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Clinical Trials of Xenotransplantation and Brain-Computer Interfaces: Commonalities and Cautions in Ethics Policy

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ABSTRACT

The quest of medicine to restore function to diseased or damaged human organs has journeyed from human-to-human transplantation to animal-to-human xenotransplantation and now to brain-computer interface implantation. Despite the disparate nature of the latter two technologies, similar ethical questions arise. We explore the history and ethics of xenotransplantation, some of the current technologies supporting the procedure, and current policy guidelines pertaining to clinical xenotransplantation. We then examine the emerging field of brain-computer interfaces. We highlight common ethical issues, including the vulnerability of potential subjects, infection risks, ownership considerations, explanation mandates, and the uncertainty of financial underwriting of technology. We discuss the concept of Ulysses contracts as a method of resolving the conflict between the interests of clinical trial sponsors and technology companies and the subjects and recipients of the permanently implanted technology. Finally, we propose considerations for the explicit delineation in clinical trials of permanently implanted technologies including xenotransplantation and brain-computer interface technologies.

1. Introduction

Many of the ethical issues surrounding human vital organ transplantation have continued from the earliest era of transplantation to the present. Most of those problems revolve around the fact of the organ gap: the supply of allograft organs has been grossly insufficient to meet the growing needs of patients with end-organ failure despite major efforts by governments and private organizations to expand the supply of organs. Tens of thousands of patients die every year because not enough allografts are available to satisfy the need. [1] Most of the ethical issues in clinical transplantation are related to conflicts about allocation of the insufficient supply to those in need. Some efforts to increase the number of medically suitable organs have met with major success—the adoption of criteria for determining brain death in the 1970s and 1980s—and moderate success—the widespread and growing implementation of donation after circulatory determination of death. [2] Yet despite these advances, policy development and modification often have the feel of rearranging the deck chairs on the Titanic.

Some relatively new technologies show promise of alleviating the organ shortage, perhaps to the extent of completely eliminating the transplant waitlist. One of the most promising is xenotransplantation (XTx): the use of animal organs to replace failing human organs. Animals can be bred specifically for their organs, providing a virtually unlimited supply of organs that will be available on demand. As experimentation has progressed rapidly, XTx is now in the early stages of clinical trials, and if the procedure proves to be clinically viable, the ethical issues related to allocation of scarce organs will disappear. In their place, however, will appear a new set of ethical concerns that have substantial implications for transplantation policy. We discuss those below.

In recent years, the development of mechanical and digitally-driven devices to augment or substitute for human functions has reached the point of justifying clinical trials, some of which have already begun. Replacing worn-out human parts with artificial substitutes created a television bonanza for the Six Million Dollar Man in the 1970s. The thought of bringing back the injured hero, NASA test pilot Steve Austin, "Better than he was before. Better, stronger, faster…" enthralled audiences those decades ago. He was the first "bionic man," if only in fiction. The fiction has become and is becoming reality with the growing field of brain-computer interfaces (BCIs). Advances in this arena will eventually require clinical trials to evaluate their safety and efficacy, which raises ethical and policy questions that have commonalities with the established modalities of allograft organ transplantation and its less well-established cousin, XTx. We will explore some of the emerging ethical concerns in the evolution of clinical trials of XTx and BCIs.

1.1 HUMAN-TO-HUMAN TRANSPLANTATION

Transplantation of human organs into other human beings with end-organ failure was first successful 70 years ago with transplantation of the kidney from a man to his identical twin brother, a rare fortuitous pairing. [3] The surgical techniques of implanting organs were not difficult, but organ availability in the early days was limited to recovering organs from people who had suddenly died: uncontrolled donation after circulatory determination of death (DCDD). In response to this shortage, the idea of neurologically-determined death—so-called brain death—was suggested in 1968 and became law in the US and Europe in the 1980s. The availability of brain-dead donors greatly increased the number of medically suitable organs for transplantation from the 1970s onward. Early pioneers in organ transplantation developed drugs, such as corticosteroids and azathioprine, aimed at confounding the normal function of the immune system to reject foreign organs. A seminal event was the introduction of cyclosporine in the late 1970s, which led to routine unrelated-donor transplantations of kidney, heart, liver, lung, and other organs using aggressive regimens of immunosuppressive drugs. [4]

