Clinical trials for implantable neural prostheses: understanding the ethical and technical requirements

Marcello Ienca, Giacomo Valle*, Stanisa Raspopovic**

Neuroprosthetics research has entered a stage in which animal models and proof-of-concept studies are translated into clinical applications, often combining implants with artificial intelligence techniques. This new phase raises the question of how clinical trials should be designed to scientifically and ethically address the unique features of neural prostheses. Neural prostheses are complex cyberbiological devices able to acquire and process data; hence, their assessment is not reducible to only third-party safety and efficacy evaluations as in pharmacological research. In addition, assessment of neural prostheses requires a causal understanding of their mechanisms, and scrutiny of their information security and legal liability standards. Some neural prostheses affect not only human behaviour, but also psychological faculties such as consciousness, cognition, and affective states. In this Viewpoint, we argue that the technological novelty of neural prostheses could generate challenges for technology assessment, clinical validation, and research ethics oversight. To this end, we identify a set of methodological and research ethics challenges specific to this medical technology innovation. We provide insights into relevant ethical guidelines and assess whether oversight mechanisms are well equipped to ensure adequate clinical and ethical use. Finally, we outline patient-centred research ethics requirements for clinical trials involving implantable neural prostheses.

Lancet Digit Health 2025; 7: e216–24

Published Online January 9, 2025 https://doi.org/10.1016/S2589-7500(24)00222-X

*Contributed equally

Laboratory of Ethics of Artificial Intelligence and Neuroscience, Institute for Ethics and History of Medicine, School of Medicine, Technische Universität München, Munich, Germany (M Ienca PhD); **College of Humanities, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland** (M Ienca); **Laboratory for Neuroengineering, Department of Health Science and Technology, Institute for Robotics and Intelligent Systems, ETH Zürich, Zürich, Switzerland** (G Valle PhD, Prof S Raspopovic PhD); **Department of Organismal Biology and Anatomy, University of Chicago, Chicago, IL, USA** (G Valle); **Department of Electrical Engineering, Chalmers University of Technology, Gothenburg, Sweden** (G Valle); **NeuroEngineering Laboratory, Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria** (Prof S Raspopovic)

Correspondence to: Prof Stanisa Raspopovic, NeuroEngineering Laboratory, Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, 1090 Vienna, Austria **stanisa.raspopovic@meduniwien.ac.at**

Introduction

In a recent clinical trial involving groundbreaking neuroprosthetic technology,[1] a paralysed individual received a brain implant that allowed him to access the internet and communicate directly with external technologies and environment (digital communication) through the implant (eg, typing and wheelchair and cursor control, etc), eliminating the need for the slow method of using a mouth stick. This implant improved his life substantially, enabling him to switch between websites and audiobooks easily, and even engage in conversations while playing chess. However, about a month after implantation, he noticed a decline in cursor control precision and delays between his thoughts and computer actions. This might have resulted from the electrodes losing their connection, disrupting the connection quality between his brain and the computer. This issue was partially counteracted by re-setting and improving the decoding algorithms. This case highlights the potential challenges in advancing neural prostheses technology.

Implantable neural prostheses encompass a spectrum of implantable systems that establish a functional connection between the human nervous system—either peripheral or central—and robotic or other digital technology.[2] Peripheral neural prostheses interact with the peripheral nervous system to control prosthetic limbs, diminish pain, or restore sensation by translating neural signals from residual muscles or nerves into electromechanical actions (nerve–machine interface).[3–9] Brain–machine interfaces connect with brain tissue directly, enabling the brain to interact bidirectionally with computers or other electronic devices.[10–15] Some neural prostheses focus primarily on translating neural signals into digital commands (eg, for the control of prosthetic devices), and others enable stimulation capabilities. These neural prostheses include clinically established neurostimulation systems, such as implants for spinal neuromodulation,[16] which have already been widely adopted for the treatment of chronic pain, and novel paradigms. Newer such stimulation devices to treat or restore sensorimotor functions include upper and lower limb neuroprostheses;[3–9] spinal cord-stimulating systems for walking, grasping, or blood pressure restoration after stroke or spinal cord injury;[17–20] or brain stimulation.[21]

Neural prostheses research is now entering a new phase in which animal models and proof-of-concept studies are increasingly being translated into clinical trials and, ultimately, into novel clinical applications, propelled by large international research collaborations and industrial interest. Clinical trials are ongoing to translate technological breakthroughs in human–machine systems[22] into the language of the nervous system and deliver electrical stimulation to the residual nerves,[3–9] spinal cord,[17–20] or brain[10,12–15] of individuals with neurological disabilities (figure 1). Companies such as Neuralink[24] and Blackrock Neurotech[25] are developing multiwire brain implants, and various neural prostheses are being produced by Inbrain Neuroelectronics,[26] Synchron,[27] Precision Neuroscience, Paradromincs, and CorTec Neuro. ONWARD Medical[17] is testing spinal interfacing for spinal cord rehabilitation after injury, and Iota BioScience,[28] Neuros Medical,[29] Neuronoff,[30] Galvani Bioelectronics[31] are implanting peripheral nervous system electrode devices into the somatosensory and autonomic nervous system to gain certifications for pain treatment, among other companies.

Companies developing clinical neural prostheses need to validate their products and are expected to adhere to responsible innovation paradigms such as the Organisation for Economic Co-operation and Development Recommendation on Responsible Innovation in Neurotechnology.[32] However, whether current clinical trial

