Neuron
NeuroView

Device Removal Following Brain Implant Research

Demetrio Sierra-Mercado,[1,2,7] Peter Zuk,[2,3,7] Michael S. Beauchamp,[4,5] Sameer A. Sheth,[4] Daniel Yoshor,[4] Wayne K. Goodman,[6] Amy L. McGuire,[2] and Gabriel Lázaro-Muñoz[2,*]
[1]Department of Anatomy & Neurobiology, University of Puerto Rico, School of Medicine, San Juan, PR
[2]Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, TX, USA
[3]Department of Philosophy, Rice University, Houston, TX, USA
[4]Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA
[5]Core for Advanced MRI, Baylor College of Medicine, Houston, TX, USA
[6]Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA
[7]These authors contributed equally
*Correspondence: glazaro@bcm.edu
https://doi.org/10.1016/j.neuron.2019.08.024

The development of implanted neural devices to manage neurological and psychiatric disorders or to restore loss of physiological function is a rapidly advancing area of neuroscience research. We consider whether investigators of brain implant studies have an obligation to facilitate device explantation for participants who request it at study conclusion.

Research examining brain implants aimed at managing treatment-resistant medical conditions or restoring physiological function is increasingly common. At the conclusion of such studies, questions arise about management of the implanted device. One option is continued access to device functionality and maintenance for individuals who benefit from the intervention (Lázaro-Muñoz et al., 2018). But what if participants do not benefit from an investigational brain implant? There are generally two options: leave the device implanted but inactive or remove the device (explantation). Here, we examine whether investigators of brain implant studies have an obligation to offer and cover the cost of device removal.

While device removal is usually offered at the end of brain implant studies, clinical trials of deep brain stimulation (DBS) and adaptive DBS (aDBS), for example, generally do not offer to cover the cost (Lázaro-Muñoz et al., 2018). If a study participant requests device removal at study conclusion, researchers will typically contact the participant's public or private health insurance, if any, to assess whether insurance will cover the cost. Insurance programs generally have no legal obligation to cover device removal unless it is deemed medically necessary for physical reasons (e.g., infection, allergies, device component breakage). Even in cases in which removal is medically necessary, participants may still be required to pay a high deductible for the procedure. Notably, reasons for removal such as psychological distress and strong individual preference are not typically considered medically necessary. Thus, at the moment, some participants could be required to bear the financial cost of explantation themselves—for example, approximately $11,500 for DBS device explantation (Chen et al., 2017).

Do researchers have an ethical responsibility to alleviate this burden? If so, what are the particular contents and limits of this obligation? We first summarize the legal backdrop against which these questions arise. We then consider potential sources of ethical obligation to cover the cost of device removal. The results of this analysis are important for stakeholders such as public and private research sponsors, researchers, research hospitals, device manufacturers, insurance providers, institutional review boards (IRBs), current and future research participants, neuroethicists, and policymakers as they collaboratively develop and implement ethically justified post-trial management plans for brain implant research.

Legal and Policy Background

In the United States, most federally funded research must comply with the Common Rule (United States Department of Health and Human Services, 2016, 45 CFR 46), which tasks IRBs with making determinations about risks and benefits of research protocols. IRBs typically do not require researchers or sponsors to cover the cost of removing investigational devices, and we are not aware of any legal cases that have addressed the issue. International ethics guidelines, such as those of the Council for International Organizations of Medical Sciences and the World Health Organization (Council for International Organizations of Medical Sciences and the World Health Organization (CIOMS/WHO), 2016), affirm that researchers and other relevant stakeholders should, when possible, make post-study provisions for patients who benefit from research. But such declarations do not address the unique circumstances presented by brain implant research, such as potential removal of a study device from the participant's body when the research provides no benefit. Furthermore, even though such documents may influence legislation regarding some areas of medical research, they are not themselves legally binding. Thus, there are no clear legal requirements in the United States for researchers or sponsors to cover the cost of device removal.

Similarly, there are no clear requirements set by funding agencies in the United States as to who must pay for device removal. While the National Institutes of Health (NIH) does not impose specific obligations on researchers regarding device removal, the NIH BRAIN Initiative grant application guidelines for this type of research require that researchers include a plan that addresses neuroethical considerations such as "ethical and practical considerations of invasive device maintenance and ultimate

removal'' (RFA-NS-19-001). These guidelines also require a long-term ''plan for the care of patients at the end of the study and after the study period, if appropriate'' and include examples such as ''explant of indwelling devices once the approved study period is complete'' and ''surgical removal of batteries'' (RFA-NS-19-001, RFA-NS-18-021, RFA-NS-18-023). However, this only establishes a requirement to provide a plan of some kind. Thus, there is currently not an obligation established by funding agencies such as NIH to offer and cover the expense of removing the devices implanted for study purposes. But is there an *ethical* obligation to do so?

