# How Past Biomedical Interventions Inform the Emerging Ethical Concerns Surrounding Artificial Organs

A Research Paper submitted to the Department of Engineering and Society

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

**Juan Martin Carrasco Carvajal**

Spring, 2021

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Advisor

Sean M. Ferguson, Department of Engineering and Society

# How Past Biomedical Interventions Inform the Emerging Ethical Concerns Surrounding Artificial Organs

According to the United Network for Organ Sharing (UNOS) and the Health Resources & Services Administration, there are currently more than 109,000 people in the U.S. on the waiting list for a lifesaving organ transplant. One person is added to this list every minute and 17 people waiting for an organ transplant die every day (*Organ Donation Statistics*, 2018). The emerging field of tissue engineering presents one possible future solution to this problem in the form of on-demand organ printing. It is important to note that scientists are still far from being able to print fully functioning complex organs that are biocompatible and have proper vasculature (Yasinski, 2020). However, the successful development and implementation of organoid models, organ on a chip models, and smaller tissue constructs point to the tremendous potential for 3D bioprinting. Therefore, it stands to reason that the research focus and direction of the field of tissue engineering make organ printing an inevitable reality one day.

Despite this promise and the hype that is present in the media and news headlines, there is a lack of literature addressing the ethical implications of 3D bioprinting artificial organs (Vermeulen et al., 2017). To ensure future success of this technology, it is important to start envisioning and preparing for ethical landscape surrounding the technology. When anticipating the societal impact of a new technology, it is useful to look at previous technologies that share similarities. In doing so, it is necessary to first establish the justifications for such comparisons that allow predictions to be made about future ethical concerns. The present work considers the successes and failures of past implantable biomedical interventions and how they inform the future of this emerging technology of synthetic tissues and artificial organs. In doing so, these ethical concerns will be evaluated from the perspective of researchers, bioethicists, and other experts involved in this field.

## Establishing an Anticipatory Ethics Framework

The absence of this conversation about social and ethical concerns is made apparent by the lack of clear, standardized regulations or guidance over how this kind of research with synthetic tissues should be applied to humans and translated to the clinic. A recent publication in the Journal of Medical Ethics revealed these gaps in regulation by examining the current practices when testing artificial organs on brain-dead patients (Truong, 2019). They noted that of particular concern were the questions of candidate selection, transparency, and sensitivity. This initial effort by key actors including researchers and bioethicists is the beginning of a larger conversation that needs to happen. Examining expert material from researchers and ethicist – such as the aforementioned study in the Journal of Medical Ethics – will shed light on what ethical aspects of the technology in question require more attention from future stakeholders.

The present effort to establish an anticipatory framework for the problems that will arise from artificial organs will draw from the work of Hutchison & Sparrow (2016) who conduct a similar analysis by comparing artificial organs to the pacemaker. The authors identified five key features of the pacemaker which gave rise to many ethical concerns. These features are implantation, complexity, software, continuing improvement of technology, and commercial interests. The authors explore a variety of ethics concerns that arise out of these features and ultimately claim that the same issues will likely arise with artificial organs since the technologies share those features. A similar approach will be applied herein drawing comparisons to multiple past biomedical technologies from the perspective of the aforementioned experts as it is understood from available literature.

## Comparing Past and Future Biomedical Technologies

The three biomedical interventions chosen for consideration are pacemakers, insulin pumps, and artificial joints. These medical devices represent a sampling of different biomedical technology platforms and have an interesting history of clinical translation dating back to the middle of the 20$^{th}$ century. This time span allows a thorough retroactive analysis of their development, successes, and challenges through

the years. They also each effectively demonstrate key ethical concerns to be discussed. There are three features which these devices share that justify the comparisons to be made with artificial organs. First, all three engineered devices have varying degrees of complexity and require some form of invasion into the patient's body or life. Bioprinted organs will undoubtedly be complex constructs with multiple cell types, biomaterial scaffolds, growth factors, and potentially even drugs. Additionally, the ultimate goal of on-demand organ printing is direct implantation into the patient to replace damaged or diseased organs. As such, this will no doubt require some form an invasive procedure – likely surgery. The second key feature which these past devices share with artificial organs arises from the nature of implantation. These are exogenous, man-made devices which not only become physically integrated with the patient body but also support or even replace vital bodily functions. So, these devices inherently bring with them questions of privacy, patient autonomy, and proprietorship. These concerns will likely be even more pressing with artificial organs which will potentially completely replace existing organs and will be capable of complete biological integration with the patient's body. The final shared feature in this ethics framework is that these engineered devices these interventions are subject to updates, upgrades, and general improvements. This raises a host of ethical concerns including financial conflicts of interest and limited accessibility to treatment which will explored below.

