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Ethical Challenges of Risk, Informed Consent, and Posttrial Responsibilities in Human Research With Neural Devices
A Review

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IMPORTANCE Developing more and better diagnostic and therapeutic tools for central nervous system disorders is an ethical imperative. Human research with neural devices is important to this effort and a critical focus of the National Institutes of Health Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Despite regulations and standard practices for conducting ethical research, researchers and others seek more guidance on how to ethically conduct neural device studies. This article draws on, reviews, specifies, and interprets existing ethical frameworks, literature, and subject matter expertise to address 3 specific ethical challenges in neural devices research: analysis of risk, informed consent, and posttrial responsibilities to research participants.

OBSERVATIONS Research with humans proceeds after careful assessment of the risks and benefits. In assessing whether risks are justified by potential benefits in both invasive and noninvasive neural device research, the following categories of potential risks should be considered: those related to surgery, hardware, stimulation, research itself, privacy and security, and financial burdens. All 3 of the standard pillars of informed consent—disclosure, capacity, and voluntariness—raise challenges in neural device research. Among these challenges are the need to plan for appropriate disclosure of information about atypical and emerging risks of neural devices, a structured evaluation of capacity when that is in doubt, and preventing patients from feeling unduly pressured to participate. Researchers and funders should anticipate participants' posttrial needs linked to study participation and take reasonable steps to facilitate continued access to neural devices that benefit participants. Possible mechanisms for doing so are explored here. Depending on the study, researchers and funders may have further posttrial responsibilities.

CONCLUSIONS AND RELEVANCE This ethical analysis and points to consider may assist researchers, institutional review boards, funders, and others engaged in human neural device research.

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Developing tools to alleviate the considerable burden of neurologic, neuropsychiatric, and substance use disorders (hereafter, central nervous system [CNS] disorders)[1-3] is an ethical imperative.[4-6] Human research is essential to the National Institutes of Health (NIH) Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative's quest to advance diagnostic and therapeutic approaches to these disorders.[7] This research frequently involves new or expanded use of invasive and noninvasive neural devices, raising important ethical challenges.

Many ethical issues in human neural device research are encountered in other clinical research, especially device research.[8] Even so, existing ethical frameworks often need to be applied to the specific context of neural device research and appropriately interpreted; additional guidance may be necessary.[5] Despite existing literature addressing the ethics of neural device research, especially deep brain stimulation (DBS),[9-11] further discussion and guidance on various ethics challenges is needed.[5] Considering these ethical challenges is also timely, as human studies will likely increase with advances in neuroscience. The NIH BRAIN Initiative Neuroethics Working Group thus prioritized this area for consideration; this article is the result of a subsequent NIH workshop. Although recognizing many ethical challenges in human neural device research, analysis of risk, informed consent, and posttrial responsibilities to research participants were the challenges that were considered to be critical. This article provides ethical analysis and key points to consider for researchers, institutional review boards (IRBs), funders, and others engaged in human neural device research, particularly regarding neuromodulation devices.

The State of the Science

Various invasive and noninvasive devices that record and/or modulate CNS function are under investigation. These devices may present an important adjunct or alternative treatment for CNS disorders, especially when pharmacotherapy has limited efficacy or intolerable adverse effects. Neural device research also can advance knowledge about the CNS.

Invasive neural devices require an incision or insertion to place or implant the device in a person; for example, under the skull, below the dura, or within the brain. The most established invasive modality is DBS, a programmable and adjustable implant of electrodes into specific deep brain structures that delivers electrical impulses to alter circuit function and overcome abnormal activity.[12] The US Food and Drug Administration (FDA) has approved DBS for treating Parkinson disease, essential tremor, and medically refractory epilepsy, and granted humanitarian device exemptions for drug-refractory dystonia and obsessive-compulsive disorder. Deep brain stimulation is being investigated for other disorders not adequately controlled by pharmacologic therapy, including major depression,[13] chronic pain,[14] Alzheimer disease,[15] obesity,[16] addiction,[17] and traumatic brain injury.[18]