Ethical Considerations

While there is no clear legal requirement to pay for the cost of device removal, there may be an ethical obligation to do so. According to the *partial-entrustment model* of researchers' obligations to their study participants, the discretion that participants give researchers over important aspects of their health and the vulnerability that this generates creates a ''limited duty of care'' that obliges researchers to appropriate acts of compassion, engagement, and gratitude beyond what is required to complete research objectives (Richardson and Belsky, 2004). The specific contents and scope of these obligations depend upon the particular research context, especially the burden that the study protocol places on participants, their vulnerability, and the feasibility of care that goes beyond that necessary to achieve the scientific goals of the study.

Compassion

Compassion entails ''being attentive and reasonably responsive to an individual's needs and perspectives'' (Richardson and Belsky, 2004). From the perspective of brain implant research participants, there may be a variety of reasons that device removal rises to the level of a need. These may include: (1) a strong preference to have the device removed from one's body, (2) psychological distress associated with the continued presence of the implanted device, (3) ability to undergo magnetic resonance imaging (MRI) (which is contraindicated for some implanted devices), or (4) a preference to avoid the risk of injury, allergy, or infection associated with having a foreign object implanted in one's body. Researchers should be attentive and responsive to these perspectives and the needs they affirm, particularly because most participants will not have the resources to finance device removal on their own and no participant can remove the device without highly specialized medical intervention. In addition, participants arguably have a right of self-determination to refuse the continued presence of an invasive device in their bodies. This, in turn, creates a corresponding obligation on behalf of the researchers who placed the device. Thus, when feasible, acting with compassion in this context involves facilitating device removal.

Engagement

Researchers recruit individuals for brain implant studies with the main goal of collecting data to generate generalizable knowledge. Richardson and Belsky argue that researchers should consider how their skills and discoveries could benefit the patient even beyond the scope of the research endeavor (Richardson and Belsky, 2004). This approach would ensure that researchers engage study participants as whole people and not solely as sources of research data (Richardson and Belsky, 2004; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Engagement therefore involves taking up an attitude of *respect for persons*. If, once data are collected, a participant is left on their own to work out how to cover the cost of removing the device, this arguably disrespects the participant by treating them as only a means to the end of obtaining data—especially when it is predictable that most will not be able to cover these costs.

In invasive neuromodulation research, respect for persons implies a duty of non-abandonment (Fins, 2009) and therefore a recognition both of the participant's preference for removal and of the researcher being well positioned to assist in returning the participant, to the extent that it is possible, to their preferred pre-trial state. That the researcher is so positioned, together with the fact that the continued presence of the device is a direct consequence of the research, supports an obligation to facilitate device removal.

Gratitude

Brain implant research places significant burdens on participants who undergo neurosurgery and also generally participate in lengthy sessions in which researchers gather experimental data and data related to the device's effectiveness and safety. Fulfilling obligations of gratitude ideally takes the form of reciprocity. For participants who respond to the intervention and wish to continue it beyond the course of the study, this may require facilitating continued access to device functionality and maintenance to reciprocate participants' efforts and bearing of the burdens placed on them by the research protocol (Lázaro-Muñoz et al., 2018). But how might the idea of reciprocity apply in the case of device removal?

An important principle concerning reciprocity is the *principle of fairness* (Hart, 1955; Rawls, 1971; Klosko, 1992). Rawls encapsulates the principle as follows: ''We are not to gain from the cooperative labors of others without doing our fair share'' (Rawls, 1971). In other words, those who share in the benefits of a cooperative schema should share in the burdens. An essential corollary of this idea is that those who share in the burdens should share in the benefits. Sometimes, however, this corollary principle cannot be fulfilled, such as when an individual (e.g., a DBS study participant) shares in the burdens but is unable to share in the benefits (because she is a non-responder to the intervention). In situations like these, we need a revised principle: that those who share in the burdens *without* benefit should, when feasible, be relieved of *further* burden.

This revised principle supports a researcher's obligation to facilitate post-study device removal because removal often constitutes relief of a burden to the participant. Relative to a participant's pre-study state, device removal is not a positive benefit but instead a restoration of the pre-intervention circumstance. In the case of device removal, reciprocity therefore consists in (1) recognizing that participants have born the burdens of study involvement and (2) the taking on by researchers of the burden of facilitating device removal in order to relieve participants of the further burden of living with an unwanted device.

The plausibility of an obligation to relieve participants of this burden is again strengthened by the fact that the presence of the device is a direct consequence of study participation. This marks an important difference between brain implant trials and other forms of medical research. In the case of drug trials, for example, use of the drug can be discontinued at the conclusion of the research, ending the intervention. In clinical trials of brain implants, the end of the study may not constitute the end of the intervention due to the continued presence of the device in participants' bodies. The residual nature of such interventions places special obligations on researchers that are not present in many other forms of medical research.

