Innovation in neurosurgery: Evaluation of neurosurgical innovation, related ethics, and solutions

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Oversight and Ethical Regulation of Conflicts of Interest in Neurosurgery In the United States

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***Introduction**: Developmental incentives are fundamental to surgical progress, yet financial and professional incentives inherently create conflicts of interest (COI). Understanding how to manage COI held by neurosurgeons, industry, hospitals, and journal editors, without thwarting progress and innovation is critical. **Methods**: This article aims to present an overview of COI associated with innovation in neurosurgery, and review ways to manage these in an ethically sound manner. A review of the literature was performed to assess conflicts of interest that affect neurosurgical innovation, and review ways to manage COI of various parties while adhering to ethical standards. **Results**: COI are inherent to collaboration and innovation and are therefore an unavoidable component of neurosurgery. The lack of a clear distinction between clinical practice and innovation, ability to use devices off-label, and unstandardized disclosure requirements create inconsistencies in the way that conflicts of interest are handled. Additionally, lack of requirements to compare innovation to the standard of care and inherent bias that affects study design and interpretation can have profound effects on the medical literature. Conflicts of interest can have both direct*

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and downstream effects on neurosurgical practice, and it is possible to manage them while improving the quality of research and innovation. ***Conclusions****: Conflicts of interest are inherent to surgical innovation and can be handled in an ethically sound manner. Neurosurgeons, device companies, hospitals and medical journals can take steps to proactively confront bias and ensure patient autonomy and safety. These steps can preserve public trust and ultimately improve evidence-based neurosurgical practice.*

Introduction

A conflict of interest (COI) is a competing goal or motivation held by an individual or organization. They may stem from the potential for profit but may also arise from responsibility for multiple people or groups. Among the two, the latter is perhaps the more ubiquitous and difficult to discern. While COI is unavoidable and may go without impact, they also create to the possibility that decisions will adversely affect one group in the interest of another. In neurosurgery, COI is problematic if it adversely affects decision making and causes real or potential harm to patients or compromises the trust a patient places in neurosurgeons. Thus, it is important that COI is appropriately and ethically managed in order to respect patient autonomy, ensure beneficence of treatment, and avoid maleficence.

In neurosurgery, the medical device industry plays an important role in promoting innovation by helping to fund and facilitate research. The field's strong dependence on technology, however, creates many such COI for neurosurgeons involved with industry and in the development of new devices. In 2014 alone, payments to U.S. neurosurgeons tracked by the Open Payments Database - which was instated by the Affordable Care Act to publicize payments to physicians from medical device and pharmaceutical companies - surpassed $100,000,000. Notably, 1% of neurosurgeons received 54% of the payments tracked by this database.[4] While the contributions of neurosurgeons provide critical insight for new technology and financial compensation may reward risk and help to stimulate neurosurgeons to innovate, problems may arise if the business interests of a particular company impact clinical decision making and patient care through neurosurgeons with COI. Even among the many neurosurgeons without a financial stake in the medical device industry, there are numerous other nonfinancial COI and incentives for innovation. The desire to advance a career in academia, improve financial outcomes, publish papers, and gain status all create biases that can affect clinical decision making and patient care. While these are important to the success and advancement of neurosurgery, it is critical that care is taken to address the COI that naturally develop during these innovative pursuits so that patient safety is always protected. Furthermore, it is critical to remember that these supposed relationships can benefit patients by giving them access to cutting edge treatments that bring hope, and providing physicians with new knowledge and understanding of the field. Many forces are at play in the lives of all surgeon-innovators, and the neurosurgical literature could benefit from a robust discussion of the ethical principles and difficulties associated with COI in innovation. Here, we evaluate various COI that affect the neurosurgeon, industry, healthcare systems, and neurosurgical literature from an ethical perspective.