The enormous success of allotransplantation in saving lives, however, was not unmitigated. The need for organs brought the new problem of the growing organ gap, an ever-increasing disparity between the supply and the demand for organs. Over the last two decades, the supply has increased still more by the resurgence of DCDD, this time from dying patients who are not brain dead: controlled-DCDD. The supply still has fallen far short of demand. New forms of DCDD have emerged in recent years, such as normothermic regional perfusion, which results in healthier organs than in previous techniques of organ recovery. [5,6] The organ shortage has been addressed illicitly in some countries by procuring organs from nonconsenting prisoners and persecuted minorities. [7]

The ethical-philosophical foundation of current organ-recovery techniques, including brain death and all forms of DCDD has been from the beginning and still today remains highly controversial. [8] While widely accepted as valid, the declaration of death that necessarily precedes removal of organs (because of the dead donor rule) has been challenged as a convenient legal and ethical fiction that enables the saving of tens of thousands of human lives every year. [9] Many ethical problems would be solved and questions answered if a non-human source of organs or other means of compensating for end-organ failure were available. XTx may provide a solution to that dilemma.

2. Xenotransplantation

Peter Gorer coined the term "xenotransplantation" in 1961, referring to transplantation of tissues or organs between a donor and recipient of different species.[10] Developments over the last half-century have required a more nuanced definition.

Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues of organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs. [11]

Although our focus is on vital organ transplantation, the investigational and ethical issues we discuss generally apply to the full range of XTx technologies.

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The cause célèbre of human XTx was the "Baby Fae" case in 1984. Baby Fae was a newborn suffering from the congenital heart defect, hypoplastic left heart syndrome, which was an untreatable fatal disease at that time. Leonard Bailey replaced the baby's malformed heart with a baboon heart at Loma Linda Medical Center.[12] Although the baby lived for only 20 days, this operation was a proof of principle that XTx could eventually become clinically useful in human beings.

Since Bailey's seminal work, XTx has been used experimentally among various combinations of sheep, pigs, baboons, and chimpanzees with varying degrees of success. On an evolutionary scale, researchers believed that the use of non-human primate organs would have the greatest chance of success in humans. However, the close proximity of these animals to human beings genetically and intellectually along with burgeoning animal rights case law have moved professional and public acceptance away from a primate source for XTx organs.

2.1 EMERGENCE OF THE PIG

The pig has emerged as a viable farmed alternative for xenotransplant organs for many reasons. Pig organs are comparable to human organs in size and anatomy. Domestic swine have several advantages. Pig herds can be maintained in sterile conditions, the animals multiply rapidly with multiparous births, and they grow rapidly, making a variety of organ sizes readily available. In addition, they have been farmed as a food source for human consumption for many thousands of years, so do not impose the same emotional burden on the public that primates carry.

Despite these advantages, native porcine organs are incompatible with human immune systems, which mount a hyperacute rejection response to porcine organs, owing to pre-existing antibodies against the carbohydrate moiety α-galactose-1,3-galactose (α-Gal). [13,14] Novel technologies for manipulating stem cell cloning led to the creation of a pig line with the deletion of the α-Gal gene. This advance lowered but did not eliminate the human immune response to pig organs. The first pig-to-human organ xenotransplants took place in 2021 in brain-dead recipients and were shown to function in the short term without hyperacute rejection. [14]

Over time, a number of genes offensive to human immune systems have been deleted from pigs. The deletion of four pig genes responsible for hyperimmune responses, with addition of six genes to abrogate the immune response and production of microvascular blood clots created a pig with 10 genetically engineered (10-GE) genes. [14] A heart from this prototype pig was transplanted into a human recipient, who survived for 7 weeks. [14] Most recently, a 10-GE pig kidney transplant has functioned for 8 weeks. [15,16] Chinese scientists have produced pigs with three gene knockouts and three to six transgene insertions directed at the major targets of the human immune response. [17] These molecular technologies promise to make pig-to-man XTx clinically feasible. Cooper et al. question whether the individual genetic modifications in the swine should have been tested before jumping to the 10-GE pig modification in clinical trials. [18]