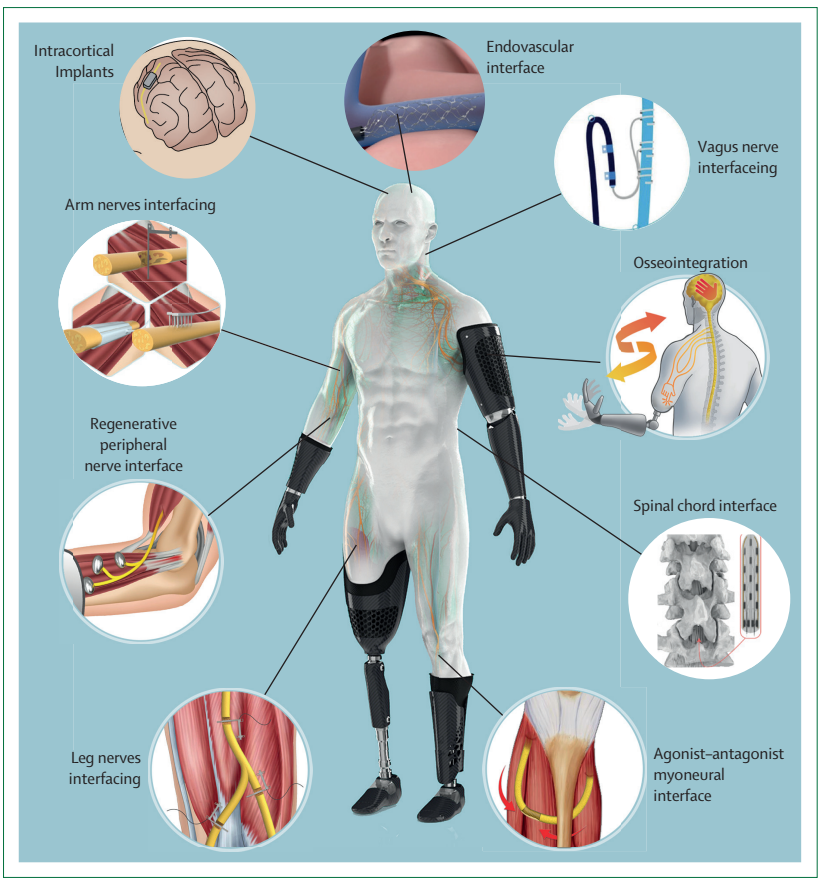

Figure 1: **Overview of implantable neural prostheses**
Different neurotechnologies for human nervous system interfacing. Various types of neural electrodes and surgical techniques are used in individuals with neurological disease to restore sensory motor functions. Illustrations for the intracortical implant and spinal cord interface were adapted from Donati and Valle.[23]

models are suitable to provide corroboration of these neuroengineering efforts by a solid understanding of neural prostheses mechanisms, an adequate notion of safety, and a comprehensive evaluation of the technology's effect on the subjective experience of patients is unclear. Although standard parameters, such as long-term functionality and stability, are crucial to ensure clinical validation of novel neural prostheses, more mechanistic underlying processes are poorly understood. Access to tissues after implantation is limited,[33] giving few insights into how the tissue–electrode interface evolves over time in humans. Furthermore, although private sector research on implantable neural interfaces might meet formal ethical and regulatory standards, such as the Council for International Organizations of Medical Sciences guidelines for human research,[34] whether these frameworks are well suited to address the complexity of neural prostheses is uncertain.

Most clinical and preclinical research on neural prostheses has focused on efficacy and safety, in analogy with assessment methods in pharmacological research.[35,36] However, neural prostheses differ from pharmaceuticals in many aspects. First, they are complex cyberbiological devices that integrate elements of computing technology with the biological functioning of the nervous system; hence, they are equipped with their own capacity to acquire and process data.[37] Therefore, they are unsuitable for traditional safety and efficacy evaluations used in pharmacological research. Second, as neural prostheses often rely on machine learning algorithms for classification and feature extraction, their assessment requires a causal understanding of algorithmic mechanisms and scrutiny of their information security and liability standards.[38] Third, most neural prostheses have a greater effect on human psychology than other implantable technologies such as cardiac pacemakers. By interfacing with the human nervous system, they thereby interface with all activities and functions, including psychological functions such as consciousness, cognition, and affective states. For instance, somatosensory peripheral nervous system stimulation boosts patients' sensorimotor performance, at the same time influencing their conscious pain perception[3] and cognitive processes such as body perception, cognitive load, and multisensory integration.[8,39]

In this Viewpoint, we argue that the technological novelty of neural prostheses—especially their unprecedented capability to acquire and algorithmically process neural data and affect the subjective psychological experience of the patient—might generate novel challenges for technology assessment, ethical oversight, and clinical validation. Safety considerations relating to data, algorithms, and psychophenomenological variables are often not fully considered when evaluating therapeutic outcomes for clinical neural prostheses.

Neuroethical challenges: subjectivity, privacy, and non-maleficence

Implantation of neural prostheses in humans raises ethical challenges.[40] Although some of these challenges (eg, risk of infection and bleeding) are common to any other implantable medical device, we have identified a cluster of ethical challenges that are either unique to, or greater for, clinical trials of neural prostheses, and that require careful consideration when planning and conducting such trials.

Effect on subjective experience

Implantable neural prostheses stimulate the nervous system and, therefore, influence psychological faculties such as consciousness, cognition, and affective states. As such, their assessment is not reducible only to third-person observations, usability tests, and safety assessments but also requires phenomenological explorations from the first-person perspective of users (figure 2). Empirical neuroethics methods such as qualitative interviews and focus groups might be useful; nevertheless, research of this type is scarce. Substantive weaknesses persist with regard to the assessment of

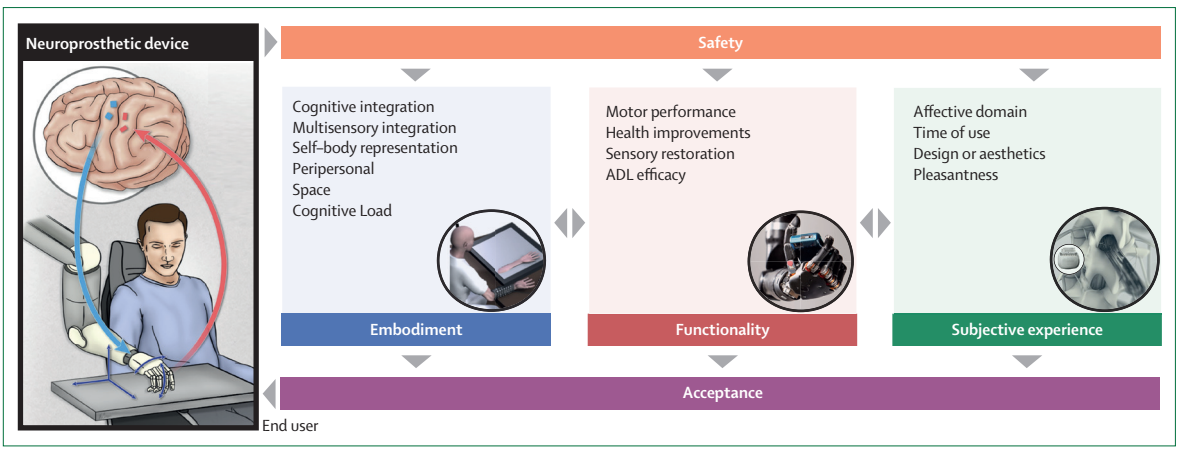

Figure 2: **Key dimensions for the assessment and validation of subjective experiences with neural prostheses**
ADL=activities of daily living.