Neurosurgeon

Neurosurgical outcomes are increasingly being measured by various factors including quality of life, invasiveness of a procedure, and recovery time, all of which contribute to the complexity of surgical decision-making.[2] This is further complicated in the setting of novel procedures where complication rates and outcomes may be unknown or come with considerable uncertainty.[33] Without evidence that overwhelmingly supports a particular clinical decision, it is unavoidable that decisions are, at times, made based on personal experience. Personal experience and knowledge is undeniably an important source of guidance in surgical decision making, yet this flexibility leaves room for COI to inevitably influence decisions regarding procedures and use of devices in particular. Patients nonetheless expect that neurosurgeons make ethically sound decisions and avoid the influence of COI.[36] Introduction of medical devices to improve outcomes in neurosurgery is not inherently unethical in itself, is essential to move neurosurgery forward as a field, and can be carried out in an ethical fashion.

Furthermore, it is often hard to distinguish clinical care from innovation and research in neurosurgery. Whereas institutional oversight is required in the setting of formalized clinical research and novel devices, there is little oversight in place for innovative procedures.[35] Many of these procedures typically involve a gradual deviation from typical practice with the goal of improving the care for the patient.[8] An example of this is endoscopic endonasal meningioma surgery. Some argue that because of the nature of surgery overall and neurosurgery specifically, performing a new procedure or using a novel device should not be subjected to oversight at all.[31] This leaves many decisions related to innovation in neurosurgery up to the discretion of the individual surgeon, opening the possibility that financial or nonfinancial COI can inadvertently sway the surgeon.

All physicians may be influenced by both direct and indirect incentives. Direct incentives include financial ties to industry, which can create monetary incentives to use particular devices for financial gain and incentives to publish on novel techniques to improve academic standing. Indirectly, relationships with beneficiaries, including colleagues and industry representatives, may provide undue influence on decisions regarding medical devices. Similarly, using novel approaches can also give the physician an opportunity to improve their financial compensation, expand their referral volume, increase operative productivity, and improve their reputation.

While the neurosurgeon is the best equipped and should be able to discuss the risks and benefits of a procedure, the process of obtaining informed consent and how a procedure is portrayed to the patient may be affected by a physician's biases, experience, and financial COI, all of which affect physician estimates of risk.[11] These concerns highlight the importance of being aware of financial and nonfinancial COI, and how they may influence consent and subsequently a patient's autonomy. Surgeons are more likely to inform patients of complications they have personally encountered, for example.[7] In surgical practice there is a robust culture of innovation outside the formalized structure of randomized controlled trials (RCTs) and a lack of a clear distinction between clinical decision-making and innovative practice. Thus, there is variation in the evaluation of whether something is considered innovative

practice or a novel application, and there is a possibility that COI could affect how a procedure is portrayed, often unbeknownst to the physician. Furthermore, there is no formal oversight of patient consent, and no requirement that COI be disclosed in a clinical setting.

In addition, even if a patient is made aware of the innovative nature of a procedure and physician COI, they can sometimes fall victim to the assumption that novel is necessarily better.[2] Therapeutic misconception is the idea that patients do not fully understand the difference between treatment and research, and may believe that their providers will always act in their best interests. This has been shown in trials in which 100% of patients expect positive results.[3, 18] This is in addition to biases of the patient, which can affect their ability to adequately consent. Often, the severity of a diagnosis can influence a patient's acceptance of their prognosis and risks associated with procedures once they are informed. This is true even in the case in which a patient is determined to be fully competent of giving informed consent.[49] This is further complicated by the nature of surgery, in which there is not always a distinct boundary between innovation and clinical practice. Furthermore, there is often very limited available information about the long-term risks of innovative procedures, which can render an informed discussion about risks and benefits of a procedure impossible by no fault of the physician. Therefore, it may be hard for patients to assess the severity of the COI, even if a neurosurgeon discloses all relevant information. Neurosurgeons have the ethical responsibility to ensure that a decision is made which the patient understands, agrees with, and is in the best interest of the patient, even if COIs are present.