Researchers are investigating closed-loop brain stimulation systems, in which additional recording strips are placed, usually over the cortical surface, and brain activity measures are informing the stimulation parameters. Closed-loop systems incorporate feedback between input and output signals to effectively exert control over the targeted neural circuit.[19] Closed-loop systems "seamlessly" adjust to symptoms, but raise ethical questions such as who has control of the device.[20] Responsive neurostimulation, a closed-loop intracranial stimulation system, has been approved for treatment-refractory epilepsy.[21]

Beyond DBS, brain-computer interfaces decode motor intentions from cortical signals in patients with tetraplegia, enabling user-driven control of assistive devices such as computers and robotic prostheses.[22] Electrical stimulation of the spinal cord and muscles is used in individuals with spinal cord injury to retrain motor circuits and improve residual capabilities.[22]

Noninvasive neuromodulation involves the external application of magnetic, electrical, or sonic stimulation to modulate CNS function. For example, the FDA has cleared electroconvulsive therapy[23] and repetitive transcranial magnetic stimulation[24] for depression. Researchers are testing new indications for transcranial magnetic stimulation, as well as transcranial direct current stimulation, magnetic seizure therapy, and other modalities. Optimal dosing, spatial and temporal targeting, and mechanisms of action are being studied, even for approved indications. Techniques such as transcranial magnetic stimulation can be concurrently or consecutively combined with neuroimaging and electrophysiological techniques to assess effects and optimize subsequent stimulation.[25] Further research will improve insights into mechanisms of different noninvasive devices, dose-response associations, and methods for ensuring safety and efficacy. Finally, along with regulatory and oversight frameworks, future research could help elucidate the safety and/or effectiveness of nonmedical uses of noninvasive neuromodulation devices (eg, attention enhancement). For example, transcranial direct current stimulation is already sold directly to consumers for nonmedical uses.[26]

Analysis of Risk

Sources of Risks

Most research with invasive or noninvasive[27] neural devices entails some risk. Determining the type and extent of risk is fundamental to evaluating the ethics of neural device studies, to protect research participants from unnecessary harm, inform risk-benefit evaluations by IRBs, and enable informed consent.[28,29] Human neural device research poses risk from at least 6 sources, during and possibly after the trial. Although some risks are similar to those from devices implanted elsewhere in the body, other risks take on special meaning to research participants because of the brain's centrality to, for example, mental states and identity. **Box 1** summarizes the main points to consider regarding the analysis of risk.

First, surgery for implanting or replacing invasive neural devices poses risks such as intracranial hemorrhage, stroke, infection, and seizures.[30,31] General perioperative complications are uncommon but can be severe, such as deep vein thrombosis, pulmonary embolism, or adverse effects of anesthesia.

Second, implanted device hardware poses risks, including infection, malfunction, erosion, and migration or fracture of leads, which may require additional surgery or explantation.[30-32] In addition, devices can fail, resulting in risks associated with sudden treatment termination and/or another surgery. Implanted devices may be contraindicated for some magnetic resonance imaging[30] or cardiac pacemakers.[33]

Box 1. Points to Consider in the Analysis of Risk in Neural Device Research

1. Evaluating and minimizing risks in each proposed study is fundamental to the ethics of research.
2. Researchers should anticipate and describe the degree and types of expected risks for each study based on available evidence, while recognizing uncertainties.
3. Clinical research with neural devices poses risks from at least 6 sources: risks related to surgery, hardware, stimulation, the research itself, privacy and security, and financial burdens.
4. Although research with invasive devices entails risks (eg, surgical) that research with noninvasive devices does not, most sources of risk are relevant for both invasive and noninvasive devices. Invasiveness itself is not a sufficient parameter for determining risk.
5. Evaluating possible changes to personality or behavior may be challenging, as these could be experienced as harmful or beneficial or be an explicit goal of treatment.
6. Research risks should be justified by the potential benefit to the participant and/or the importance of the knowledge expected to be gained.
7. Acceptable levels of research risk are generally higher for studies that offer possible therapeutic benefit for participants.