first-person experiences of users of neural prostheses.[41] Most studies have focused on potential instead of actual users, involved only non-impaired individuals, used exclusively quantitative (not qualitative) metrics, or enrolled users of non-invasive interfaces to assess invasive ones. Only one (1·3%) of 73 studies[42] involved a user of implantable neural prostheses and conducted semi-structured interviews over a 6-month period after implantation, but this study focused narrowly on task ease. Qualitative studies exploring user perspectives on implantable neural prostheses often report their methods inadequately and address a narrow set of usability questions as opposed to broader experiential aspects, leading the authors to the conclusion the subjective experience of brain–computer interface users has been rarely researched. Similarly, Tbalvandany and colleagues[43] have reported that few substantive studies have addressed the subjective dimension of neural prostheses.

For neural prostheses that bidirectionally communicate with bionics devices or computers, quantitative–qualitative metrics are needed to assess the degree of acceptance of neural prostheses holistically. As inspired by the context of limb neuroprostheses,[22] we propose that a generic neural prosthesis device can be quantified using a series of four metrics. First, a sense of pleasantness or naturalness is needed. To achieve complete incorporation of the neural prosthesis, patients need to experience complete natural use of the artificial device, particularly when neural prostheses are adopted to restore a lost sense. Novel bio-inspired algorithms[23,44] and assessment tools to restore a natural sensory experience are being developed,[13,45] including for pain[46] and thermal sensations.[47] Second, validated and standardised questionnaires should be used. These questionnaires contain approximately 10–20 questions in which patients are asked to rate how much they perceive the device as their own on a numerical scale.[45,48–50] Control questions are provided to help to account for patients who might give higher ratings to please the experimenter. Third, multisensory integration is needed. Neural prostheses should allow the integration of information from different senses, similarly to healthy individuals. Psychophysical mathematical models help to investigate how the sensory feedback (natural or artificial) is being integrated by users.[39,45,50] A similar measure has also been developed for interoception,[51] which is connected to both somatic and autonomic (vagus) nerve stimulation.[52] Other quantitative and qualitative descriptors of how the neural prosthesis is perceived and how it matches the resemblance of the patient's body part are proposed.[45,48–50,53] Among these, peripersonal space[54] measures the space surrounding humans that they can reach. Since the boundaries of peripersonal space can expand after extensive tool use, the same approach can be applied to neural prostheses and a user's peripersonal space boundaries will be expanded. Fourth, cognitive load should be assessed. The amount of mental effort or cognitive load during neural prosthesis use correlates to the level of sensory–motor integration.[39,44,50] Measuring brain activity (eg, with electroencephalogram) or mental performance (eg, spelling or counting accuracy) of the user while performing a main motor activity, or communicating with a computer, within dual-task paradigms,[39,50] allows for the assessment of the mental resources required to use the device in everyday activities.

Incorporating subjective quantitative metrics into standard evaluations can improve patient experience, adherence, and satisfaction, thereby enhancing the success of novel neural prostheses in clinical and real-life settings (figure 2). This comprehensive approach could better predict the clinical adoption and usability of neural prostheses beyond the laboratory, ultimately benefiting patient care.

Privacy and data security

Neural prostheses rely on the acquisition and processing of both structural and functional neural data to treat neurological disorders. Therefore, conventional risk parameters such as probability of infection or overstimulation

are insufficient to assess their safety. Data security standards should also be evaluated, as neural data are considered sensitive and require a higher threshold of protection than data from other sources such as data relating to metabolism (eg, metabolite concentrations) or movement (gait patterns).[38] Several studies have identified privacy and security vulnerabilities in neural prostheses.[55] At least four types of vulnerabilities can be recognised; namely, unauthorised data extraction; unsecured data transmission; interface hijacking or sabotage; and privacy policies that are ambiguous or based on weak consent procedures. Research has shown the possibility of performing malicious side-channel attacks on users of neural prostheses, resulting in hijacking or sabotaging of legitimate components of the neural prostheses, such as stimulation parameters.[55] Studies that have assessed the data management practices and privacy policies of consumer-grade, non-invasive neural prostheses have observed that they often transmit context-rich data without secure channels and state-of-the art privacy preserving technologies, often under weak or ambiguous privacy policies.[37] The same risk applies to implantable neural prostheses. To mitigate privacy and security risks in neural prostheses, the introduction of a new test named the Mental Data Protection Impact Assessment has been proposed.[56] The Mental Data Protection Impact Assessment is a framework for mitigating privacy and security risks in neural prostheses, requiring the assessment of necessity, proportionality, and risks to fundamental rights, alongside measures such as audits or algorithmic redesign to address risks by design.

Bias and explainability

Neural prostheses-based systems that use machine learning and other artificial intelligence (AI) components[14,57] can incorporate biases.[58–60] AI bias is an anomaly in the output of machine learning algorithms, mostly due to prejudiced assumptions made during algorithm development process or biases in the training data.[61,62] Biases, such as latent bias from spurious correlations, data selection bias from unrepresentative datasets, and interaction bias from user interactions (particularly common in unsupervised learning), can affect the efficacy and ethics of neural prostheses. These biases can lead not only to suboptimal efficacy outcomes but also to ethical violations, such as discrimination. For example, if the stimulation models are trained on datasets that do not exhaustively represent all target patient subgroups, they are more likely to discriminate against those subgroups not adequately represented.[63] To minimise bias in neural prosthesis algorithms, training data should inclusively represent the diverse demographics and characteristics of the target subgroups, including gender, ethnicity, race, geography, and clinical profiles. For instance, an algorithm for peripheral nervous system treatments, such as pain relief, should factor in gender-specific data such as experiential and sociocultural differences in pain experience between men and women, as well as hormonally and genetically driven sex differences in brain neurochemistry.[64] However, gathering large, diverse datasets is challenging in neural prostheses research, which is often limited to a small number of participants.