Industry

The close ties between the field of neurosurgery and the medical device industry is critical to the advancement of clinical care. Payments made to physician-innovators for their expertise and time can help drive innovation forward, incentivize progress, and compensate for personal risk. This process also allows physicians to become well versed in the utilization of new devices and learn about the devices directly from the company.[29, 48] The goals of the medical device industry, however, are naturally focused on a return on investment, which may be hard to align with the goals of academic research. This opens the possibility that industry involvements may lead to poor trial design, inadequate enrollment decisions, biased data interpretation, or inadequate reporting of adverse events if not handled appropriately.[37] While financial COI is an inevitable component of progress in neurosurgery, it is important that these COI are managed in a way that is ethically sound and clinically practical.

Physicians are listed as an inventor in about 20% of medical device patents.[16] The constant input and feedback provided by physicians to device manufacturers is crucial in the development of medical devices, and care can be taken to ensure that it does not interfere with clinical decisions. Richard Thaler, who received of the Nobel Prize for his work in behavioral economics, explained the irrational nature of human thought and decisions. For example, the "endowment effect" is the idea that we disproportionally ascribe more value to something we already own that to an equivalent product that we would like to own.[27] Similarly, the "IKEA effect" is the idea that

we value products that we created over equivalent products made by others.[38] Thus, the surgeon is at risk for unknowingly overvaluing devices or procedures that he/she helped create/optimize due to bias. In this realm, it is important to note that the bias and any related actions are unintentional.

In addition to their role as a device innovator, surgeons are often integrally involved in the early implementation of novel medical devices, consult with industry, sit on advisory boards, and receive industry funding for research - all of which drive innovation but can create a source of COI.[19, 26] In the state of Massachusetts alone, payments made to orthopedic surgeons totaled to almost 8 million dollars from July 2009 - December 2011. In this study, at least 40% of surgeons reported as receiving payments in four of the included surgical specialties (Neurosurgery, Orthopedic Surgery, Ophthalmology, Plastic Surgery).[28] These payments are thought to affect a surgeon's ability to be impartial if evaluating treatment options for patient, and may provide undue pressure on a physician to opt for a particular device due to previously favorable personal interactions or financial incentives.[19]

In a clinical setting, unintentional favorability towards a particular company is strong in surgical fields and it is common for industry representatives to be present in the operating room, where they often develop close personal relationships with surgeons.[26] Vendors are frequently present during operations to provide on-the-spot input in the use of novel hardware and surgical instruments. Input from surgeons can provide device manufacturers the valuable clinical insight needed to determine what areas to improve on, identify what limitations exist in the current technology, and ensure that the products are patient-focused.[2, 10, 26, 41] There is also the risk that the relationship with industry could compromise patient care.[20, 45] Unintentionally and indirectly, favorability between physicians and industry may also result from gifts and other material benefits that are perceived as normal by the physician and representative, but may be regarded as bribery from the perspective of the patient.[13, 30] Thus, the lack of agreement over what is deemed appropriate among surgeons and the public further complicates this issue of how COI can affect care.

Hospital

Hospitals may also have COI that affect the ability to provide care in the best interest of their patients. Hospitals often invest in new technologies in order to improve the status of the institution, patient volume, and quality of care.[33] When choosing a new technology from a vendor, hospital systems are often faced with choices that include certain "benefits," such as discounts or additional provided equipment. These further increase the costs incurred by the system, which in turn are passed onto payers. An investment in a novel surgical or imaging technology gives healthcare institutions an inherent incentive to use the technology to offset the costs associated with implementation and provide the service directly to patients who may benefit. While the potential for revenue gained from adopting new technology is important to improve the field over time, many patients may have no need for a technology that may only provide them with marginal benefit at an increased cost but may view the innovation as superior regardless.

Similar to our knowledge of new procedures, the data available on new technolo-

gies is often incomplete, biased, or conflicting. For example, the use of intraoperative MRI significantly increases the expense of treatment for the patient because the high cost of implementation and prolonged operative time, yet many feel that the improved imaging brings substantial benefit. The data on whether this improves outcomes remains a subject of debate.[52] Regardless, the belief that new, expensive, innovative approaches will improve outcomes affects the patient and may influence their decisions. This may be especially true in patients with particularly devastating diseases as is seen in neurosurgery. Therefore, hospitals have an added incentive to implement these innovative, expensive technologies in order to help patients before conclusive supporting evidence is available.

