Continued access to investigational brain implants

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Brain implants are being trialled for their potential to ameliorate treatment-resistant conditions or to restore function. However, there are no clear guidelines for continued access to brain implants for trial participants whose symptoms improve with these devices.

Public and private research sponsors are investing in the development of next-generation deep brain stimulation (DBS) systems, brain–computer interfaces (BCIs) and neuroprosthetics. These devices aim to ameliorate serious treatment-resistant brain-related conditions or to restore function to individuals with disabling deficits. Often, participants in the trials of such technologies have suffered from their condition for many years and experienced several unsuccessful treatments. Device implantation exposes participants to the risks of neurosurgery and those associated with testing the device. Typically, much is done to protect against these risks. On the other hand, given the investigational nature of the device, the prospect of benefit for participants is far from assured. However, it remains unclear what happens at the end of the trial if a participant's symptoms improve with the investigational device.

In 2017, the 6 month, double-blind, sham-controlled BROADEN trial reported no statistically significant antidepressant effects of subcallosal cingulate DBS in treatment-resistant depression[1]. Only individuals who had unsuccessful trials of pharmacotherapy, psychotherapy and electroconvulsive therapy were eligible to participate. After the initial sham-controlled period, the sponsor stopped recruitment. However, enrolled participants continued in the trial; all received active stimulation for 6 months and 77 agreed to participate in a 4 year follow-up study. Thirty months after the start of the initial trial, the sponsor terminated the follow-up study. At that point, 47% of participants showed at least a 40% improvement in depression symptoms and 21% had achieved remission[1]. Some participants wanted to keep the device. However, the sponsor had agreed only to cover the cost of implant removal or a rechargeable battery[2]. Thus, participants who wanted to continue to benefit from the device had to rely mostly on personal funds and researchers' advocacy for donations to keep it functioning[2]. This is the norm, not the exception, in brain-implant trials. In fact, most sponsors do not cover the cost of device removal or a rechargeable battery.

Brain implant maintenance — including visits to clinical specialists, battery replacement, device repairs and treatment of infections and possible re-implantation after infection — involves serious costs. Even if a participant benefits, government and private health insurance plans often deny coverage for investigational brain implants[3]. Yet, maintaining a device is prohibitively costly for many, if not most, participants.

Continued access to investigational interventions has been discussed in the context of drug trials, such as those for HIV/AIDS medications in developing countries[4] (see the Council for International Organizations of Medical Sciences and World Health Organization (CIOMS/WHO) guidelines, and the US National Bioethics Advisory Commission (NBAC) report). However, even in that context, no clear guidelines have been adopted in the United States. Guidance is urgently needed as to whether, and under what circumstances, participants in brain-implant trials should receive continued access.

Ethical considerations

Unlike in clinical practice, there is no fiduciary relationship between researchers and study participants. However, some argue that when clinical researchers recruit participants, they enter into a partial-entrustment relationship that gives rise to a limited duty of care[5]. In brain-implant trials, consenting participants authorize researchers to conduct neurosurgery and collect extensive data. In exchange, per the theory of partial entrustment, researchers are obliged to provide ancillary care if, for example, something goes awry and a participant is harmed.

At least three moral obligations support a limited duty of care — that may include continued access — beyond the research protocol. First, the duty to act with compassion requires that researchers take reasonable steps to respond to participants in need. For participants with treatment-resistant disorders who do benefit, the investigational device is the only option that addresses their health needs. Second, although the primary goal of research is to generate generalizable knowledge, researchers should engage with participants as whole people and treat them with respect, not simply as a means to an end — a research ethics principle known

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as 'respect for persons' (see the Belmont Report). Once data are collected, leaving a participant alone to cover the costs of maintaining the device — even though most are predicted not to be able to cover these costs — arguably disrespects the participant by treating them merely as a source of data. Third, participants are increasingly considered partners in the research enterprise and arguably should receive more reciprocation for their participation, for example, in the form of return of results or continued access to beneficial experimental devices.

'Participants as partners' is one of the core values of the US National Institutes of Health (NIH)-All of Us Research Program, which aims to collect genomic, medical and lifestyle data from at least 1 million US participants. The Program involves potential participants in its Steering Committee, and offers participants access to individual results (see NIH-All of Us Participation and The Dish: Participants as Partners). Relatedly, the CIOMS/WHO guidelines explain how sponsors and researchers should consult with potential participants about plans and responsibilities for continued access. In brain-implant trials, sponsors and researchers stand to benefit from participants' data, which potentially translate into publications, grants, patents and profit. Therefore, sponsors and researchers arguably ought to reciprocate participants' contributions, by providing continued access to the device, if it provides benefit.

The strength of the moral obligation to provide care beyond the study protocol depends on several factors, including the vulnerability of participants and the potential impact on the ability to conduct the research. The more vulnerable and burdened the participant is, the higher the debt of gratitude or reciprocity. Participants in these trials undertake considerable risks and burdens, including: neurosurgery; extensive batteries of medical, psychological and cognitive tests; and many study visits. As few experts can adequately maintain these devices, participants are uniquely dependent on the researchers. If researchers and sponsors do not have the resources to provide continued access, or if providing continued access substantially impairs their capacity to continue their research for the benefit of the patient population, the strength of the obligation to provide continued access significantly weakens. Covering the costs of continued access for every participant who benefits may be too onerous and may seriously stifle development of these technologies. However, even if sponsors cannot cover the entire costs, they can take reasonable steps to anticipate and build in the costs of facilitating continued access into their funding proposals, to the extent it does not severely disrupt their research goals.

A path forward

Investigators and sponsors must develop a plan, in consultation with their institutional review boards (IRBs), for facilitating continued access, and must clearly communicate that plan to participants during the informed consent process.

Guidance is needed on how long this obligation extends. Determining a reasonable duration for which continued access should be facilitated will depend on many factors, including: the participant's health, available treatment alternatives, the development of novel treatments, costs and the commercial availability of the device. Sponsors and researchers, in consultation with IRBs, should determine the minimum duration for which continued access will be offered. Given there are few experts in this area, researchers should be reasonably available after the trial to provide care and programming. If clinicians show that the brain implant effectively manages an otherwise treatment-resistant condition, public and private health insurance should consider this intervention medically necessary and provide coverage, even before it obtains regulatory approval.

Finally, determining whether to provide continued access to a particular participant should involve a thorough risk–benefit analysis by the researchers, the participant and ideally an independent clinician representing the participant's interests. This analysis should consider the clinical benefit experienced by the participant and unknown risks, to the extent possible. The sponsor should be allowed to monitor the individual's response to the implant and to stop facilitating continued access if the brain implant ceases to manage symptoms.

Conclusions

Brain implants represent potential treatments for individuals who have endured serious, long-term, treatment-resistant illnesses or disabilities. Investment in and the development of these emerging technologies will be essential. However, for this research to be conducted responsibly, taking reasonable steps to facilitate continued access for participants who benefit from these technologies is an ethical imperative. Public sponsors and regulatory agencies, together with researchers and patients, should establish and enforce adequate guidelines that can be adopted by IRBs and, hopefully, by industry sponsors in the United States and internationally. It is the responsibility of all stakeholders — including sponsors, researchers, participants and policy makers — in brain-implant research to take action.

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Competing interests
The authors declare no competing interests.

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