## Insulin Pumps

### Patient Privacy

The insulin pump is essentially a simplified artificial pancreas in that it compensates for impaired blood glucose regulation in patients with Type I diabetes – a chronic condition characterized by lack of insulin production and secretion by the pancreas (Alsaleh et al., 2010). The device is a small computerized pump connected to an injection site on the patient's abdomen or thigh via tubing to deliver small amounts of insulin throughout the day depending on the programmed settings. These settings require calibration and adjustment by the user and their healthcare provider according to the patient's daily schedule, activity level, and even what food they consumed at a given meal (Quintal et al., 2019).

The need to provide detailed personal information on such a regular basis is worth consideration as it poses an unavoidable threat to the patient's privacy and comfort. This form of invasiveness is one that is easily overlooked. Further patient privacy concerns also arise from the use of patient information transmission features of modern insulin pumps which send the patient's clinical data between the device, a web platform (https://www.diasend.com and https://www.carelink.minimed.com are the most popular), and a third party application accessible to the patient's healthcare provider as well. This system is inherently vulnerable to security breaches by hackers who can even potentially modify the data thus delivering an incorrect, life-threatening insulin dose to the patient (Quintal et al., 2019). Therefore, the question needs to be asked whether increasing complexity of a device is necessary or beneficial when handling such delicate health information. Patient privacy is similarly at the center of the discussion around ethics concerns of tissue engineering and future artificial organ technology. In the case of bioprinted artificial organs, the source of cells is an issue which presents opportunity for invasions of privacy. For example, in a paper submitted to the 2021 International Conference on Biomaterials, Artificial Organs, and Tissue Engineering (ICBAOTE), the authors reference a review which identified two key issues in regards to harvesting human cells for biofabricating organs for implantation to another patient (Al-Darkazly, 2020). The first is the need to protect the privacy of the donor through anonymization of the donor cell samples. Deidentified human cell lines are currently employed in biomedical research including tissue engineering so this practice will have to extended to bioprinting artificial organs (Varkey et al., 2015). The second is the need for determination of who, if anyone, has ownership over the cells used for tissue engineered organs. This issue needs to be resolved in order to reconcile the fact that the cells from one donor are growing in another person's body. Further, ownership over the cells would allow researchers to patent their work and perhaps even the cell lines used if, for example, they have some novel genetic modification (Varkey et al., 2015). However, the latter raises the question of if a person's cells should be patentable by another entity whether a researcher or a company.

### Public Accessibility to Novel Technology

While insulin pumps exemplify an advancement in type 1 diabetes care, this therapy is unfortunately not accessible to all. In the United States, studies have shown that non-Hispanic white youths with higher socio-economic status are more likely to have access to insulin pump therapy. Additionally, they found that lower education, low socioeconomic status, and life misfortunes often pose as barriers to access to insulin therapy(Quintal et al., 2019). This trend is ubiquitous in the United States healthcare system where the insurance coverage offered to people of lower socioeconomic status often does not cover insulin pumps and other expensive treatments. Another way in which the allocation of treatments is influenced through clinical trial enrollment. Past historical injustices, misconduct, and victimization towards minorities in the United States healthcare system, including unethical experimentation and compromising of informed consent, has resulted in very low rates of clinical trial enrollment among minorities (Phillips, 2020). This vast underrepresentation of minorities in clinical trials creates a disproportion in the resources to study diseases affecting whites versus minorities and ultimately results in more therapies and medications for diseases affecting whites versus minorities. This lack of equal access to insulin pumps and other medical technologies will likely be even more apparent with clinical translation of artificial organs which will have a very high cost. This highlights how the tendency for technological improvement also yields increasing costs and therefore limits accessibility. How successful or impactful can a new biomedical technology really be if it is only offered to a small subset of the population? These high costs mean that all the benefits of medical technology produced by publicly funded research will only be accessible to a small, affluent subset of the population (Varkey et al., 2015).

