary elements of disclosure [28–33], the Nuremberg Code [34] promulgated in the late 1940s and the Belmont Report [35] in the 1970s addressed the centrality of informed consent as well as the research context, but did little to address how external economic forces might impinge upon the patient's self-determination and autonomous choice.

More recently, and from a European source, has come the Opinion of the European Group on Ethics and Science and New Technologies to the European Commission (EGE) entitled 'Ethical Aspects of ICT (Information and Communication Technologies) Implants in the Human Body' [36]. This comprehensive document set within a context of shared European values, like human dignity, speaks of the limits of the 'freedom of individual free choice' when such consent violates fundamental and inviolable principles like human dignity. According to the EGE's speculative analysis, such affronts might occur when computer–DBS interfaces somehow compromised personal privacy or tethered an individual in such a way as to compromise free movement or autonomy.

Notwithstanding these limits placed on consent, we would still assert that the economics of DBS research and practice necessitate that additional disclosures occur. While these disclosures are necessary, as per the analysis of the European Group, they would be insufficient if consent were being requested for practices that were somehow contrary to deeply held values. With this in mind, we would amend current consent practices as follows:

a. Patients and/or their legally authorized representatives should be made fully aware of putative conflicts of interest in all informed consent discussions.

b. Investigators should err on the side of over-disclosure to ensure transparency in this process. In all cases, as a minimum, information about corporate relationships and/or IP rights (as determined by investigators in consultation with institutional officials) should be shared with prospective participants and/or their surrogates.

c. Elements of disclosure include any receipt or promised receipt of payments, royalties, fees and stock options made to the investigator and his or her team or institution. It might also include the name(s) of the manufacturer(s) of any device or component of device (electrode, pacemaker) that is being implanted and information about any role that these additional companies might have in funding the research.

d. Investigators should seek to avoid the 'therapeutic misconception' by inappropriately labeling an investigational device as a 'therapy' or as 'therapeutic' while it remains investigational [37, 38].

2.2.5. Corporate compliance, and academic and corporate role sequestration. The range of individuals and entities involved in DBS research necessitate that there are consistent and systemic efforts to regulate this research and corporate compliance related to applicable laws and ethical norms. This also requires that institutional entities appreciate their discrete responsibilities. To these ends:

a. Investigators, institutions and any corporate sponsor should adhere to all regulatory requirements to evaluate new devices or established devices for new applications using an appropriate device approval pathway [39].

b. Investigators receiving funding from corporate sources should work closely with their institutional officials to ensure compliance with their local conflict-of-interest panels to whom full disclosure of the nature and scope of these relationships should be made. This includes payments, stipends, royalties and stock options [21].

c. Notwithstanding any adverse impact on the market standing of a corporate sponsor, all adverse events should be reported to the proper local and governmental regulatory bodies [40]. Central to the discernment of toxicity and adverse events is the constitution of a Data Safety Monitoring Board (DSMB) that has the requisite expertise to evaluate questions of efficacy and toxicity for this area of specialized research. In this way, the ethical principles of both beneficence (efficacy) and non-malefiecence (toxicity) can best be balanced and proportionate.

d. Investigators who conduct sponsored research should not have, or assume, corporate fiduciary roles, as board members entrusted with potential oversight responsibility of their own research and conduct. Membership on scientific advisory boards is appropriate so long as there is role sequestration with respect to corporate governance [21].

e. Academics who conduct such research should not also be employees of the companies sponsoring their work. All consultancies should be vetted by their local institutional conflicts boards [21, 41].
f. In order to maintain clarity about roles and ensure proper oversight, we recommend that any consultancy payments to investigators from corporate entities remain less than or equal to half of the investigator's yearly academic salary and in all cases represent fair market value of the services provided [42].
g. Corporate sponsors and investigators should seek to avoid therapeutic misconception by avoiding the adoption of promotional language that inappropriately labels an investigational device as a 'therapy' or as 'therapeutic' [37, 39].

2.2.6. Presentations and publishing. The range of potential conflicts, diversity of funders and peculiarities related to device development and DBS necessitates that these relationships are properly disclosed and communicated to the broader scientific community through scholarly publications and presentations.

a. Investigators should not present findings or publish data at programs or publish in journals whose editorial content is controlled by their sponsor. They should not engage in selective reporting of results [43] and we agree that there should be mandatory disclosure of DBS trial results [44].
b. Investigators should always assume responsibility for their written work and abjure corporately sponsored ghost-written publications.
c. As a question of academic freedom and the conduct of science, investigators should be neither delayed in nor precluded from publishing negative results because of a potential adverse market impact upon on a corporate sponsor.
d. When a DBS trial registry is available, investigators should register their results [45].
e. Investigators should seek to disclose and justify their interactions with industry in their published works, and peer reviewers and editors should seek such disclosure and explication as an element of publication submission [17].
f. Journals should carefully review 'disclose and justify' attestations and have a policy on disqualifying conflicts of interest and publication. Given the unavoidable involvement of industry, investigators and their institutions in DBS research, journals should not make categorical judgments about the suitability of a paper solely based on the presence of a disclosed conflict. Such conflicts, if properly disclosed and managed, can provide an important perspective that is otherwise unobtainable in the literature. As such, they should be viewed with editorial neutrality.