Third, stimulation can cause adverse effects. For example, headaches and, rarely, seizures are associated with transcranial magnetic stimulation,[34] and speech disturbances, paresthesias, and affective function disruptions are associated with DBS.[35] Adverse effects depend on the level and loci of stimulation and can often be alleviated by adjusting the settings (sometimes involving compromises between adverse effects and benefits).[27,32] Stimulation-induced adverse effects can occur if electrode placement in implanted devices or coil orientation in noninvasive devices is suboptimal.[32,36] Some studies report DBS effects on cognition (eg, word-finding difficulties), and also atypical risks such as effects on personality, mood, behavior, and perceptions of identity, authenticity, privacy, and agency.[20,32,37] In rare cases, these effects were long term and possibly irreversible.[32] Such atypical risks are poorly understood, variable, and unpredictable. Effects on personality and behavior may be intended or unintended, and beneficial for some individuals and harmful to others.[20] Furthermore, patients may evaluate these effects differently than their family or caregivers. Further research should assess the likelihood of personality or behavior changes, characterize when changes are problematic, and weigh these risks against possible therapeutic benefits.

Fourth, research may involve incremental risks, including risks from procedures performed strictly for research purposes (eg, extending clinically indicated surgery to perform intracranial recordings for research), as well as emerging or unanticipated risks. Furthermore, research may entail an uncertain likelihood of benefit and possible loss of obtained or perceived benefits if the study is discontinued. Researchers should plan to monitor adverse effects during trials (including psychosocial adverse effects) and respond by taking appropriate measures. This monitoring is especially important for early device studies.

Fifth, neural device research often involves privacy and security risks. For example, analyzing aggregate brain data may disclose individual private information. Privacy risks may increase as more data are being recorded (especially continuous recording, which is possibly a future neural device feature) and technological capabilities for combining data increase, but exist even for post hoc analyses of clinically acquired data (eg, analyzing sleep physiology architecture from epilepsy implants). Investigators, IRBs, and funders should weigh the social and scientific value of data sharing against robust analyses of privacy risks. Furthermore, wireless devices and data transmission raise concerns about hacking.[38] Third-party hacking of a device may allow unauthorized data extraction or changing device settings, which could pose serious health risks.[38] Hacking could also occur with other implantable devices; the FDA has guidance on device cybersecurity.[39]

Sixth, neural device research may pose financial risks for participants both during and after a study. After participants complete or discontinue a study, they may be left with costs for device maintenance, continued access, or explantation. This financial burden can significantly affect patients and their families and/or could lead to health risks.

Each research protocol should be evaluated for these 6 sources of risk. Invasiveness by itself is not a sufficient parameter of risk. Although risks of surgery and implanted hardware are specific to invasive devices, both invasive and noninvasive devices have risks from other sources. Rather, in evaluating risks, parameters such as the degree and type of harm, the likelihood of harm, and irreversibility[40] should be assessed. In determining risk levels, IRBs should be as precise and consistent as possible. United States federal regulations define risk levels, such as minimal risk or nonsignificant risks; however, these definitions may not correspond to common uses of these terms.

Acceptability of Risks

For clinical research to be ethical, potential risks to research participants are minimized and potential benefits to participants and society are proportionate to, or outweigh, the risks.[28,41] These requirements are grounded in the ethical values of beneficence, nonmaleficence, and nonexploitation.[28] Acceptable levels of risk are generally higher for studies with possible therapeutic benefits for participants.

The limits of acceptable risk in research with a prospect of benefit to participants are dependent on context. More protection is appropriate for certain device characteristics (eg, permanence) or for certain vulnerable groups (eg, adults with impaired capacity to consent). Protecting vulnerable groups by exclusion, however, may deprive them of the benefits of research and expose them to additional risks if interventions are later used without adequate data.