Unlike other laboratory animals that are regulated by the Animal Welfare Act, regulation of XTx falls under both the US Food and Drug Administration (FDA) as a medical product and the US Department of Agriculture (USDA) as livestock. Schwartz notes that genetic modification of pig organs "may not be categorized as a drug exposure although it is technically a medical procedure." [19] The USDA may retain authority in the process because they are charged with regulating animal, including swine, carcasses and parts, including organs. Additional legislation or regulations may be needed to protect the farmed genetically modified swine as well as the humans receiving xenotransplants. [19]

2.2 MORE THAN PUTTING LIPSTICK ON A PIG: HUMAN-PIG CHIMERAS

The previous gene manipulations have tinkered with the normal expression of the pig genome to make porcine organs more acceptable to the human immune system. Another approach is to manipulate the pig genome into generating human rather than porcine organs. In groundbreaking research, Wang *et. al.* deleted the genes responsible for the differentiation of stem cells into the proto-kidney in pig embryos.[20] Induced pluripotent human stem cells (iPSCs) were manipulated to overexpress survival genes (MYCN and BCL2). The deficient pig embryo cells were merged with the human overexpressing iPSCs to create an interspecies chimeric blastocyst. These blastocysts were implanted into a sow and allowed to develop to an early gestational stage. PCR confirmed that the resulting embryonic kidneys contained the human genetic contribution.[20]

An important cause for concern, however, is the fact that the human iPSCs also differentiated into neuronal tissues in the brain and spinal cord.[20] Humanized cells were also found in the liver and heart. These occurred at a very low rate, and fortunately, no humanized cells were found in the pig germ cells. Concerns such as these have led to varying laws and guidelines in different countries regarding creation of human-animal chimeric blastocysts. A law banning federal funding for such research in the US was lifted in 2016, but National Institutes of Health guidelines currently prohibit the breeding of animals that contain human cells. In the United Kingdom, creating human-animal chimeric blastocysts is illegal without approval, even investigations that are privately funded.[21] The law in this area is still very much in flux globally.[22]

Schwarz explores the issue of human-porcine chimeras and the possibility that human cells in the nervous system of the pig could result in the development of human-like characteristics in the brain. The development of an intellectually enhanced pig would raise ethical questions as to whether farming such a chimera should be permitted. [19] Schwarz suggests an interesting proposition that would have "…Congress or judges redefining the definition of persons as any organism that contains a certain amount of human specific DNA. If there was a percentage threshold that delineated the line between personhood and property status, then there could be laws developed that held the percentage of human DNA modification to a certain level." [19] At the current time, clinical trials of XTx of human-pig chimeric organs are not allowed in the United States.

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2.3 ETHICAL CONCERNS IN XTX CLINICAL TRIALS

2.3.a. Vulnerability of XTx Recipients

In the United States, strong regulations protect human subjects in experimental research. The Belmont Report suggested additional protection for those persons who are considered "vulnerable" as subjects for research, such as prisoners, persons with issues of mental health, and children. Certain patients who are desperate might qualify for non-standard care, but in the eyes of medical ethics, desperation has not qualified as vulnerability. However, we believe that current XTx candidates should be classified as vulnerable because of their desperation. In general, they are not candidates for a traditional human-to-human transplant for reasons such as disqualifying comorbidities (e.g., significant cardiac or vascular disease or irreversible lung dysfunction), a history of active or recent cancer, or chronic infections that could worsen with immunosuppression; yet they are dying from organ failure and have nowhere to turn but to XTx.

XTx potential subjects are also vulnerable due to the publicity and notoriety surrounding these new advances. For instance, the longest surviving genetically modified pig kidney transplant recipient was chosen partially due to her previous donation of one of her own kidneys to someone else. The altruism angle to her story added to its notoriety, was readily promoted by the transplanting institution, and was widely reported by the media. [15,16]

2.3.b. Infection Concerns in XTx

Early objections to XTx included the potential for transmission of animal viruses into humans, including the Porcine Endogenous Retrovirus (PERV). No cases of PERV transmission have been documented, and the newest porcine-engineered models have deleted the PERV DNA from the porcine genome, precluding expression and infection. The very low risk of zoonotic infection has been cited as a reason for revising the regulatory framework and make it less stringent. [18]

However, the world has recently endured the SARS-CoV-2 pandemic, so worries surrounding animal-to-human transmission of viruses remains high. Recent genomic manipulations raise the inauspicious possibility that the creation of a "more human" pig either through deletion of pig genes, insertion of human genes, or creation of an embryonic chimera may provide avenues for the mixing and mutation of porcine and human viruses to create novel lethal zoonoses. Current federal regulations provide a scaffolding for the surveillance of such events. [23] The implications of this possibility for future research in producing "humanized" pigs are as yet unknown.