Disclosure

The medical device industry provides an unavoidable and invaluable source of funding for clinical research that drives essential progress. Industry involvement can also have a permeating effect on the influence of research. Research funded by industry has been independently shown to report positive outcomes at a higher rate in the medical literature than research without industry funding.[5] With this in mind, a clear disclosure policy is critical to enable the reader to interpret the results. The New England Journal of Medicine was the first journal to formally require disclosure of author conflicts of interest in 1984, citing both the inevitability of industry-academia relationships and the importance of maintaining public trust.[42] Since that time, disclosure of author COI has become commonplace, and now 70% and 90% of biomedical journals requiring reporting of nonfinancial and financial COI of authors, respectively.[9] Although the increased reporting over the past few decades is commendable, it is common for journals not to define COI to the authors or to publish disclosures selectively, thus creating inconsistencies in reporting and making the lack of a disclosure difficult to understand.[14, 40] Responsible reporting of COI is important to allow the readership to understand the research presented.

Additionally, even if there is a "gold standard" device available, innovative devices do not have to be compared to it in order to be published or to be approved by the FDA, which has caused harm to patients undergoing spine surgery in the past. For example, in the case of the interspinous process devices, single arm retrospective studies were the primary research evaluating the devices for 30 years until prospective studies and two randomized controlled trials eventually found the treatment to be inferior.[34] Additionally, another study that 24% of devices approved for use for neurologic, orthopedic, and cardiovascular indications between 2005-2010 had to be recalled for safety concerns as of 2016.[23] Thus, it is important to balance the importance of pushing innovation and new discoveries forward with the necessity of upholding the rigor of the literature and evaluating devices accurately.

Disclosure of COI is far less common for journal editors than it is for authors, with less than 40% of biomedical journals require reporting of COI for the journal editors.[9] Additionally, disclosures are not commonly available on journal websites for the reader to evaluate. Given the assumption of objectivity in the peer-review process, a process in which reviewers and editors have been described as the "gatekeepers" of science,[39] disclosure of COI among editors can help to maintain the legit-

imacy of peer-reviewed publications. Some ethical incidents -for instance, the trials of recombinant human bone morphogenic protein (rhBMP) spinal implant, - have resulted in stricter oversight in the editorial process. In this case, important COI were inadequately disclosed and a biased trial design was thought to have influenced the results. There were serious and life threatening events that were found later.[15] Despite examples like these, regulation of the COI held by reviewers and editors has not yet become the standard in medical journals.[25] This systematic flaw in how we evaluate research for publication[22] can be remedied to prevent future incidents. This will enable neurosurgeons to better evaluate the literature to make informed clinical decisions in the best interest of the patients, improve the quality of the research published, and help to maintain trust between journals and the medical community.

Some journals have started to acknowledge the potential role of editorial board COIs on the literature. An example is JAMA Ophthalmology, which has developed a transparent policy in which reviewers or editors with specific COI can recuse themselves from reviewing a particular manuscript. Specifically, this policy applies if the reviewer or editor has a financial interest in a company involved in the submission, and when the editor or reviewer is employed at the same institution as an author of the manuscript.[21] Consistent, transparent reporting of relevant COI is critical to allow the readers to understand the context of the research, and can be effectively accomplished without disrupting the editorial or review process.