Further conceptual and empirical research could clarify acceptable levels of risk in studies without a prospect of therapeutic benefit. For example, because of surgical risks, intracranial recordings and/or stimulation for research without prospect of benefit are performed only in patients with clinical indications for neurosurgery.[42] However, little agreement exists on how much prolongation of surgery to collect brain activity data, or insertion of research components in addition to standard of care devices, is acceptable; little agreement also exists on acceptable risks associated with sham surgery or devices as control interventions.[6,43] An example of research with no or unknown prospect of direct health benefits, but possible social value, is research on neural devices for nonmedical purposes (eg, attention enhancement). Addressing concerns

about the safety and effectiveness of current do-it-yourself use is important because it may involve more frequent sessions than have been studied, a lack of screening to identify individuals at heightened risk of complications, and uncertainties about regulatory oversight.[26,44,45]

Regulations and oversight structures aim to protect research participants.[46] Institutional review boards should consistently apply appropriate safeguards as additional protections for certain populations and should consistently apply limits to research without therapeutic benefit in neural device research. The FDA regulates medical devices but most class I devices (low risk) are exempt from needing an application.[47] Furthermore, FDA oversight is not required for devices used in basic physiological research when a future marketing submission or treating a disease is not intended,[47] although other oversight structures may apply.

Informed Consent

Informed consent is an important part of human participants' protections, grounded in the ethical value of respect for persons.[28,29] However, practical and theoretical challenges persist in obtaining informed consent for clinical research, and some challenges are exacerbated in neural device research. Because neural device research affects the brain in predictable and unpredictable ways, facilitating informed consent by considering participants' values, interests, and preferences[28] may be especially important. Referring physicians may help patients explore how trial participation might align with their values. **Box 2** summarizes the main points to consider regarding informed consent.

The informed consent process entails disclosure of relevant information to a decisionally capable person who makes a voluntary decision to enroll.[48,49] All 3 pillars of consent—disclosure, capacity, and voluntariness—raise challenges in neural device research.

Box 2. Points to Consider in Obtaining Informed Consent for Neural Device Research

1. Informed consent is an important way to protect human participants.
2. Obtaining informed consent entails disclosure of relevant information to a decisionally capable person who makes a voluntary decision to enroll in the study.
3. Participants should be informed about risks and benefits, alternatives, which interventions and add-on procedures are purely for research, which interventions are experimental, and plans for device failure or long-term support (eg, device maintenance).
4. Neural device research may involve atypical (eg, personality changes) and possible emerging risks, about which it may be challenging to decide what information to disclose and how to disclose it.
5. Some patients will not have the capacity to consent. In case of doubt, researchers should plan for assessing consent capacity, which involves structurally evaluating the patient's understanding, appreciation, reasoning, and choice about participation.
6. Depending on the nature of the study, federal regulations, state regulations, and institutional policies may allow a legally authorized representative to make research decisions for those without decision-making capacity.
7. Other patients may have capacity to consent but an impaired ability to communicate, for which researchers should optimize supports for consent or assent (eg, using augmentative and alternative communication tools).
8. Participants should understand that participation is voluntary. Researchers should be sensitive to concerns about potential pressures on patients due to a lack of alternative therapies or prior relationships with clinicians-investigators.

Disclosure

Federal regulations require disclosure of research procedures and interventions, reasonably foreseeable risks and benefits, alternatives, that participation is voluntary, and more.[41] For neural device research, relevant risks from the 6 sources identified above should be disclosed. Participants should also be informed about procedures that are purely for research, whether the procedures or interventions are experimental, the incremental nature of science, and plans for posttrial care (eg, device maintenance or explantation).