A public health concern about zoonoses is that such an event could affect not only the XTx recipient but also those with whom they came in close contact such as family members or intimate partners. Given that possibility, the questions arise of whether close contacts should be advised of this risk and whether they should undergo the same surveillance as the subject. It seems certain that the risk of zoonoses emerging, affecting others, and perhaps even causing a pandemic, although low, cannot be reduced to zero. Moreover, no threshold for determining an acceptable level of risk has been determined. These are important issues for current efforts to develop protocols for clinical trials of XTx. Until now, several pig-to-human transplants have been performed on a compassionate-use basis, resulting in new information that can be used in developing future research proposals. As of this writing, the FDA has cleared two biotechnology companies to initiate pig kidney transplant studies. They are scheduled to begin sometime in 2025, but no dates have been set. [24]

2.3.c. Subject Rights Versus Lifelong Surveillance

A recent review thoroughly covers the ethical issues surrounding XTx, including the risks associated with the potential emergence of zoonoses noted in the previous section. [25] A particularly discomforting issue, the question of mandatory surveillance post-transplant, deserves special attention.

The initial 2001 federal regulations of XTx were revised and updated in 2016 by the FDA. [11] Some of the original regulations, reaffirmed in 2016,[26] required XTx recipients to undergo passive screening for infections, which included pre-transplant specimens, immediate post-transplant specimens, and specimens up to every five years until the recipient's death. Their families and close contacts were also to be monitored. The specimens were to be maintained for at least 50 years. [11]

The life-long surveillance required by the US Public Health Service and the FDA is tantamount to an abrogation of the right to withdraw from a clinical trial, as we have argued previously. [27] In the 2016 revision, the FDA document noted that life-long surveillance should be included in the informed consent document, but did not reduce its requirement. [26] Several aspects of surveillance have not been addressed in law or regulations, to our knowledge. Abrogation of the right to withdraw from a clinical trial violates one of the oldest tenets of research ethics, first formally stated in the Nuremberg Code: "During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible." [28]

The conflict between the required surveillance and the right to withdraw has been neither resolved nor even officially addressed. Moreover, the problem of how it could be enforced has not been determined—few avenues for enforcement seem reasonable short of draconian public health quarantine laws. During the consent process, a potential subject could have three options: accept the conditions for XTx, including mandatory, potentially life-long surveillance, face the consequences of exclusion from the XTx study if those conditions are refused, or accept the premise that withdrawal from the trial would result in mandatory explantation of the XTx. (To make matters worse, explantation might reduce but would not remove the possibility of a future zoonotic infection.) Whether offering those choices is coercive or is a reasonable necessity for public safety is an active question for debate. We have previously argued that the psychiatric model of Ulysses contract, by which a subject would give prior consent to the subsequent act of irrevocable lifelong surveillance, might be a reasonable model to follow in the case of XTx. [27]

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Perhaps as nettlesome as the question of the right to withdraw from an XTx study is the question of participation in the consent process of the subject's close contacts who are at risk for contracting a putative zoonosis. Contacts should be informed, according to the FDA, but is that enough? Should intimate contacts be required to assent to the procedure or perhaps even consent, without which consent is not complete, ruling out the transplant? [29] While no current law requires consent by anyone other than a competent adult or their legal surrogate, the ethical aspects of these issues currently continue to be debated.

2.4 XTx CONTINUOUS IMPROVEMENT

Consumers of rapidly developing technology, such as cell phones, are routinely offered upgrades to the latest technology. These upgrades ensure consumer loyalty to the supplier of the technology. Consider recipients of the first generations of genetically engineered XTx. Ten genetic modifications currently combine to create less immunogenic XTx kidneys, but it is mere speculation to know where that field will be in 2 years. Should the initial recipients of genetically modified organs be blocked from access to the latest technology?

In other words, should the interest of the clinical trial sponsor and trialists in completing the study override the competing interest of the recipient in potentially upgrading their organ to one that is safer or more efficient? The same question could apply to a recipient whose disease state with a XTx improves to such a level that they would then be eligible for the standard of care human-to human transplant.