3. Conclusion

The unavoidable mix of industry and academia makes it essential that DBS practitioners, investigators and sponsors adhere to high ethical standards that will sustain this work for the long haul. We hope that this document provides ethical guidance for the management of conflicts of interest for all those engaged in the development of therapeutic deep brain stimulation for neuropsychiatric disorders and serves as a moral compass for this journey of discovery.

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Competing interests. JJF and CSK are unfunded co-investigators in the DBS in MCS clinical trails funded by Intelect Inc. The authors have previously published on deep brain stimulation for psychiatric disorders. BN holds a patent on DBS for obsessive–compulsive disorder and has received limited funding from Medtronic, Inc. for research travel and education. HSM has been, and remains, involved in studies of DBS for depression funded by non-industry foundation sponsors. She holds consults and receives licensing fees for intellectual property related to DBS for depression from St Jude Medical, and holds a physician sponsored IDE for non-industry funded ongoing studies. VS and TS received limited funding from Medtronic Inc. for an investigator-initiated study of DBS for treatment resistant major depression. VS is a shareholder of a German limited society (so-called GmbH) developing novel stimulus sequences for DBS treatment-optimization in parallel with the design of DBS-related system software and hardware. He also holds a patent for DBS for dementia. VS has also received funding from Medtronic, Inc. for presentations. CSK receives limited funding from Medtronic for an industry sponsored trial for DBS for treatment resistant depression and is Co-PI on a NINDS grant examining the ethics of control in DBS for Parkinson's disease and a co-investigator in an NIMH funded study examining DBS for the treatment of OCD. She is co-author on a patent filed for the treatment of neuropsychological disorders.

References

[1] Deuschl G *et al* 2006 A randomized trial of deep-brain stimulation for Parkinson's disease *N. Engl. J.Med.* **355** 896–908

[2] Denys D, Mantione M, Figee M, Van Den Munckhof P, Koerselman F, Westenberg H, Bosch A and Schuurman R 2010 Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive–compulsive disorder *Arch. Gen. Psychiatry* **67** 1061–8

[3] Goodman W K *et al* 2010 Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design *Biol. Psychiatry* **67** 535–42

[4] Bewernick B H *et al* 2010 Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression *Biol. Psychiatry* **67** 110–6

[5] Lozano A M *et al* 2008 Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression *Biol. Psychiatry* **64** 461–7

[6] Malone D A Jr *et al* 2009 Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression *Biol. Psychiatry* **65** 267–75

[7] Fins J J 2010 Deep brain stimulation, free markets and the scientific commons: Is it time to revisit the Bayh–Dole Act of 1980? *Neuromodulation Technol. Neural Interface* **13** 153–9

[8] Fins J J 2003 From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of neuropsychiatric research *Neurosurg. Clin. N. Am.* **14** 303–19

[9] Kringelbach M L and Aziz T Z 2009 Deep brain stimulation: avoiding the errors of psychosurgery *JAMA* **301** 1705–7

[10] Bell E, Mathieu G and Racine E 2009 Preparing the ethical future of deep brain stimulation *Surg. Neurol.* **72** 577–86

[11] Fins J J and Schachter M 2001 Investigators, industry and the heuristic device. Ethics, patent law and clinical innovation *Account. Res.* **8** 219–33

[12] Cohen D 2010 European Medicines Agency tightens rules on conflict of interest *Br. Med. J.* **341** 5902

[13] AAMC Task Force on Financial Conflicts of Interest in Clinical Research 2003 Protecting subjects, preserving trust, promoting progress I: policy and guidelines for the oversight of individual financial interests in human subjects research *Acad. Med.* **78** 225–36

[14] Committee on Conflicts of Interest in Medical Research, Education, and Practice. Board on Health Sciences Policy of the Institute of Medicine 2009 *Conflicts of Interest in Medical Research, Education, and Practice* ed B Lo and M J Field (Washington, DC: The National Academies Press)

[15] Opinion of the European Group on Ethics and Science and New Technologies to the European Commission (EGE)