## Pacemakers

### Challenges in Clinical Trial Design

Internal pacemakers are implanted biomedical devices with electrodes connected directly to the heart in order to deliver short electrical impulses to the heart which regulates cardiac rhythm in patients with a low resting heart rate (Kotsakou et al., 2015). These devices are subject to FDA regulation under the Center for Devices and Radiological Health as a Class III device due to the nature of the risks

involved with implantation and defibrillation (*U.S.C. Title 21 - FOOD AND DRUGS*). As such, researchers developing these devices are required to provide data from clinical trials that demonstrates safety and efficacy of the device – a process similar to that of pharmaceutical drug approval. However, the typical randomized double-blind clinical trial design for pharmaceuticals is not easily extended to these devices because this requires subjecting the control group to the risks of surgery without actually giving them the therapy – an apparent ethics violation (Citron, 2012). Unlike pharmaceuticals which can have systemic side effects and require careful determination of a therapeutic window, – the dose which maximizes efficacy and minimizes toxicity – the nature of biomedical devices is to provide a specific localized action upon the target tissue. Therefore, the ethics of unknowingly withholding treatment from subjects for the sake of a clinical trial are questionable (Citron, 2012). The FDA has offered some guidelines on this issue by encouraging the use of crossover trials in which the patient population is split in half and randomly assigned to the control or experimental group. Halfway through the trial period they switch the groups so that each patient effectively serves as their own control (Citron, 2012). This design works well with pacemakers which can be switched on and off; however, this solution does not extend to future fully functional bioprinted artificial organs without electrical components that can be easily switched on or off. Therefore, this issue exemplified by pacemakers presents a real ethics issue for the future and has been identified by those in the field. In fact, the issue of clinical trial design in tissue engineering was noted by Al-Darkazly et al. in their 2020 study submitted to the 2021 ICBAOTE. They cited two other works which call for a comprehensive regulatory framework from the FDA regarding production of medical devices and clinical trial design (Varkey et al., 2019; Varkey et al., 2015). As we envision the future of artificial organs, there is a need for a clinical trial design which does not subject patients to unnecessary risks of surgery or withhold treatment from patient groups, yet produces scientifically reliable safety and efficacy data. This

### Proprietorship and Patient Autonomy

Delegating authority over the deactivation of pacemakers is a critical ethics question identified by Citron et al. (2012) in their review of ethics considerations in medical device development. They report a

lack of clear guidelines for the course of action when the patient is close to death and cardiac pacing therapy is no longer desired or perhaps not medically appropriate. In these cases, the device will deliver a series of shocks to the patient in a useless attempt at revival which can be very painful and cause muscle spasms which are disturbing for the loved ones watching. However, protecting a patient's right to accept or refuse treatment after being informed of the options is a cornerstone of the United States healthcare system. Though some guidelines have been proposed by independent groups and researchers, there is still no agreement on what the proper course of action is (Citron, 2012). This issue is one that could also apply to artificial organ technology in cases where, for example, the patient is succumbing to comorbidities and wishes to discontinue or reject the use of a life-sustaining organ. If the organ still has multiple years of vitality left, who makes the determination of whether the patient should receive or keep the organ? The latter also raises a very peculiar ethics question which is that of proprietorship. If the device is supporting the patient's life and is inside their body then can the manufacturers or patent assignees have any claim to it? In the case of traditional organ donation, proprietorship is not problematic since the organ belongs to a fully consenting donor who is often already deceased. However, in the case of organs that are manufactured by biotechnology companies using patented technology and perhaps even patented cell lines, it is possible that companies will want to keep their claim on these organs. This has implications in the aforementioned decision to discontinue treatment because there are external stakeholders besides the patient.

The issue of patient autonomy is further complicated when it comes to research on artificial organs. Parent et al. (2020) identified a lack of laws and guidelines regulating testing and research of artificial organs and similar tissue engineering work on deceased subjects. The authors say this work is critical to successful clinical translation of bioprinted organs but it needs to be done in an ethical manner. The central issue identified in this context is getting consent from the deceased subject's family or loved ones. In an interview with Brendan Parent, bioethics professor at NYU medical center and lead author of the aforementioned study, he reiterates the necessity for biomedical research with artificial organs on deceased subjects but also emphasizes the need to get authorization from family members or ensure that

extending given consent for organ donation to research work is not an ethics violation (Evans, 2019). This work was funded by United Therapeutics and arose from their need for guidelines before proceeding with their tissue engineering work in the absence of government guidelines (Truong, 2019). This highlights the need for a larger conversation on the ethics of artificial organs as the field of tissue engineering moves closer and closer to the reality of on-demand organ printing.