Despite the scientific incentives to complete an ongoing clinical trial, withholding a more effective new treatment from subjects in order to continue a trial should be considered unethical, a lesson learned from the Tuskegee syphilis trial. [30]

3. Brain-Computer Interfaces

Animal organs are not the only solution to problems related to human frailty, disease, age, injury, and disability: BCIs have recently become the subjects of increasing experimentation. Channeling the Six Million Dollar Man, for example, technologies and machines that connect to the human brain are being implanted to restore functions lost by injury, age, or disease. BCIs have already been tested in clinical trials to re-establish brain and muscle connections severed by a stroke or accident, restoring movement, speech,[31,32] and vision.

Four major types of BCIs have been identified:[33] 1) neuromedical applications, 2) user authentication, 3) gaming and entertainment, and 4) smartphone-based applications. [33] For our purposes, we will discuss only the implications of the first category, neuromedical applications. To examine the risks of BCIs and compare them with the risks of XTx, we will explore the vulnerability of the recipients, the transmissible infection risks of BCIs to the recipients and their close family members, the potential loss of privacy, permanent changes in the recipients, and ownership issues. While no BCIs have currently been approved by the FDA for sale as medical devices, many devices are in ongoing clinical trials. At least 21 research groups are active in BCI trials, and 28 clinical trials have been conducted over the last 25 years. [34] As the technology progresses, the time of implantation is increasing, now up to 40.2 months in trials.[34] BCI development and trials have largely been siloed, with no national or international registry to track best practices and outcomes. [34]

3.1 ETHICAL CONCERNS IN CLINICAL TRIALS OF BCI

3.1.a. Vulnerability

XTx potential recipients are medically vulnerable persons whose clinical situations disqualify them from receiving a human organ transplant, or whose disease progresses too rapidly for a human organ to become available. They are desperate to extend their lives, and the promise of XTx may seem to outweigh any risks. Like the XTx patients, persons living with neurodegenerative diseases or who experience catastrophic injury may be desperate to regain lost function or to continue to communicate. These persons are no less vulnerable in an ethical sense than the subjects enrolling in XTx trials. BCI implants are also problematic due to the permanence of the implantation, similar to XTx.

Promises of BCI augmentation beyond the restoration of function may also produce undue pressure on neurodegenerative patients. The promotion of BCIs as the technology of the future is encapsulated in the mission statement of Neuralink: "Restore autonomy to those with unmet medical needs today, and to unlock human potential tomorrow."[35] Neuralink also posits, "Redefining the boundaries of human capabilities requires pioneers."[36]

In the case of BCIs, it may be difficult to assess whether a subject retains the ability to provide informed consent for research purposes because of anatomic or functional brain alterations produced by the BCI.[37] In addition, the vulnerable patients or subjects may also have difficulty communicating their understanding of risks of a BCI and may be less likely to ask questions. [38] The Belmont Report definition of vulnerable populations seems applicable for subjects involved in BCI research.

3.1.b. Infection Risks of BCIs

Infection risks and decreased sensitivity of the brain tissue to implant signals due to scarring and foreign body reactions are considerations encountered during surgery to implant BCIs. [37,39] Such changes make subsequent surgeries and implants more difficult, similar to repeated transplantation of organs. For a BCI implant, the permanent change in surrounding human brain tissue or the signaling of the brain tissue as re-purposed by the BCI could result in a change of the subject's personality or identity. [40] A BCI that was initially viewed as autonomy-enhancing could exhibit maleficence towards its human host, like Hal 9000 in the film *2001: A Space Odyssey*.[41] Considering the putative risks of artificial intelligence generally, the BCI could evolve into a completely different entity within the human host and cause changes in the host's behavior that could endanger both the host and others.

The nature of clinical infections is generally understood as disease caused by an agent such as bacteria or viruses, but in a more general sense, an infection is the state produced by the establishment of a harmful external

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agent in or on the body of a suitable host. In that sense, a BCI can become infected and could transmit an infection to others. External malfeasance could infect a BCI through illicit hacking, termed "brain-hacking", a violation of "neurosecurity",[38] producing substantial harm to the wearer of the device, and even to close family and associates who wear similar devices or to other devices through the Internet of Things.[42] Malware infecting a BCI is only one example of cybercriminal activity that can collectively be termed "neurocrime."[38] Fear of zoonoses arising consequent to XTx drove the development of the ethical and federal regulatory requirements for life-long surveillance and repeated sampling, even at the expense of the autonomy of the recipient.[11] However, it seems a stretch to imagine that BCIs should be sampled, backed up, removed, and kept for 50 years, as must be done with biological samples of XTx recipients.