Feasibility for Researchers

However, these arguments in favor of researcher obligations related to device removal cannot be considered in isolation from the feasibility of imposing additional burdens on the research enterprise. Researchers also have ethical obligations to other participants, to funding sponsors, and to the patient population that could one day benefit from this research. Therefore, researchers should not be obligated to cover costs related to device removal if it is incompatible with the sustainability of the research enterprise that initiates the relationship that grounds the obligation in the first place.

This may have different consequences for ongoing research projects than it does for ones yet to be initated. Due to pre-approved budget allocations, current projects may be limited in their ability to reassign resources to cover the costs or otherwise facilitate removal. Research institutions where these studies take place might consider covering the cost of removal, and funding agencies could offer supplemental funds. That said, while the estimated cost of, e.g., $11,500 for DBS removal is not trivial, it is likely that not many participants will want the device removed. There are those who benefit from the device and thus will likely want to continue the intervention, and there are those who will be satisfied with having the device remain implanted but inactive (i.e., turned off and, potentially, non-neural components removed).

Researchers seeking funding for new studies, on the other hand, can and should build these costs into their budgets. Public funding agencies, for their part, must go beyond requiring merely a long-term plan of some kind with device removal as an optional topic to consider. They should in fact require and provide funding for device removal for those participants who wish to have an investigational brain implant explanted and for whom explantation is a reasonable option from a safety standpoint. Agencies like the NIH possess the institutional power and financial means to make it feasible for researchers to facilitate device removal. Because such agencies have a responsibility to ensure that research they sponsor is conducted in a maximally ethical way, they arguably have a derivative obligation to provide researchers with the resources needed to fulfill those researchers' obligations. These considerations also apply to private research sponsors and device manufacturers, who likewise have an obligation to ensure ethical conduct of research that they support or from which they benefit.

Conclusion

Clinical trials of neural implants offer hope to people with treatment-resistant conditions or loss of physiological function. In order for this research to move forward in a maximally responsible way, it is imperative that stakeholders, such as public and private research sponsors, researchers, research hospitals, device manufacturers, insurance providers, IRBs, current and future research participants, neuroethicists, and policymakers collaboratively develop and implement ethically justified post-trial management plans that address device removal. Research sponsors are likely in the best position to establish and financially back requirements for offering to cover the cost of device removal following brain implant trials, but this is an issue that all stakeholders should be involved in addressing.

ACKNOWLEDGMENTS

Research for this work was supported by a BRAIN Initiative grant from the US National Institute of Mental Health of the National Institutes of Health, Award Number R01MH114854 (G.L.-M., W.K.G., and A.L.M.), a Supplement on R01MH114854, and by the Brain & Behavior Research Foundation (NARSAD) to D.S.-M. The views expressed are those of the authors alone and do not necessarily reflect views of the NIH, NARSAD, Baylor College of Medicine, Rice University, or the University of Puerto Rico.

DECLARATION OF INTERESTS

D.Y. is an investigator in a clinical trial for a visual cortical prosthesis for Second Sight Medical Products (Sylmar, CA); W.K.G. has consulting agreements with Biohaven Pharmaceuticals and Neurocrine Biosciences; Medtronic Inc. has donated devices to an NIH-funded study led by W.K.G.; S.A.S. has consulting agreements with Koh Young and Medtronic; D.S.-M., P.Z., M.S.B., A.L.M., and G.L.-M. declare no competing interests.

REFERENCES

Chen, T., Mirzadeh, Z., Lambert, M., Gonzalez, O., Moran, A., Shetter, A.G., and Ponce, F.A. (2017). Cost of deep brain stimulation infection resulting in explantation. Stereotact. Funct. Neurosurg. *95*, 117–124.

Council for International Organizations of Medical Sciences and the World Health Organization (CIOMS/WHO) (2016). International ethical guidelines for health-related research involving humans, 4th ed., Available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

Fins, J.J. (2009). Deep brain stimulation, deontology and duty: the moral obligation of non-abandonment at the neural interface. J. Neural Eng. *6*, 050201.

Hart, H.L.A. (1955). Are there any natural rights? Philos. Rev. *64*, 175–191.

Klosko, G. (1992). The Principle of Fairness and Political Obligation (Rowman & Littlefield).

Lázaro-Muñoz, G., Yoshor, D., Beauchamp, M.S., Goodman, W.K., and McGuire, A.L. (2018). Continued access to investigational brain implants. Nat. Rev. Neurosci. *19*, 317–318.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979). The Belmont Report, Available at. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html.

Rawls, J. (1971). A Theory of Justice (Harvard University Press).

Richardson, H.S., and Belsky, L. (2004). The ancillary-care responsibilities of medical researchers. An ethical framework for thinking about the clinical care that researchers owe their subjects. Hastings Cent. Rep. *34*, 25–33.

United States Department of Health and Human Services (2016). 45 CFR 46, Available at. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html.