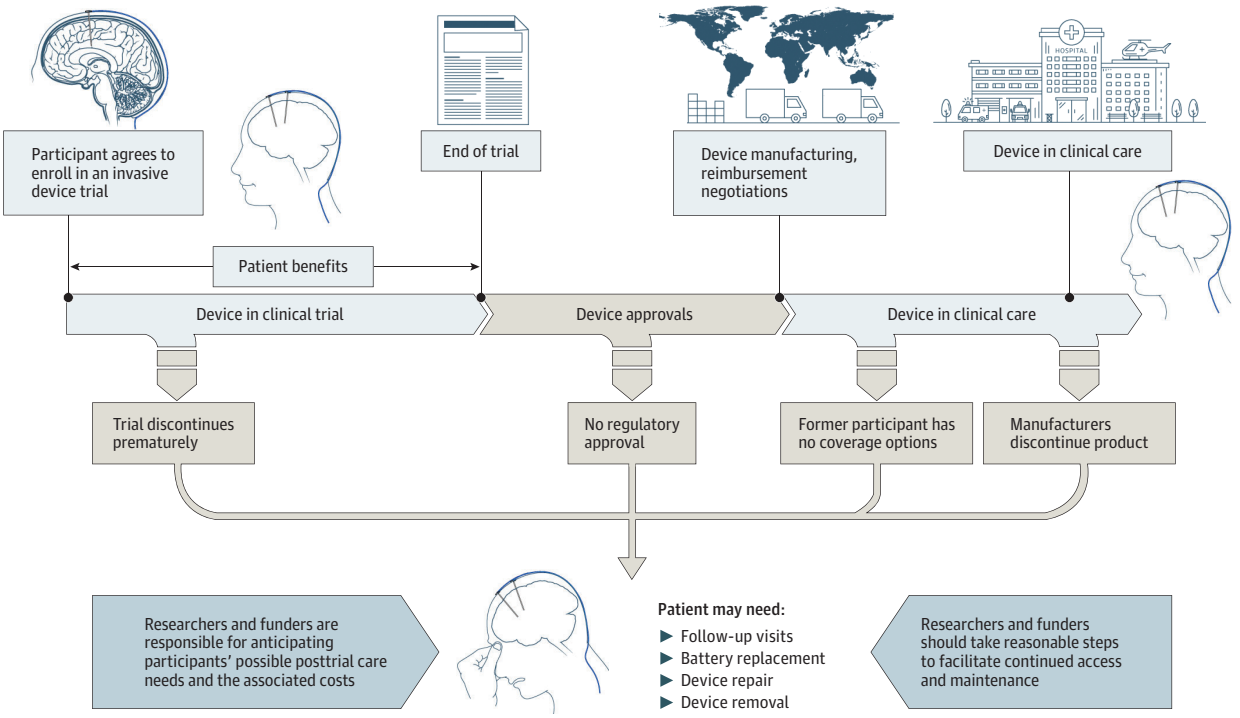
Decisions should be made about how to disclose any "reasonably foreseeable" emerging or atypical risks associated with a neural device (eg, changes in personality). Disclosing atypical risks is complicated by diverse individual preferences and value systems, which may affect what information participants wish to receive and how participants or their families might perceive certain changes. For example, some participants may perceive neural stimulation as enhancing their sense of empowerment and authenticity, while others may perceive it as undermining their level of control or authenticity.[20,50] Furthermore, researchers may draw on experience from disclosing similar types of adverse effects from neuropharmacologic therapies (eg, dopamine agonists leading to impulsive behaviors such as pathological gambling[51]). Decisions about disclosing emerging risks (ie, adverse events where the details or relevance are still unclear; for example, events reported in a single case or small number of somewhat different cases) may also be challenging. A multidisciplinary team may be helpful in navigating these challenges.

Communicating information effectively to research participants may be difficult, as study information may be complex and some brain disorders impair cognition.[42] Furthermore, research participants may have difficulties distinguishing between the imperatives of clinical research and standard clinical care, or not recognize purely research procedures (ie, therapeutic misconception).[52,53] This possibility is of particular concern when research procedures are coupled with clinical procedures and/or when risk to benefit ratios are unfavorable. Depending on the patient and study profile, more elaborate consent procedures than a one-off and one-to-one model,[6] as well as testing comprehension of risks and benefits, may be appropriate.[11]

Capacity

Another informed consent challenge for neural device research arises from the link between various brain disorders and impairments in making or communicating decisions.[6] Capacity to consent is usually presumed in adults, but when investigators or clinicians are unsure about a participant's capacity, more formally assessing decisional capacity can be important. Capacity assessments are decision specific and evaluate patients' understanding, appreciation, reasoning, and choice about participation in a proposed research

Figure 1. Potential Paths for Neural Devices and Implications for Posttrial Access and Maintenance



The blue timeline shows the neural device developmental path; brown indicates scenarios in which trial participants may have posttrial needs. The dark blue boxes include recommendations for researchers and funders.

study.[54] Capacity assessment should use a systematic approach that corresponds to the legal and ethical concepts of informed consent and capacity. Some evidence-based capacity assessment tools have been developed, such as the MacArthur Competence Assessment Tool for Clinical Research.[54] In some studies, a legally authorized representative, as determined by US federal and state regulations as well as IRB guidance, may make research decisions for those without decision-making capacity.[55]