3.1.c Subject Rights Versus Mandatory BCI Explantation

If an XTx fails or is removed without a replacement organ, the clinical trial subject will likely die. If the subject, manufacturer, or clinical trial sponsor demands removal of a BCI, its removal would likely leave the subject worse off than before its introduction, although the outcome might not lead to immediate death. The term "explantation" refers to "the procedure of removing an implanted neural device from a user, which is an option that may be open, offered or even required after a clinical trial is completed or discontinued."[43]

Tubig and Gilbert have studied BCI explantation,[43] and have identified four broad reasons for removing the BCI. The first is for safety reasons if the BCI has become unsafe to the user through malfunction or through augmentation of undesirable psychiatric features or other side-effects. Secondly, the BCI may not work at all, or may not provide the intended therapeutic benefit. A third reason for explantation may be the end of the clinical trial itself, with subsequent withdrawal of the sponsor support for the device. Fourth, the legal ownership of the implanted device may be ceded to the company rather than the recipient.

The safety case for explantation is the most straightforward. Unintended actions of the recipient or subject due to faulty inputs from the BCI may lead to questions of product liability, responsibility, and accountability. [37] Tubig and Gilbert cite a case of a patient with Parkinson's disease who received deep brain stimulation with the goal of improving motor function, but the patient subsequently developed manic and megalomaniacal psychiatric symptoms.[43] In the second reason for removal, the BCI may malfunction due to device design or programming error, or due to hacking, leaving the recipient in their pre-implant state.[38] These first two explantation scenarios are ethically transparent cases of beneficence versus non-maleficence. However, the third scenario of the end of the clinical trial explantation gives us pause.

No widely accepted ethical guidelines or regulations for clinical trials mandate that a sponsoring company provide or arrange for ongoing support for participants when the trial ends if the intervention is successful. However, ethical principles suggest the importance of providing post-trial access to successful interventions under certain circumstances. Ethical guidelines such as the Declaration of Helsinki indicate that post-trial access to successful interventions should be considered, as a matter of *justice as fairness*, particularly for participants who could benefit from continued treatment and lack alternative options.[44] Also, the principle of *beneficence* indicates that sponsors and researchers are expected to ensure that potential benefits are balanced with the risks participants take during a trial, including access to effective treatments when appropriate. Such benefits might include providing continuing support after the trial ends. Moreover, respect for the subject's *autonomy* demands transparency about what they can expect after the study ends; thus, participants should be informed during the consent process about whether and under what conditions post-trial access to the intervention will be provided. If the sponsor of a clinical trial is obligated to maintain the BCI indefinitely, this obligation could be satisfied by an escrow account to guard against the company's failure as a business.

How then, should the device be handled at the end of a BCI trial or in cases of malfunction? Tubig and Gilbert have eloquently described the effects of BCI explantation on the recipient's personality, identity, autonomy, authenticity, agency, and/or self (PIAAAS). In their research, recipients described the loss of a BCI as "…experiencing that trauma of losing your own identity again…if you really do identify with the device, it becomes a part of you…"[43] Clearly, informed consent with a discussion of how the trial will end is essential. Ordinarily, at the end of the trial or in case of malfunction, the final decision to remove the BCI must remain with the subject whose bodily integrity is protected by common law prohibitions against assault and battery arising from unwanted touching. (Conversely, if a subject demands that a device be removed, the removal is at the discretion and decision of the physician.)