Although AI biases might self-correct over time through further testing on diverse datasets, bias mitigation efforts, and iterative improvements by companies refining their technologies, their ethical implications ethical implications require immediate attention, especially during early testing and usage stages when user trust and device reputation are formed. Proactively addressing biases early can prevent long-lasting negative effects on user acceptance and perceived device reliability.

Integration of explainability and the human-in-the-loop model can address these limitations,[65] as the acceptance of AI in the neural prostheses field is strongly hindered by the intrinsic black-box nature of AI models and the trade-off between performance and interpretability.[66,67] The human-in-the-loop model involves human oversight in AI stages such as training and monitoring, enabling dynamic user–AI interaction for continuous improvement and ethical alignment, including informed consent and user empowerment. Application of human-in-the-loop to neural prostheses can occur in design, development, calibration, customisation, training, learning, monitoring, and maintenance.

Explainable AI interprets AI models, providing user-friendly explanations of decisions while analysing the algorithm's reasoning and potential biases regarding input and outcomes. Explainable AI can mitigate unfair bias and identify possible prejudice and discrimination in AI predictions for neural prostheses.[68,69] Explainable AI is not only technically beneficial but also enhances legal compliance since the EU General Data Protection Regulation grants individuals a right to obtain "meaningful explanations of the logic involved" in "automated (algorithmic) individual decision-making".[70]

AI and agency

AI-driven neural prostheses,[65] such as closed-loop and neuroadaptive systems, might influence the sense of agency of users as the algorithms used during classification and decoding could generate outputs that override their intentions and volition. This potential loss of agency could result in feelings of alienation, estrangement, or simple discomfort. Clinical trials should assess whether neural prostheses cause any drift in the user's sense of agency and whether their outputs align with the user's intentions. In addition, whenever AI algorithms are used, researchers have a moral obligation to use explainable AI methods to ensure transparency, explainability, and auditability. We suggest that any algorithm embedded in neural prostheses should be amenable to ex-ante and post-hoc inspection. This type of AI algorithm is not currently common since most

neuroadaptive interfaces rely on opaque neural networks.[71] Acquisition of robust data for emerging neural interfaces often requires a large user base, which might not yet exist; however, this should not hinder the pursuit of preliminary data and ethical assessment frameworks. Although large-scale data are invaluable, high-quality, in-depth data from smaller cohorts can provide meaningful insights, especially regarding subjective experiences and biases in AI development. Early-phase trials and pilot studies with small numbers of participants are essential to identify and address issues that could scale into significant challenges. Qualitative data and case studies are crucial in early stages, offering detailed insights into user experience and device interaction. This approach helps to anticipate problems and develop solutions before widespread clinical adoption, informing the design and development process and avoiding major revisions or ethical missteps later.

Conflicts of interest and liability disclosures

In 2022, a study found that high-cost spinal cord simulator devices were no better than placebo for treatment of a common type of chronic pain.[72] This finding raises concerns about bias in neural prosthesis interface studies funded by device manufacturers or industry-backed surgeons,[73] prompting calls for increased scrutiny from insurers and Medicare. This situation highlights the need for well defined control conditions in such studies. Ethical boundaries in industry-led neuroprosthesis research are often unclear, as many private companies do not publish research results or disclose ethical safeguards.

We propose that privately funded and company-led neuroprosthesis research should follow the same institutional review board approval and data transparency standards as publicly funded research. Beyond standard conflict of interest disclosures, neuroprosthesis manufacturers should provide clear statements of responsibility and liability for research malpractice or device malfunction. In private–public partnerships, researchers need to disclose the rights retained by private funders over the research data and specify accountability to the institutional review board and other oversight bodies.

Establishing a secure safety net for forced explants

An additional responsibility towards research participants pertains to the patients' right to withdraw from the study. This right is widely recognised in research ethics, but how it can be protected in neural prostheses research is unclear. Explanting a device is more complicated and requires more time than discontinuing a drug trial.[74] Patients could also have the right to keep the neural prostheses at the end of the study, which might be difficult since, often, a specialised team is needed for device maintenance over time. The forced explantation of neural implants has recently surfaced as an ethical dilemma; specifically, whether, and under what circumstances, removal of an implanted neural device against the wishes of the patient could be justified. Situations necessitating such action include medical complications, device obsolescence, malfunctioning, or a manufacturer's failure to provide ongoing support. Forced explantation raises numerous ethical considerations, including patient autonomy, informed consent, bodily integrity, and the potential psychological effect on the individual who has integrated the neural prosthesis into their personal identity or daily functioning. Discontinuation of the study could have profound neuropsychological consequences, especially if the device proves to have a causal role in a patient's sense of self. This situation occurred recently when bionic eye and brain implant companies became bankrupt, leaving users unsupported or even requiring forced explantation.[75] To avoid this risk in the future, companies should establish a proactive, morally responsible plan before initiation of clinical trials.

This plan could include establishment of a trust fund, whereby companies set up a protected fund specifically