For neurosurgical journals, disclosure policies regarding COI for reviewers and editors are not particularly strict. For example, The Journal of Neurosurgery and related journals, require that the editorial board members annually submit a disclosure statement. The editor-in-chief and editorial board members can then recuse themselves from reviewing any manuscript in which they have a COI that would affect their ability to be impartial.[1] One study of the spine journals found that at least 29% of editors of five leading spine journals had a financial conflict of interest reported at meetings, of whom 22% did not disclose. Of these editors with a financial COI, 76% of their financial relationships were with major medical device companies and 42% had more than $10,000 disclosed in a source other than the journal.[25]

At surgical meetings, device manufacturers frequently sponsor discussions about products and surgical dilemmas. These events may also unduly influence the clinical judgment of attendees, particularly if financial or other material incentives are present or if COI is not adequately disclosed to allow the reader to assess the content in context. It is particularly concerning that among physicians attending industry sponsored lectures, the sponsorship was shown to have a favorable effect on drug prescribing patterns.[47] This highlights the importance of mandating the reporting of COI and the role that the funder played in the work to allow the reader to judge the quality and independence of studies and form their own conclusions about the presented results, if desired.

Oversight and Ethical Regulation of Conflicts of Interest

The field of neurosurgery has traditionally given neurosurgeons the right to autonomy and self-governance, as well as the responsibility to act in the best interest of the patient despite COI. A physician has a moral obligation to act in the best interest

of the patient, and physicians take an oath to uphold ethical standards. Nevertheless, in the modern world, COI are particularly powerful forces that could be examined closely, and the effects of COI are not always overt to the beholder.

In particular, thought could be given to the oversight and management of neurosurgical COI by governments, institutions, the surgical community, institutions, and medical journals. Any attempt at ethical oversight and regulation should aim to encourage respect for patient autonomy in treatment decisions and preserve the rigor of the scientific literature without hindering innovation and progress. Declaration of COI is a simple yet tool that can help improve patient autonomy by giving patients, readers, and others knowledge of COI and thereby allowing them to inquire further, while also strengthening the integrity of physicians by reminding them of their duties to the patient. Solutions to COI can be achieved by bringing all parties together to develop a framework that ensures patient safety, optimal outcomes, and continuous innovation through a balanced, workable, and ethical collaboration.

Government Oversight

In the U.S., legal disclosure of financial COI was not required of physicians until more recently. In 2010, the Sunshine Act was enacted as part of the Patient Protection and Affordable Care Act (PPACA) to require physicians to report certain types of consulting fees, compensation, or company ownership in companies with at least one product covered by Medicare. This is intended to prevent inappropriate power of industry over clinical judgment.[46] Patients admittedly do not fully understand the extent of relationships between the device industry and physicians,[19] and find some of the gifts that physicians commonly accept to be immoral, yet patients are not necessarily in favor of stronger government regulations.[13] While the websites for the Sunshine Act are publicly searchable, the data available are difficult to interpret and not always accurate,[1] and there is a lack of public knowledge about the sites and what the COIs mean for patient care. Arguably, if the patient is unaware of the reporting, legal disclosure does little to reduce the influence of COI in practice.[26] While public disclosure is an important step in legal reporting of COI, it does not have a major effect on day-to-day patient care and may need to be supplemented with policies to address when additional consent, disclosure, and patient education is specifically needed. Examples could include standardized disclosure for innovative circumstances, such as off-label use of devices, and requiring disclosure of financial COI to patients when it involves an implant or device relevant to their care. It is important to note that disclosure to patients is not inherently negative, as it also shows a level of familiarity with the product and expertise in the field, as has been shown from the patient's perspective.[44] Furthermore, providing patients with the available information could preserve patient autonomy by ensuring that they have at least a minimal level of knowledge regarding their neurosurgeon's ties with industry and whether the device they are having implanted is innovative in nature.

Institutional Regulation

Though disclosure policies exist at the majority of medical schools, only 1% of institutions surveyed required disclosure to research subjects and many policies used vague

language and inadequately defined terminology, thus leaving the responsibility of reporting up to the physician.[32] If surgeons are to remain autonomous, patients expect accountability and sound decisions, regardless of COIs.[17] Awareness of the effects of bias and disclosure does little to change behavior,[12] further supporting the need for stricter institutional enforcement of COI policy.