## Artificial Joints

### Conflicts of Interest

The articular surface replacement (ASR) hip developed by DePuy Orthopedics (a subsidiary of Johnson&Johnson) is an interesting case study of regulatory failures and ethical violations in the medical device industry. This device was launched in the late 1990s and over the next ten years there were reports of many complications including pain, inflammation, infection, tiredness, nausea, visual impairments, limited mobility, tinnitus, heart palpitations, depression, and high revision rates meaning the need to re-operate. By 2010, high premature failure rates were discovered and the company's R&D division found that they had used incorrect or inadequate standards for assessing implant performance (Johnson & Rogers, 2014). After a two-year period of strong denial, DePuy Orthopedics eventually issued a worldwide recall on all ASR hips and the company now faces over 10,000 lawsuits (Racine, 2013). A number of ethics violations were discovered including surgeons receiving royalties and direct financial inducements from DePuy, surgeons being paid by DePuy to speak at events, surgeons failing to disclose their financial stake to patients thereby compromising informed consent, and surgeons failing to properly report or act upon the discovery of these problems (Johnson & Rogers, 2014; Racine, 2013). At the root of all these ethics violations and conflicts of interest is the multidisciplinary collaboration between physicians and biotechnology companies that is required for the development of medical devices due to their complexity. It is important to anticipate this issue with artificial organ technology and initiate efforts to mitigate it since artificial organs will require similar, if not greater, levels of collaboration due to its complexity. Varkey et al. (2015) note the need for future physicians implementing artificial organ

technology to declare any conflicts of interest as part of good clinical trial design and to ensure informed consent is provided. Seeing as how their work was cited in the 2021 ICBAOTE, it is a conversation that is just starting and needs to continue.

### Need for Regulation

The example of DuPuy's ASR hip recall also revealed a severe lapse in regulation on behalf of the FDA. It revealed the FDA's inability to properly enforce its adverse event disclosure rules even in the even that a company does not comply. Further, although the administration claims the power to impose legal and financial sanctions on non-compliers, it also states on their website that it "relies on the goodwill and cooperation of all affected groups to accomplish the objectives of the regulation" (Racine, 2013). This lack of enforcement is also evidenced by a study that found that four out of five clinical trials which were subject to the FDA's 2007 policy to publish all clinical trial data on it's website did not comply and not a single company faced consequences. So, while DePuy and its partner surgeons failed to report the issues with the ASR hip, the question must be asked whether reporting these issues to the FDA is enough to fulfill one's ethical obligations. Looking to the future, this issue is further complicated by the fact that bioprinted organs are likely to be combination products requiring regulation from multiple regulatory bodies. Tissue-engineered skin is one such example because this product would include pharmaceuticals, medical devices, biologics, and application of surgical procedures all of which are regulated by different rules and agencies between the FDA and the Department of Health and Human Services (Varkey et al., 2019). Additionally, as previously mentioned, artificial organ research will require research on recently deceased subjects. Currently, hospitals and universities in the United States have no oversight body to review research on deceased subjects (Capel, 2019). Furthermore, existing internal review boards are not appropriate regulatory bodies for overseeing this kind of research because they oversee work on human subjects and deceased subjects present different concerns which merit the focus and consideration of a separate review committee (Evans, 2019; Parent et al., 2020). It is clear that the necessary institutions and rules to ensure ethical standards and practices with all work associated with artificial organs in the future are currently not in place. Without establishing a proper regulatory system

for the emerging technology of artificial organs and tissues, the regulatory failures revealed during the ASR hip case study will only be exacerbated in the future. The tendency for improvement in biomedically engineered devices as well as the inherent complexity of these devices will continue to require new ethics considerations that merit new rules and guidelines moving forward.

## Conclusion

This analysis revealed numerous ethics concerns and questions that will likely surround artificial organ technology in the future on the basis that this technology shares key similarities with past insulin pumps, pacemakers, and artificial joint which presented a host of ethical concerns. Among these are patient privacy and autonomy concerns, limited accessibility to treatment, device proprietorship concerns, need for better device regulation, potential for conflicts of interest, and challenges in clinical trial design. While this is not an exhaustive list it offers directions for future discussion on the topic in the hopes that this conversation will become a priority among bioethicists and tissue engineering researchers.

## References


Al-Darkazly, I. A. A. (2020). Optimization of Mechanical Properties of Alginate Hydrogel for 3D Bio-Printing Self-Standing Scaffold Architecture for Tissue Engineering Applications. *International Journal of Biomedical and Biological Engineering*, *14*(12), 419–427.