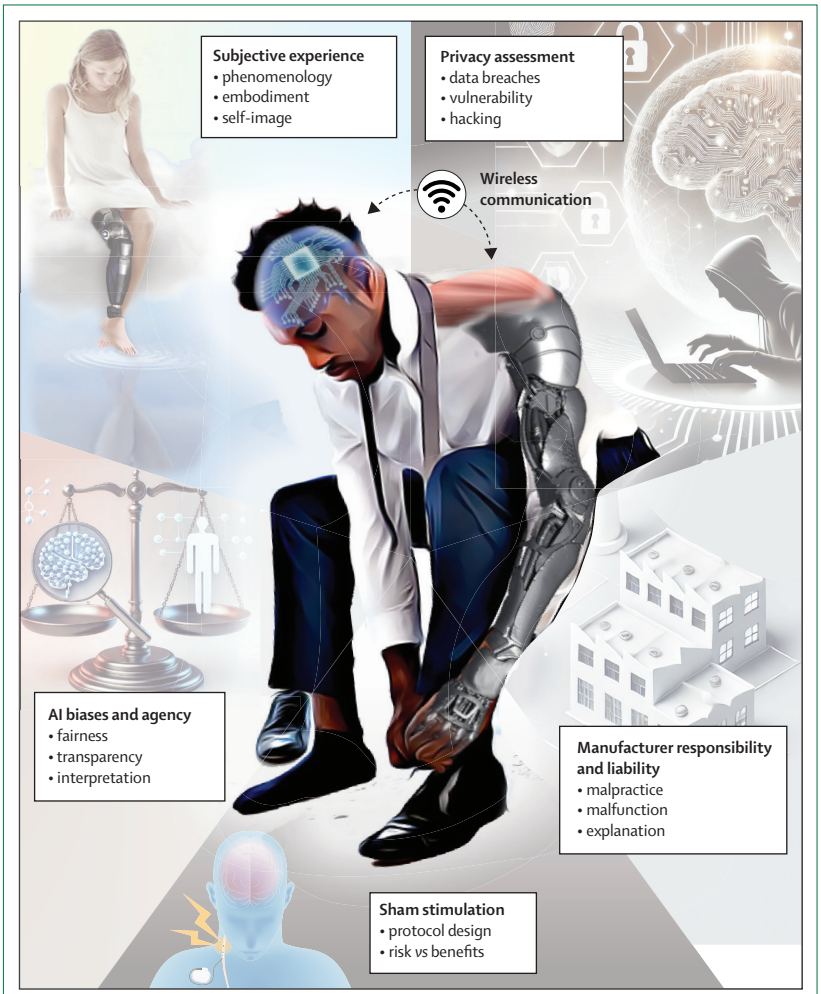

Figure 3: **A research ethics framework for clinical trials on implantable neural interfaces**
AI=artificial intelligence.

Panel: **Requirements for clinical trials of neural prostheses**

Complementary quantitative–qualitative evaluations of the effect of the interface on the users' psychological state and phenomenological variables
These evaluations should focus on embodiment, functionality, and subjective experience, considering user acceptance of the technology with patient-centred methods

Incorporation of data security and privacy impact assessment into the safety evaluation
Data breaches and vulnerability to malicious hacking should become part of routine safety evaluations, such as those evaluating biomedical side-effects, implementing state-of-the-art, privacy-preserving technology and privacy impact assessments, including the Mental Privacy Impact Assessment

Inspection for artificial intelligence (AI)-based algorithmic bias
Fairness, transparency, and inclusivity should guide trial design and compilation of training datasets; biases can be mitigated by ensuring the best achievable representativity of the population and using explainable AI and auditing methods

Inspection of any drift in the user's sense of agency and misalignments with the user's intentions caused by AI-based autonomous or semi-autonomous decision making
This is particularly important for bidirectional neural prostheses that combine risk prediction and neurostimulation

Establishment of disclosure statements by manufacturers, with clear ascriptions of responsibility and liability in case of research malpractice or device malfunction
In case of private–public partnership, researchers should disclose who owns the research data, who is accountable to institutional review boards and other oversight bodies, and how they will meet their post-trial obligations to research participants

Establishment of a secure financial and operational safety net by the neural prostheses-producing companies before clinical trials begin
This safety net should include a dedicated trust fund, comprehensive insurance, partnership agreements for contingency, rigorous ethical review with explicit patient consent, adherence to stringent regulatory requirements, and long-term support commitments to safeguard against the ethical and practical issues of forced explantation due to company bankruptcy or other unforeseen events

Demonstration that the benefit of including sham stimulation for implantable neural prostheses outweighs the risks for research participants
Study designs based on no stimulation or sham induction of small precepted stimuli should be preferred over sham stimulation under the perceptual threshold

designated for covering the costs associated with the potential future explantation of devices. This fund should be insulated from the company's operating funds to protect patients in the event of financial trouble. Insurance policies should also be considered, whereby the procurement of compulsory insurance helps to cover explantation costs, shifting financial risk from the company to the insurer. Partnership agreements with companies, institutions, or government bodies could be set up; these agreements would take over the responsibility of care in the event of bankruptcy and could include commitments to maintain the devices or provide for their safe removal and would require technical interoperability across different neural prosthesis systems. Ethical review and inclusion of a contingency plan for company insolvency, detailing protections for trial participants and harm-prevention measures, is also important. There should be assurance, before data collection, that participants are fully informed about the risks, including what would happen in the event of the company's bankruptcy, and that they consent to these terms explicitly. Finally, long-term follow-up and support should be provided, with a commitment to sustained post-trial support, potentially through alliances with health-care providers, ensuring patient care throughout the lifespan of the neural prosthesis, irrespective of the company's future.

The dilemma of sham stimulation

Neural prostheses involving neurostimulation capabilities raise ethical questions related to sham simulation and the restoration of pain sensation. Proper sham stimulation mimics both the method of active stimulation and its effects. The characteristics of an active stimulation method include stimulation sites, electrode montage, and sensory experiences. These common characteristics can give participants the illusion of receiving active stimulation; this could lead to placebo effects and induce cortical and behavioural changes. Overall, there are three main ways to implement sham: by not stimulating at all, by stimulating under the perceptual threshold, or by releasing small precepted stimuli, insufficient for treatment purposes.

We believe that sham stimulation studies based on implantable neural prostheses are ethically legitimate only if the study's benefits (eg, direct health benefits for the patient) significantly outweigh the risks involved in the procedure. Implantation of invasive neural prostheses carries health risks such as infection, surgical complications, and bleeding,[22,74] offering no therapeutic benefit in sham procedures. Thus, sham stimulation should only occur among users of non-invasive neural prostheses, or among users with pre-implanted invasive neural prostheses (eg, patients who had previously undergone implantation of a neural prosthesis for medical purposes). In either case, however, both the scientific benefit of the study and its effect on embodiment, functionality, and subjectivity need to be assessed. For example, if stimulation occurs under the threshold of perception, the autonomic nervous system (eg, changing vascularisation or sweating) could still be affected, which constitutes unacceptable risk.