Patients with communication impairments (eg, expressive aphasia or locked-in syndrome) may have decisional capacity but require special supportive measures to express their preferences. In these cases, researchers should optimize supports for consent or assent, by using augmentative and alternative communication tools (eg, written communication or using pictures). Experimental brain-computer interfaces may allow artificial speech synthesis from continuous decoding of neural signals underlying covert (or imagined) speech; however, establishing reliability is required before use of such tools in medical decision-making.[56,57]

Voluntariness

Researchers should ensure that patients know that declining research participation will not jeopardize their clinical care. Effective treatment options are limited for many CNS disorders. Some disagreement remains about whether having no therapeutic options or offering certain incentives (eg, secondary benefits) influences the voluntariness of research enrollment decisions.[58,59] Further conceptual and empirical research could elucidate constraints on voluntariness.

An ongoing debate in research ethics is who should obtain informed consent, as clinicians, researchers, and study coordinators each have pros and cons.[60] The dual role of clinician-researcher is particularly complex for neurosurgeons in research with invasive devices.[42] Patients may feel unable to say no to neurosurgeons with whom they already have a clinical relationship, yet neurosurgeons may understand the study details best.[42] In the absence of empirical data and specific guidance supporting who should obtain consent, IRBs and researchers trade off these considerations differently. Best practices from other fields may be helpful. For example, when clinician-researchers with dual roles obtain informed consent in pediatrics, offering parents the opportunity to discuss the study with another person is recommended.[60] A similar team approach has been suggested for invasive neural devices.[6,42]

Posttrial Responsibilities

Researchers, device manufacturers, and funders have responsibilities to anticipate and plan for participants' posttrial needs linked to trial participation (**Figure 1**).[10,61,62] The researcher-participant relationship creates a limited responsibility to provide care beyond what the study's scientific validity and safety requires.[63] In addition, avoiding exploitation of research participants, promoting participant welfare and minimizing harm, and respecting participants as persons (not just as means) support posttrial responsibilities.[61,64,65] Many patients receiving DBS expect researchers to provide posttrial medical care, expertise, and equipment (batteries).[20] Engineers and basic

scientists consider appropriate posttrial access important in brain-computer interface research.[66] However, budgets for invasive device trials frequently do not cover the costs of, for example, device removal or replacing a depleted battery.[61] Some funders currently have no mechanisms for supporting posttrial care. Furthermore, health insurance plans deny coverage for investigational implants,[67] requiring participants who benefit from investigational devices to rely on personal funds and researchers' advocacy for donations.[61] No definitive ethical or regulatory frameworks, or even standard practices, exist regarding posttrial responsibilities in neural device research.[61] **Box 3** summarizes the main points to consider regarding posttrial responsibilities.

Ethical frameworks only recently have addressed researchers' and funders' posttrial responsibilities. The 2000 version of the Declaration of Helsinki first introduced a responsibility to assure posttrial access to investigational agents for participants.[68] Its subsequent revisions and other influential guidelines call for consideration and planning for posttrial access.[64,69-71] Beyond facilitating ongoing access to a drug or device, researcher and funder posttrial responsibilities may include sharing data, providing clinical care, device maintenance, and even long-term surveillance of risks and cost-effectiveness. These responsibilities are complex and not fully resolved.[65] For example, should participants in control groups receive access to the investigated therapy? Furthermore, most existing guidance focuses on drugs while acknowledging that devices pose additional, unresolved challenges.[70] The extent and locus of posttrial responsibilities is currently determined on a case-by-case basis. More guidance, including guidance specific to neural devices, is needed.[61] Most agree that posttrial responsibilities are limited, shared among stakeholders, and should be determined before the trial starts (if possible).[64,70]

Box 3. Points to Consider for Posttrial Responsibilities in Neural Device Research