However, in light of the PIAAAS implications discussed by Tubig and Gilbert, we raise the possibility that subjects in their native (non-augmented) state before BCI implantation should enter into a Ulysses contract, obligating their future self (augmented) to consent to the removal as per the trial design. Ulysses contracts are a mechanism by which a patient pre-commits a future self to a course of action chosen by the past self, and empowers others to act on the decisions made by the patient in the past.[45] These have been used in psychiatry to obligate patients to receiving medicine or treatment even if the patient declines to consent at the present time.[45] While Ulysses contracts in medicine face challenges, we have argued previously in the case of XTx that they are appropriate adjuncts of informed consent in clinical trials of technologies that may have unforeseen future ramifications. [27]

While the Ulysses contract concept strengthens the position of the BCI clinical trial sponsor in the enforcement of the trial protocol, this is balanced against the emerging concept of "neurorights," which encompasses the "specific vulnerabilities and rights related to the brain and mind." [44] Neurorights ethics supports the BCI subjects' interests and obligates the clinician-investigators and BCI clinical trial sponsors to post-trial support of the subjects. [44]

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Under neurorights ethical theory, at the end of the trial, the clinician-investigators may not abandon the subjects. The clinician-investigator must clearly separate and explain their role as a trialist from that of a treating physician. In the case of a subject in whom the BCI has been successful, the clinician-investigator should be allowed to inform the subject that they have the right to withhold consent for removal of the BCI, even if the subject had previously given future consent. [46] The study subject retains the right to a treating physician who may act as an advocate for their clinical interests and retention of the device outside of the trial. If the study design allows for a potential retention of the device by the recipient post-trial, then the trial sponsor should have a business plan for continued support of the device.

3.2 BCI TECHNOLOGICAL UPGRADES: WHO OWNS THE BCI?

In the human-to-human transplantation paradigm, it is clear that the recipient owns the transplanted organ through voluntary donation. In XTx, the same rights of organ ownership would be assumed to apply but could be challenged by the companies with a vested interest in the laboratory-grown genetically modified organs.

How then do we view BCI ownership? Does that ownership remain with the company sponsor of a trial, or does it vest in the subject/recipient once implanted? Does the concept of ownership of a BCI exist on a spectrum of integration into the physical tissue or the thoughts and personality of the recipient, beyond the actual structure of the implant?

In the case of Rita Leggett, a recipient of a neural implant in a research trial, the study sponsor went out of business and no longer supported the implant function. [43] The subject attempted to purchase the implant, but was denied because no infrastructure existed to support the function of the implant. [43] She subsequently underwent surgical removal, but reported that the removal "was like taking away that part of myself that made me complete." [46]

The story of Ms. Leggett is her tragic loss of function with the explantation of the BCI. A corollary to the loss of function via explantation is the stagnation of function with the progression of technology. The BCI technology of today is likely to be eclipsed within 5 years. If the BCI trial subject has at least partial ownership rights to the implant, can the subject advocate for an upgrade in BCI technology? When does the interest of the subject outweigh the interest of the company in the completion of the trial? If the trial has already reached a conclusion, does the company have a continuing obligation to early technology subjects for ongoing maintenance or upgrades?

Answers to these and many other questions are not currently clear. As BCI trials and companies proliferate,[34] it is important that the legal and ethical questions of ownership and maintenance be explicitly disclosed to clinical trial subjects. Due to the permanence of the BCI, the trial sponsors should be required to have a plan for financial maintenance of the BCI after the end of the trial.

3.3 UNIQUE RISKS OF BCI: PRIVACY AND OWNERSHIP OF BRAIN DATA AND THOUGHTS

Privacy is the "freedom from unauthorized intrusion." [47] A BCI recipient has given authorized consent for some violation of privacy through the intrusion of the BCI hardware itself. However, unauthorized entities may query BCIs to access private information about the recipient, such as their social security number, banking account numbers and personal identification number, and home address, possibly violating the privacy of the recipient with an unwanted disclosure. [38] Substantial loss of privacy could occur if a medical insurance company or employer had direct access to personal information that the BCI recipient would prefer to remain confidential, or if a cybercriminal were to gain access to the BCI.[38] A potential also exists for coercion of a subject through inputs from the BCI. [38]

Unique to BCIs is the question of who owns the data derived from the subject's brain: the subject, the owner of the implant, the study sponsor, or a combination? Where is the data stored? Who can access that data and for what purpose? At least one researcher has suggested that BCI data stored in the cloud could be accessed by large language learning models, raising many different concerns about privacy. [35]

The US Government Accountability Office has proposed an explicit consent for data sharing, which can be withdrawn, or a mechanism by which the subject could store their data outside of the implant. [48] The state of Colorado also has recently added neurological data to the Colorado Privacy Act. [49]

4. Concerns Common to Clinical Trials in XTx and BCIs: Ethics and Regulatory Issues

Substantial differences exist between the ways XTx and BCIs are regulated and approved for human use. Regulatory oversight of XTx is provided by the FDA's Center for Biologics Evaluation and Research[50], while BCIs fall under the purview of the FDA's Center for Devices and Radiological Health. [48] XTx studies require Investigational New Drug Application for clinical trials, while BCIs typically require an Investigational Device Exemption. Safety and efficacy considerations for XTx focus on preventing development and transmission of zoonoses, while those for BCIs focus on surgical safety, device functionality, and local tissue effects, such as infection and scarring.