Conclusions

Clinical trials for emerging implantable neural prostheses, including industry-initiated and industry-funded trials, should be welcomed as they hold promise to accelerate innovation and the delivery of clinically effective neurotechnological solutions for people in need. At the same time, this research could occur without clear guidance and in the context of unresolved ethical complexities. In general terms, neural prostheses require a more holistic understanding of the notion of risk

Search strategy and selection criteria

References were identified through searches of PubMed with the terms "neural interface", "neuroprosthetics", "neural stimulation", "implantable brain-computer interface", "implantable medical device", "clinical trials", and "ethics" from Jan 1, 1990 until May 1, 2023. Additional articles were identified through searches of the authors' own files and via citation-chaining from the primary sources. Only papers published in English were reviewed. The final reference list was generated based on originality and relevance to the broad scope of this Viewpoint.

compared with both pharmacological research and non-neural medical implants. For neural prostheses, risk cannot be reduced to biomedical risk, but instead involves emerging risks such as phenomenological changes, algorithmic biases, and malicious hacking (figure 3). Furthermore, the current dynamic of industry-led research on neural prostheses requires the clarification of conflict of interest, research ethics oversight, liability, and post-trial duties. Although end-user data during the nascent stages of these technologies are scarce, we believe that anticipating and addressing these ethical and functional issues proactively is both possible and essential. By doing so, the design, development, and iterative improvement of such devices can be better informed, potentially avoiding more significant revisions or ethical missteps after widespread adoption.

In addition to existing ethical guidelines and national regulations for patient research, we have proposed seven requirements for clinical trials of neural prostheses (panel). Introduction of these seven requirements into trial planning requires a multilevel approach to governance that considers technical standards, medical device and data regulation, national regulations on human research, and ethical guidelines for biomedical research involving human participants. For example, specific requirements for neural prostheses, addressing phenomenological effects, data security, algorithmic bias, and company discontinuity, could be incorporated into the ISO 14155 Standard.[76] In parallel, amendments to the EU Medical Device Regulation[77] could incorporate specific clauses that require manufacturers to address non-conventional safety risks associated with implantable neural prostheses, such as off-target effects on subjective experience, algorithmic bias, vulnerability to hacking, and proactive obligations in case of forced explantation. Finally, non-mandatory governance (also called soft law) provides suitable grounds to implement the required normative interventions, such as by introducing recommendations on neural prostheses clinical trials in upcoming neurotechnology-focused guidelines such as the upcoming UNESCO Recommendation on Neurotechnology, or even by adding amendments to existing research ethics guidelines such as the Council for International Organizations of Medical Sciences guidelines.

Contributors

MI, GV, and SR co-wrote this manuscript. GV and SR made the original figures. All authors edited, proofread, and authorised submission of the manuscript, but the final submission decision was made by the corresponding author.

Declaration of interests

MI has received honoraria for reports commissioned by the Council of Europe, and receives honoraria from and serves on the ethics advisory board of IDUN Technologies, a start-up company producing in-ear electroencephalogram earbuds. MI recieves royalties from books published with Oxford University Press, Cambridge University Press, and Routledge. SR held shares of SensArs Neuroprosthetics Sarl, a start-up company dealing with the commercialisation of neuro-controlled artificial limbs, until 2023. GV declares no competing interests.

Acknowledgments

This project received funding from the ERA-NET Neuron–Swiss National Science Foundation (HybridMinds number 32NE30_199436), the Techniche Universität München Seed Funds (EthBCI number 5110957; MI), the Chicago Postdoctoral Fellowship Program at University of Chicago (GV), the European Research Council under the EU's Horizon 2020 research and innovation programme (FeelAgain grant agreement number 759998), and the Swiss National Science Foundation (MOVE-IT number 197271; SR). The funders had no role in the Viewpoint's design, manuscript preparation, or submission. The illustration of the endovascular interface was provided by Synchron, and the illustration of the vagus nerve interfacing was provided by MicroTransponder.

References

1 Vance A. Neuralink's first patient: 'it blows my mind so much'. Bloomberg. 2024. https://www.bloomberg.com/news/features/2024-05-16/neuralink-s-first-patient-describes-living-with-brain-implant (accessed June 5, 2024).
2 Zhang M, Tang Z, Liu X, Van der Spiegel J. Electronic neural interfaces. *Nat Electron* 2020; **3:** 191–200.
3 Petrini FM, Bumbasirevic M, Valle G, et al. Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain. *Nat Med* 2019; **25:** 1356–63.
4 Ortiz-Catalan M, Mastinu E, Sassu P, Aszmann O, Brånemark R. Self-contained neuromusculoskeletal arm prostheses. *N Engl J Med* 2020; **382:** 1732–38.
5 Tan DW, Schiefer MA, Keith MW, Anderson JR, Tyler J, Tyler DJ. A neural interface provides long-term stable natural touch perception. *Sci Transl Med* 2014; **6:** 257ra138.
6 George JA, Kluger DT, Davis TS, et al. Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. *Sci Robot* 2019; **4:** eaax2352.
7 Clites TR, Carty MJ, Ullauri JB, et al. Proprioception from a neurally controlled lower-extremity prosthesis. *Sci Transl Med* 2018; **10:** eaap8373.
8 Raspopovic S, Capogrosso M, Petrini FM, et al. Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Sci Transl Med* 2014; **6:** 222ra19.
9 Vu PP, Vaskov AK, Irwin ZT, et al. A regenerative peripheral nerve interface allows real-time control of an artificial hand in upper limb amputees. *Sci Transl Med* 2020; **12:** eaay2857.
10 Flesher SN, Downey JE, Weiss JM, et al. A brain-computer interface that evokes tactile sensations improves robotic arm control. *Science* 2021; **372:** 831–36.
11 de Hemptinne C, Swann NC, Ostrem JL, et al. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci* 2015; **18:** 779–86.
12 Ajiboye AB, Willett FR, Young DR, et al. Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. *Lancet* 2017; **389:** 1821–30.
13 Greenspon CM, Valle G, Shelchkova ND, et al. Evoking stable and precise tactile sensations via multi-electrode intracortical microstimulation of the somatosensory cortex. *Nat Biomed Eng* 2024; **8:** 1–17.