Alsaleh, F. M., Smith, F. J., Keady, S., & Taylor, K. M. G. (2010). Insulin pumps: From inception to the present and toward the future. *Journal of Clinical Pharmacy and Therapeutics*, *35*(2), 127–138. https://doi.org/10.1111/j.1365-2710.2009.01048.x

Capel, A. (2019, November 8). *Testing Manufactured Organs on the Recently Deceased Raises Ethical Concerns*. Medical Bag. https://www.medicalbag.com/home/news/testing-manufactured-organs-on-the-recently-deceased-raises-ethical-concerns/

Citron, P. (2012). Ethics Considerations for Medical Device R&D. *Progress in Cardiovascular Diseases*, *55*(3), 307–315. https://doi.org/10.1016/j.pcad.2012.08.004

Evans, G. (2019, December 1). *Bioengineered Organ Research on the Recently Deceased*. https://www.reliasmedia.com/articles/145383-bioengineered-organ-research-on-the-recently-deceased?v=preview

Johnson, J., & Rogers, W. (2014). Joint issues – conflicts of interest, the ASR hip and suggestions for managing surgical conflicts of interest. *BMC Medical Ethics*, *15*, 63. https://doi.org/10.1186/1472-6939-15-63

Kotsakou, M., Kioumis, I., Lazaridis, G., Pitsiou, G., Lampaki, S., Papaiwannou, A., Karavergou, A., Tsakiridis, K., Katsikogiannis, N., Karapantzos, I., Karapantzou, C., Baka, S., Mpoukovinas, I., Karavasilis, V., Rapti, A., Trakada, G., Zissimopoulos, A., Zarogoulidis, K., & Zarogoulidis, P. (2015). Pacemaker insertion. *Annals of Translational Medicine*, *3*(3). https://doi.org/10.3978/j.issn.2305-5839.2015.02.06

*Organ Donation Statistics | Organ Donor*. (2018, April 10). https://www.organdonor.gov/statistics-stories/statistics.html

Parent, B., Gelb, B., Latham, S., Lewis, A., Kimberly, L. L., & Caplan, A. L. (2020). The ethics of testing and research of manufactured organs on brain-dead/recently deceased subjects. *Journal of Medical Ethics*, *46*(3), 199–204. https://doi.org/10.1136/medethics-2019-105674

Phillips, L. (2020, October 16). *Tough on Anti-Vaxx Nonsense, Tough on the Causes of Anti-Vaxx Nonsense*. https://jacobinmag.com/2020/10/anti-vaccination-pseudoscience-experts-covid-19-science

Quintal, A., Messier, V., Rabasa-Lhoret, R., & Racine, E. (2019). A critical review and analysis of ethical issues associated with the artificial pancreas. *Diabetes & Metabolism*, *45*(1), 1–10. https://doi.org/10.1016/j.diabet.2018.04.003

Racine, J. (2013). *Orthopedic Medical Devices: Ethical Questions, Implant Recalls and Responsibility*. 4.

Truong, G. (2019, October 14). *Bioethicists guide researchers in artificial organ studies*. https://yaledailynews.com/blog/2019/10/14/bioethicists-guide-researchers-in-artificial-organ-studies/

*U.S.C. Title 21—FOOD AND DRUGS*. (n.d.). Retrieved April 11, 2021, from https://www.govinfo.gov/content/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec360e.htm

Varkey, M., & Atala, A. (2015). Organ bioprinting: closer look at ethics and policies. Wake Forest Journal of Law & Policy, 5(2), 275-298.

Varkey, M., Visscher, D. O., van Zuijlen, P. P. M., Atala, A., & Yoo, J. J. (2019). Skin bioprinting: The future of burn wound reconstruction? *Burns & Trauma*, *7*(1), 4. https://doi.org/10.1186/s41038-019-0142-7

Vermeulen, N., Haddow, G., Seymour, T., Faulkner-Jones, A., & Shu, W. (2017). 3D bioprint me: A socioethical view of bioprinting human organs and tissues. *Journal of Medical Ethics*, *43*(9), 618–624. https://doi.org/10.1136/medethics-2015-103347

Yasinski, E. (2020, February 26). *On the Road to 3-D Printed Organs*. The Scientist Magazine®. https://www.the-scientist.com/news-opinion/on-the-road-to-3-d-printed-organs-67187