1. Researchers and funders should anticipate and make plans for participants' posttrial needs linked to study participation, including device access and maintenance.
2. In this process, researchers and funders should consider various posttrial scenarios, such as device and trial failure or success, regulatory approval options, and decisions by device manufacturers to commercialize or discontinue a product.
3. Further reasonable steps should be taken to facilitate continued access to neural devices when participants are benefitting.
4. The extent of the responsibility of researchers and funders to provide or arrange for posttrial access and care is determined on a case-by-case basis and likely to be more extensive for invasive devices.
5. Researchers should inform institutional review boards and potential participants of the potential need, risks, complexities, and costs of posttrial care and whether and how maintenance and/or explantation will be provided.
6. Specific attention is warranted to safeguard access of participants with complex devices to experts with the required expertise, to safeguard access to compatible device parts and software, and to track long-term outcomes (through device registries).
7. Regulators, researchers, funders, and ethicists should continue efforts to clarify researcher and funder responsibilities for posttrial care in neural device research.

Determining the Extent of Posttrial Responsibilities

At a minimum, researchers and funders are responsible for anticipating possible posttrial care needs in neural device research, including its costs. Researchers and funders also should take reasonable steps to facilitate continued access to neural devices that are benefitting participants and may have further posttrial responsibilities as described above. Researchers and IRBs should explore available options for covering costs of continued access and device maintenance, such as inclusion in grant applications, planning ongoing studies, Medicare reimbursement for devices under Investigational Device Exemption, insurance company coverage, funder coverage for compassionate use, and others. Funders should consider options for insurance, financial contracts, or other mechanisms to support posttrial follow-up and device maintenance. Researchers should delineate viable options for posttrial device access, maintenance, and explantation, in the research protocol and in consent forms. Options for various scenarios, such as device and trial failure or success, regulatory approval options, and decisions by device manufacturers to commercialize or discontinue a product, should be considered.

Posttrial responsibilities may be greater when participants would benefit substantially from care, discontinuing care would pose substantial risks, participants are particularly vulnerable, and the financial and opportunity costs of providing care are low.[61,63-65] More guidance is needed on weighing opportunity costs (which may represent collective interests) compared with research participants' interests. Posttrial access and care may be important for noninvasive devices, but especially important for implanted devices that need long-term maintenance (eg, follow-up visits, battery replacement, and device repair) or removal. Lacking access to care may expose patients with implanted devices to risks.[72]