14 Moses DA, Metzger SL, Liu JR, et al. Neuroprosthesis for decoding speech in a paralyzed person with anarthria. *N Engl J Med* 2021; **385:** 217–27.

15 Willett FR, Avansino DT, Hochberg LR, Henderson JM, Shenoy KV. High-performance brain-to-text communication via handwriting. *Nature* 2021; **593:** 249–54.

16 Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. *Lancet* 2021; **397:** 2111–24.

17 Wagner FB, Mignardot J-B, Le Goff-Mignardot CG, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* 2018; **563:** 65–71.

18 Powell MP, Verma N, Sorensen E, et al. Epidural stimulation of the cervical spinal cord for post-stroke upper-limb paresis. *Nat Med* 2023; **29:** 689–99.

19 Gill ML, Grahn PJ, Calvert JS, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nat Med* 2018; **24:** 1677–82.

20 Squair JW, Berney M, Castro Jimenez M, et al. Implanted system for orthostatic hypotension in multiple-system atrophy. *N Engl J Med* 2022; **386:** 1339–44.

21 Shen K, Chen O, Edmunds JL, Piech DK, Maharbiz MM. Translational opportunities and challenges of invasive electrodes for neural interfaces. *Nat Biomed Eng* 2023; **7:** 424–42.

22 Raspopovic S, Valle G, Petrini FM. Sensory feedback for limb prostheses in amputees. *Nat Mater* 2021; **20:** 925–39.

23 Donati E, Valle G. Neuromorphic hardware for somatosensory neuroprostheses. *Nat Commun* 2024; **15:** 556.

24 Musk E. An integrated brain-machine interface platform with thousands of channels. *J Med Internet Res* 2019; **21:** e16194.

25 Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature* 2012; **485:** 372–75.

26 Bonaccini Calia A, Masvidal-Codina E, Smith TM, et al. Full-bandwidth electrophysiology of seizures and epileptiform activity enabled by flexible graphene microtransistor depth neural probes. *Nat Nanotechnol* 2022; **17:** 301–09.

27 Mitchell P, Lee SCM, Yoo PE, et al. Assessment of safety of a fully implanted endovascular brain-computer interface for severe paralysis in 4 patients: the stentrode with thought-controlled digital switch (SWITCH) study. *JAMA Neurol* 2023; **80:** 270–78.

28 Seo D, Neely RM, Shen K, et al. Wireless recording in the peripheral nervous system with ultrasonic neural dust. *Neuron* 2016; **91:** 529–39.

29 Kilgore KL, Bhadra N. Reversible nerve conduction block using kilohertz frequency alternating current. *Neuromodulation* 2014; **17:** 242–54.

30 Trevathan JK, Baumgart IW, Nicolai EN, et al. An injectable neural stimulation electrode made from an in-body curing polymer/metal composite. *Adv Healthc Mater* 2019; **8:** e1900892.

31 Donegà M, Fjordbakk CT, Kirk J, et al. Human-relevant near-organ neuromodulation of the immune system via the splenic nerve. *Proc Natl Acad Sci USA* 2021; **118:** e2025428118.

32 Organisation for Economic Co-operation and Development. OECD recommendation on responsible innovation in neurotechnology. 2019. https://www.oecd.org/science/recommendation-on-responsible-innovation-in-neurotechnology.htm (accessed Jan 8, 2024).

33 Valle G, Aiello G, Ciotti F, et al. Multifaceted understanding of human nerve implants to design optimized electrodes for bioelectronics. *Biomaterials* 2022; **291:** 121874.

34 Council for International Organizations of Medical Sciences, WHO. I2016 International ethical guidelines for health-related research involving humans. 2016.

35 Shepherd RK, Villalobos J, Burns O, Nayagam DAX. The development of neural stimulators: a review of preclinical safety and efficacy studies. *J Neural Eng* 2018; **15:** 041004.

36 Deer TR, Lamer TJ, Pope JE, et al. The neurostimulation appropriateness consensus committee (NACC) safety guidelines for the reduction of severe neurological injury. *Neuromodulation* 2017; **20:** 15–30.

37 Ienca M, Haselager P, Emanuel EJ. Brain leaks and consumer neurotechnology. *Nat Biotechnol* 2018; **36:** 805–10.

38 Ienca M, Fins JJ, Jox RJ, et al. Towards a governance framework for brain data. *Neuroethics* 2022; **15:** 20.

39 Preatoni G, Valle G, Petrini FM, Raspopovic S. Lightening the perceived weight of a prosthesis with cognitively integrated neural sensory feedback. *Curr Biol* 2021; **31:** 1–7.

40 Yuste R, Goering S, Arcas BAY, et al. Four ethical priorities for neurotechnologies and AI. *Nature* 2017; **551:** 159–63.

41 Kögel J, Schmid JR, Jox RJ, Friedrich O. Using brain-computer interfaces: a scoping review of studies employing social research methods. *BMC Med Ethics* 2019; **20:** 18.

42 Brown T, Thompson MC, Herron J, Ko A, Chizeck H, Goering S. Controlling our brains – a case study on the implications of brain-computer interface-triggered deep brain stimulation for essential tremor. *Brain Comput Interfaces* 2016; **3:** 165–70.

43 Tbalvandany SS, Harhangi BS, Prins AW, Schermer MH. Embodiment in neuro-engineering endeavors: phenomenological considerations and practical implications. *Neuroethics* 2019; **12:** 231–42.

44 Valle G, Katic Secerovic N, Eggemann D, et al. Biomimetic computer-to-brain communication enhancing naturalistic touch sensations via peripheral nerve stimulation. *Nat Commun* 2024; **15:** 1151.

45 Valle G, Mazzoni A, Iberite F, et al. Biomimetic intraneural sensory feedback enhances sensation naturalness, tactile sensitivity, and manual dexterity in a bidirectional prosthesis. *Neuron* 2018; **100:** 37–45.

46 Osborn LE, Dragomir A, Betthauser JL, et al. Prosthesis with neuromorphic multilayered e-dermis perceives touch and pain. *Sci Robot* 2018; **3:** 12.

47 Iberite F, Muheim J, Akouissi O, et al. Restoration of natural thermal sensation in upper-limb amputees. *Science* 2023; **380:** 731–35.