Furthermore, patients have admitted to not necessarily being able to interpret disclosures,[13] and thus it is critical to give patients the opportunity to inquire about COI and assess the associated risks and benefits[50, 51] rather than bypassing patient involvement in their own care. While disclosure of COI is typically not required, disclosure of financial gain from a device to be implanted or any role in the device's development seems reasonable, and could improve public trust in the profession. From patients' perspectives, surgeon-initiated disclosure have been well received, and have instilled trust and given the patient the sense that the surgeon is in fact an expert.[44] Additionally, some have suggested that a physician who is unwilling to discuss COI is a reason to turn elsewhere for treatment.[43] Disclosure is certainly not the norm in clinical practice, and a more robust means of reporting may help maintain surgical patient autonomy. It is important, of course, to always discuss and evaluate policy within an institution to ensure that the policy meets ethical standards for practice.

Institutional policies need clear definitions within their policies and requirements for complete transparency with all financial relationships to ensure adequate disclosure. One example of a solution on the institutional level is to prohibit inventors from being involved in clinical testing for companies for which they invented devices for or have a consulting relationship with.[48] This has been criticized as being too strict as to stifle innovation[6] and has since been relaxed, yet it also prevents unintentional bias and increases the likelihood of obtaining results that are both reproducible and generalizable. Other suggestions to reach the same results have included giving some investigators read-only access to research data, and involving researchers without a financial COI to be involved in the study design and data interpretation.[24] It is also recommended that multiple neurosurgeons, especially those without ties to the innovation, are involved in implanting a device or performing a technique for the first time. This could ensure generalizability of results, increase adherence to evidence-based practice, and improve the overall quality of research and innovation.

Literature

Additional efforts by journals could help maintain the integrity of the scientific literature. Specifically, mandated disclosure and clear definitions on what constitutes a COI could be developed by the journals. By including author COI within each article, even if the authors have no disclosures, the reader is able to interpret the results in context. With regard to editor COI, this could also be publicly available on journal websites for readers to easily find and assess for themselves. Additionally, more effort can be made to improve the methodology of studies submitted. Requiring demonstration of methods to reduce the effects of bias to publish in neurosurgical journals could help improve trust with readership and prevent misrepresentation of research, especially for studies receiving industry funding.[15] Trials published in the neurosurgical literature could aim to compare, as much as possible, innovative devices and

procedures to the standard of care, and would ideally be designed by committed investigators without a financial stake in the results. Because of the small numbers of patients seen in neurosurgical practice and the autonomous nature of surgery, anonymous reporting of adverse events and long-term outcomes could add value so data can be pooled from multiple institutions and re-evaluated to further assess quality of innovation. This can be accomplished effectively by using national registries to track long-term outcomes, or maintaining institutional datasets over time. Maintaining the quality of the published literature and allowing the reviewer and reader to understand the study in the context of COI will give him or her the opportunity to judge the quality of the methods and generalizability of results. This will allow for improved safety in the application of the literature to clinical practice, and will improve the integrity of the literature.

Nevertheless, the effects of COI spread into less regulated and rigorous forms of written communication, including social media and the "grey literature". It is important to recognize that disclosure is not the standard in these forms of communication, Given the presence of these and their influence on both providers and patients, it is increasingly important to critically evaluate the information we receive, and inform patients with what they need to make decisions. This will improve the quality of care provided.

Conclusion

Conflicts of interest that affect clinical practice are inevitable in the present day. Neurosurgeon involvement in innovation is valuable for the advancement of the field. Awareness of COI and reporting does not necessarily change practice, so all stages of neurosurgical innovation could benefit from regulatory oversight to maintain ethical, patient-centered, evidence-based practice. Regardless of the level of policy or institution, constant discussion and evaluation of policy is important to ensure that practice remains ethically sound and prevent both financial and non-financial COI from adversely affecting patients. Taking steps proactively and ensuring that practice is done ethically can prevent controversies, maintain public trust, and ultimately improve the quality of neurosurgical research and innovation.

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