[16] Nuttin B *et al* 2002 Deep brain stimulation for psychiatric disorders *Neurosurgery* **51** 519

[17] Fins J J 2007 Disclose and justify: intellectual property, conflicts of interest, and neurosurgery *Congr. Q. Neuro. Surg.* **8** 34–6

[18] Fins J J, Rezai A R and Greenberg B D 2006 Psychosurgery: avoiding an ethical redux while advancing a therapeutic future *Neurosurgery* **59** 713–6

[19] Rabins P *et al* 2009 Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior, and thought *Arch. Gen. Psychol.* **66** 931–7

[20] Fins J J 2008 Surgical innovation and ethical dilemmas: precautions & proximity *Cleve. Clinic J. Med.* **75** (Suppl. 6) S7–12

[21] Fins J J and Schiff N D 2010 Conflicts of interest in deep brain stimulation research and the ethics of transparency *J. Clin. Ethics* **21** 125–32

[22] Beauchamp T L and Childress J F 2008 *Principles of Biomedical Ethics* 6th edn (New York: Oxford University Press)

[23] Lo B, Wolf L E and Berkeley A 2000 Conflict-of-interest policies for investigators in clinical trials *N. Engl. J. Med.* **343** 1616–20

[24] Beers D O 2004 *Generic and Innovator Drugs: A Guide to FDA Approval Requirements* 6th edn (Aspen, CO, USA)

[25] Code of Federal Regulations, Title 21, Chapter 1, Part 314.3, Subpart A. General Provisions and Definitions. 21CFR314.3

[26] Bayh–Dole Act (P.L. 96-517, Patent and Trademark Act Amendments of 1980). 37 C.F.R. 401 and 35 U.S.C. 200–212

[27] Siepmann T J 2004 The global exportation of the U.S. Bayh–Dole Act *Univ. Dayton Law Rev.* **30** 209–43

[28] Schloendorff v Society of New York Hosp., 211 N.Y. 125 (1914)

[29] Zaubler T S, Viederman M and Fins J J 1996 Ethical, legal, and psychiatric issues in capacity, competence, and informed consent: an annotated bibliography *Gen. Hosp. Psychiatry* **18** 155–72

[30] Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees, 317 P.2d 170 (Cal. Ct. App. 1957)

[31] Natanson v Kline, 350 P 2d 1093, 1960

[32] Canterbury v Spence, 464 F 2d 772, 1972

[33] Annas G 1994 Informed consent, cancer, and truth in prognosis *N. Engl. J. Med.* **330** 223–5

[34] U.S. Government Printing Office 1949 *Trials of War Criminals before the Nuremburg Military Tribunals under Control Council Law No. 10* vol 2 (Washington DC: U.S. Government Printing Office) pp 181–2

[35] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979 *The Belmont Report Ethical Principles and Guidelines for the Protection of Human Subjects of Research* Department of Health Education and Welfare accessed 16 January 2011 http://ohsr. od.nih.gov/guidelines/belmont.html

[36] The Opinion of the European Group on Ethics and Science and New Technologies to the European Commission entitled, 'Ethical Aspects of ICT [Information and Communication Technologies] Implants in the Human Body'. No. 20. Adopted 16 March 2005

[37] Appelbaum P S and Lidz C W 2008 Twenty-five years of therapeutic misconception *Hastings Center Rep.* **38(2)** 5–6

[38] Fins J J 2004 Deep brain stimulation *Encyclopedia of Bioethics* vol 2 3rd edn editor-in-chief ed SG Post (New York: Macmillan) pp 629–34

[39] Fins J J *et al* 2011 Neuropsychiatric deep brain stimulation research and the misuse of the humanitarian device exemption *Health Aff.* **30** 302–11

[40] Shamoo A E 2001 Adverse events reporting—the tip of an iceberg *Account. Res.* **8** 197–218

[41] Lo B, Wolf L E and Berkeley A 2000 Conflict-of-interest policies for investigators in clinical trials *N. Engl. J. Med.* **343** 1616–20

[42] Lo B 2010 Serving two masters—conflicts of interest in academic medicine *N. Engl. J. Med.* **362** 669–71

[43] DeAngelis C D *et al* 2004 Clinical trial registration: a statement from the International Committee of Medical Journal Editors *J. Am. Med. Assoc.* **292** 1363–4

[44] Groves T 2008 Mandatory disclosure of trial results for drugs and devices *Br. Med. J.* **336** 170

[45] Schlaepfer T E and Fins J J 2010 Deep brain stimulation and the neuroethics of responsible publishing: when one is not enough *J. Am. Med. Assoc.* **303** 775–6