Common to both XTx and BCIs, however, are ethical issues that should be included in trial protocols.

1. *Vulnerability*: Clinical trials for both XTx and BCI should face additional scrutiny due to the vulnerability of the recipients. Both of these technological categories involve potentially life-saving but permanent implantation of foreign materials with life-long risks. These trials should be explicitly included in the US federal regulations of clinical trials, and reviewed by the local Institutional Review Boards (IRBs) with additional scrutiny of the vulnerability of trial participants.

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2. *Surveillance for infection risks*: Current XTx regulations explicitly call for lifelong surveillance for the subject and the recipient's close family members because of possible development and transmission of zoonoses. BCIs may also be vulnerable to infection with malware that could theoretically be transmitted to other connected devices. However, we do not argue for extension of the life-long surveillance requirements of XTx to BCI recipients and their families. Given the lack of evidence of infection risk from XTx, the onerous mandate for life-long surveillance of the recipient and family members in XTx should be reviewed routinely and potentially revised to a shorter time period when justified by the evidence.
3. *Equivalence of the right to withdraw from an XTx clinical trial and a BCI trial*: Integral to the current XTx life-long surveillance regulations is the abrogation of the right to withdraw from a clinical trial because of potential consequences to others. Similarly, if a subject wishes to withdraw from a BCI trial and substantial risk to the subject or others is identified, it might be necessary to couple the right to withdraw with a mandatory explantation of the BCI if technically feasible. In such a case, that requirement should be explicitly stated in the informed consent documents and may require a type of Ulysses contract agreement.
4. *Empowerment to act on the need to remove an organ or device:* Organs and implants can deteriorate over time or become increasingly dangerous to the recipient or others. Disagreement about what should be done may occur when such a point is reached. The question of who is empowered to act on the need to remove or replace the XTx organ or the BCI should be clarified and explicitly included in the protocol. Disagreement can be addressed in advance through use of a Ulysses contract.
5. *Implications of ownership in advancing XTx and BCI technology*: As technology evolves, the recipient of an XTx may become eligible for a human organ or a newer, less immunogenic XTx organ. Similarly, the original BCI may be eclipsed in a few years by newer technology. The clinical trial protocol should specify contingency plans if new breakthrough technology becomes available. In addition, questions of ownership or interest in permanent implantable technology should be explicitly clarified in the clinical trial protocol and consent. The ongoing financial obligations of the clinical trial sponsor for ownership of the implanted technology should also be explicitly outlined. To avoid abandonment of trial subjects with permanent implants, trial sponsors should have a transparent financial underwriting plan for the technology maintenance or upgrade for the BCI or XTx recipients.
6. *Ownership of the data and digitally recorded experiences*: Data from and information about an XTx or BCI recipient can be personally sensitive, giving rise to privacy concerns. Ownership and control of personal experiences and data — and for BCI recipients, the subject's digitally recorded experiences — should be explicitly delineated in the protocol, and governmental regulation may be necessary to protect the "neurorights" of the subjects

5. Conclusion

Human injury and disease may be treated and reversed with a variety of novel approaches, including XTx and BCIs. As these modalities continue to evolve, we must act to ensure that we don't lose the essence of our humanity because of focus on technology. Integral to this effort is the protection of human subjects in future clinical trials of BCIs and XTx. We have addressed some of the special issues affecting both XTx and BCI and have suggested some solutions to the novel ethical problems they have introduced.

This is an exciting time in the medical sciences, especially in clinical research, which is advancing the good of humanity in part by using the remarkable new tools provided by the basic sciences. Close adherence to ethical guides and strictures will redound to the benefit of the investigators who design and execute studies, biomedical science as a whole, and the patients who are the ultimate beneficiaries of clinical research.

Conflicts Of Interest:

The authors have no conflicts of interest to declare.

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