48 Graczyk EL, Resnik L, Schiefer MA, Schmitt MS, Tyler DJ. Home use of a neural-connected sensory prosthesis provides the functional and psychosocial experience of having a hand again. *Sci Rep* 2018; **8:** 9866.

49 Rognini G, Petrini FM, Raspopovic S, et al. Multisensory bionic limb to achieve prosthesis embodiment and reduce distorted phantom limb perceptions. *J Neurol Neurosurg Psychiatry* 2019; **90:** 833–36.

50 Petrini FM, Valle G, Bumbasirevic M, et al. Enhancing functional abilities and cognitive integration of the lower limb prosthesis. *Sci Transl Med* 2019; **11:** eaav8939.

51 Mehling WE, Acree M, Stewart A, Silas J, Jones A. The multidimensional assessment of interoceptive awareness, version 2 (MAIA-2). *PLoS One* 2018; **13:** e0208034.

52 Villani V, Tsakiris M, Azevedo RT. Transcutaneous vagus nerve stimulation improves interoceptive accuracy. *Neuropsychologia* 2019; **134:** 107201.

53 Risso G, Preatoni G, Valle G, Marazzi M, Bracher NM, Raspopovic S. Multisensory stimulation decreases phantom limb distortions and is optimally integrated. *iScience* 2022; **25:** 104129.

54 Di Pino G, Romano D, Spaccasassi C, et al. Sensory- and action-oriented embodiment of neurally-interfaced robotic hand prostheses. *Front Neurosci* 2020; **14:** 389.

55 Pycroft L, Boccard SG, Owen SLF, et al. Brainjacking: implant security issues in invasive neuromodulation. *World Neurosurg* 2016; **92:** 454–62.

56 Ienca M, Malgieri G. Mental data protection and the GDPR. *J Law Biosci* 2022; **9:** lsac006.

57 Willett FR, Avansino DT, Hochberg LR, Henderson JM, Shenoy KV. High-performance brain-to-text communication via handwriting. *Nature* 2021; **593:** 249–54.

58 Panch T, Mattie H, Atun R. Artificial intelligence and algorithmic bias: implications for health systems. *J Glob Health* 2019; **9:** 010318.

59 Dastin J. Amazon scraps secret AI recruiting tool that showed bias against women. Reuters. 2018. https://www.reuters.com/article/us-amazon-com-jobs-automation-insight-idUSKCN1MK08G (accessed Nov 7, 2022).

60 Hutson M. Even artificial intelligence can acquire biases against race and gender. Science. 2017. https://www.science.org/content/article/even-artificial-intelligence-can-acquire-biases-against-race-and-gender (accessed Nov 7, 2022).

61 Dilmegani C. Bias in AI. What it is, types, examples & 6 ways to fix it. AIMultiple. 2024. https://research.aimultiple.com/ai-bias/ (accessed Nov 7, 2022).

62 Kundi B, El Morr C, Gorman R, Dua E. Artificial intelligence and bias: a scoping review. In: El Morr C, ed. AI and Society. Chapman and Hall/CRC, 2023: 199–215.

63 Jwa AS, Poldrack RA. Addressing privacy risk in neuroscience data: from data protection to harm prevention. *J Law Biosci* 2022; **9:** lsac025.

64 Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. *Nat Rev Neurosci* 2012; **13:** 859–66.

65 Rajpurkar P, Chen E, Banerjee O, Topol EJ. AI in health and medicine. *Nat Med* 2022; **28:** 31–38.

66 Barredo Arrieta A, Díaz-Rodríguez N, Del Ser J, et al. Explainable artificial intelligence (XAI): concepts, taxonomies, opportunities and challenges toward responsible AI. *Inf Fusion* 2020; **58:** 82–115.

67 Burkart N, Huber MF. A survey on the explainability of supervised machine learning. *J Artif Intell Res* 2021; **70:** 245–317.

68 Goodman B, Flaxman S. European union regulations on algorithmic decision-making and a "right to explanation". *AI Mag* 2017; **38:** 50–57.

69 Directorate-General for Communications Networks, Content and Technology. Ethics guidelines for trustworthy AI. Publications Office of the European Union. 2019. https://data.europa.eu/doi/10.2759/346720 (accessed Nov 7, 2022).

70 The European Parliament and the Council of the European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (general data protection regulation). 2016. https://eur-lex.europa.eu/eli/reg/2016/679/oj (accessed May 27, 2016).

71 Zbinden J, Molin J, Ortiz-Catalan M. Deep learning for enhanced prosthetic control: real-time motor intent decoding for simultaneous control of artificial limbs. *IEEE Trans Neural Syst Rehabil Eng* 2024; **32:** 1177–86.

72 Hara S, Andresen H, Solheim O, et al. Effect of spinal cord burst stimulation vs placebo stimulation on disability in patients with chronic radicular pain after lumbar spine surgery: a randomized clinical trial. *JAMA* 2022; **328:** 1506–14.

73 Fabbri A, Lai A, Grundy Q, Bero LA. The influence of industry sponsorship on the research agenda: a scoping review. *Am J Public Health* 2018; **108:** e9–16.

74 Rubin DB, Ajiboye AB, Barefoot L, et al. Interim safety profile from the feasibility study of the braingate neural interface system. *Neurology* 2023; **100:** e1177–92.

75 Lázaro-Muñoz G, Pham MT, Muñoz KA, et al. Post-trial access in implanted neural device research: device maintenance, abandonment, and cost. *Brain Stimul* 2022; **15:** 1029–36.

76 Singh K. ISO 14155: clinical investigation of medical devices for human subjects. In: Timiri Shanmugam PS, Thangaraju P, Palani N, Sampath T, eds. Medical device guidelines and regulations handbook. Springer International Publishing, 2022: 1–18.

77 European Parliament, Council of the European Union. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending directive 2001/83/EC, regulation (EC) no 178/2002 and regulation (EC) no 1223/2009 and repealing council directives 90/385/EEC and 93/42/EEC (text with EEA relevance.). Official Journal of the European Union. 2017. http://data.europa.eu/eli/reg/2017/745/oj/eng (accessed Aug 12, 2024).