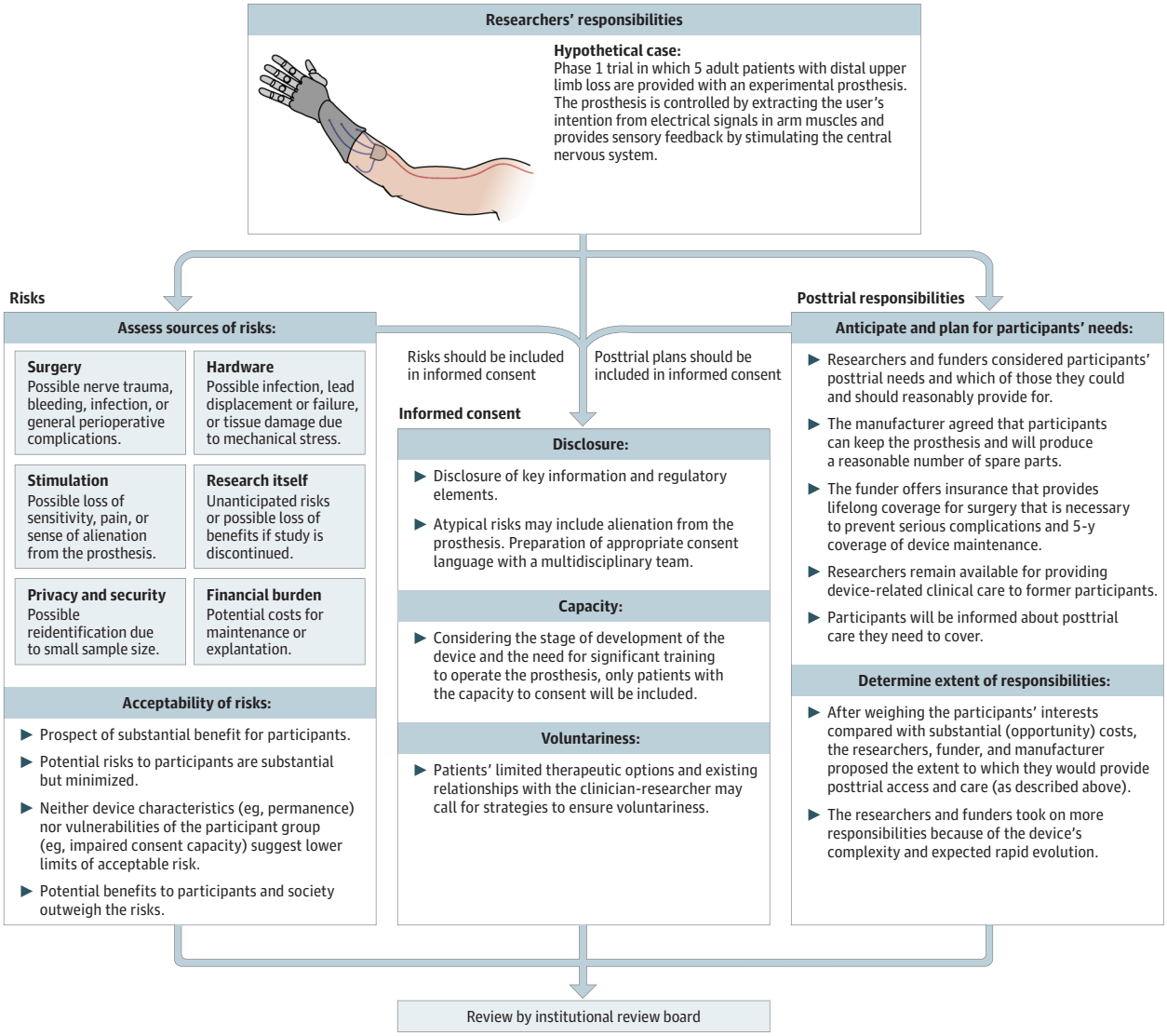
Posttrial care responsibilities for neural devices are amplified, as the brain holds special meaning to patients and atypical effects may occur (eg, personality changes).[32] Experience with other invasive devices suggests that neural devices' complexity, limited knowledge about their long-term effects, and expected rapid evolution are also sources of vulnerability for participants that warrant consideration and long-term planning.

Continued access and device maintenance is especially challenging when medical devices are complex[72] and participants need the research team's expertise, rather than their local health care professionals, to access care.[61,70] Neural devices often involve such complexity.

Ethicists called for long-term follow-up of safety, for example, using a registry, of human tissue-based products because of their potential irreversibility and unclear long-term effects.[73] Similarly, neural device registries and standardized outcome metrics should be established[6] to monitor and compare long-term adverse effects, rates of device maintenance and failure, costs, and other outcomes. Researchers, device manufacturers, funders, and health care institutions should share responsibility for creating and maintaining registries.

Neural devices will likely be continually improved over time, with early trials containing prototypes that are refined into newer models. Furthermore, neural devices (like many other devices and drugs), are subject to commercial interests, which may involve built-in obsolescence and proprietary hardware and software, effectively locking patients and clinicians into ongoing relationships with a manufacturer.[72] Similar to planning for pacemaker leads,[74,75] researchers, device manufacturers, and health care institutions should

Figure 2. Risk, Informed Consent, and Posttrial Responsibilities for a Hypothetical Case Involving a Hand Prosthesis



plan ahead to ensure that compatible replacement parts and software remain available for users with earlier neural device models and that clinicians are trained to use them.[72]

Conclusions

Developing new diagnostic and therapeutic tools for CNS disorders is an ethical imperative that requires conducting human neural device research. Such studies are only possible because research participants generously contribute. Conducting such research ethically is vital. This article provides points to consider for analysis of risk, informed consent, and posttrial responsibilities in human neural device research. **Figure 2** includes a hypothetical case to which some of these points to consider are applied. We encourage researchers, IRBs, and funders to continue to reflect on these, and other, ethical challenges in neural device research and to embrace neuroethics as a way to enhance rigorous science.

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