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ORIGINAL PAPER

Development of a Tissue Engineered Heart Valve for Pediatrics: A Case Study in Bioengineering Ethics

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Abstract The following hypothetical case study was developed for bioengineering students and is concerned with choosing between two devices used for development of a pediatric tissue engineered heart valve (TEHV). This case is intended to elicit assessment of the devices, possible future outcomes, and ramifications of the decision making. It is framed in light of two predominant ethical theories: utilitarianism and rights of persons. After the case was presented to bioengineering graduate students, they voted on which device should be released. The results revealed that these bioengineering students preferred the more reliable (and substantially more expensive) design, though this choice precludes the majority of the world from having access to this technology. This case is intended to examine and explore where the balance lies between design, cost, and adequate distribution of biomedical devices.

Keywords Bioengineering ethics · Biotechnology · Biomedical devices · Decision making

Introduction

The following case study was developed and presented in a graduate Bioengineeing Ethics course at the University of Pittsburgh during the Spring of 2005. It was intended to address biotechnological device development from the point of view of a bioengineering company prior to releasing the device to the general public. As a teaching exercise, it was designed as a mock advisory meeting for a fictional company in order to reach a voting consensus about the release of a new device.

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This new device will be used to develop tissue engineered heart valves (TEHVs) prior to surgical implantation for pediatric patients. This issue is medically relevant because there are currently few heart valve replacement options for the pediatric population. Moreover, this case was meant to address the question of how to balance design, cost, and adequate distribution of biomedical devices prior to their release. All votes were from graduate bioengineering students, in addition to the instructor. In the following pages, the facts of the case, results of voting, and future eventualities are presented. Please note that the only factual portion of this paper is the theory of the technology and design and price of the devices; no preliminary data or future eventualities are factual.

Case Study

PediaValve Corporate Overview

PediaValve is a start-up company which spun-off from academic research to develop a pediatric TEHV. They have spent the last three years developing two devices that can be used to rapidly develop TEHVs for implantation. These devices, known as bioreactors, ideally provide a sterile environment for exercising tissues or organs to make them mechanically and biologically prepared for their intended function once surgically implanted. PediaValve is one of many companies that are pursing this work, however, they are the smallest and their future will be determined by the device's success: if they do not release their device before some of the larger companies, they will likely be forced to close as they have invested all of their resources into this project. In order to decide which device should be released, the managers have called a meeting that includes PediaValve's scientists and engineers. All of the members of this meeting have a stake, either intellectually and/or financially, in the chosen product's success. The following sections represent the oral presentation given at the meeting.

Need for a Pediatric Alternative

Heart valves serve two important functions: (1) assuring that circulating blood flows in only one direction through the heart and; (2) allowing the chambers of the heart to alternately fill for ejection. Heart function is extremely impaired by valve dysfunction and valvular heart disease is a prevalent killer in the United States: in 2002, nearly 20,000 people died from various forms of the disease [1]. While valvular disease, either acquired or congenital, can easily result in death, there are options for a large portion of the population. For healthy adults, mechanical heart valves are suitable as they have excellent durability and longevity. However, for some other patient populations the situation is more problematic. Elderly patients and unhealthy young persons typically receive bioprosthetic valves (usually made from pig valves or other animal tissue) or cadaver homograft valves. The need for future surgeries and the accompanying risk make bioprosthetic valves a poor choice

for pediatric patients. Furthermore, because homografts are extremely limited for the pediatric population due to size restrictions, an ideal solution would be a TEHV that could grow with the patient once it is implanted, eliminating the need for future surgeries, which have increasing morbidity rates with each subsequent surgery.

Developing a TEHV

As just discussed, there is a pressing need for a pediatric TEHV because there are currently few satisfactory options for this patient set. However, valves must be prepared to function upon surgical implantation. Unlike cases in orthopedics, the valve cannot be immobilized to allow acclimation once implanted (this would require the heart to be stopped for an extended period of time), and the physical demands on the valve require that the implant be fully functional immediately. Once a TEHV construct has been fabricated and prior to surgical implantation, it must be trained in a bioreactor to initiate proper tissue and biological function. To address this need, PediaValve has developed two bioreactor devices that they believe offer many similar but nevertheless distinct advantages in TEHV development.

Option #1—Total Heart System

The first design was created three years ago and is called the Total Heart System (THS). The THS is, as precisely as can be obtained, a replica of the human heart. It offers near flawless hemodynamic performance and laboratory studies have been excellent. Animal trials have also been very promising with the THS. To date, 20 sheep have been explanted at 20 weeks with a TEHV developed in the THS, and these TEHVs resemble the animal's native valve. The identified pros, cons, and costs of the THS can be seen on the left in Table 1.

Option #2—Modular Valve Unit

The second design was born from the first, with the THS simplified dramatically, removing components that were costly and not deemed 'absolutely essential' in order to decrease the size and usability of the unit. The resulting design is the Modular Valve Unit (MVU). While performing essentially the same function, the MVU and THS are vastly different in their efficacy and performance. The MVU does not replicate heart function, but it is not known if this is needed, or if the TEHV can properly develop in sub-optimal conditions. Laboratory studies have shown that 25% of TEHVs fabricated in the MVU present with slight defects (as compared with 0% in the THS). These defects are important because the implanted valve will be exposed to high pressure, and defects can lead to tearing, causing the valve to fail. Animal studies have shown that the MVU develops valves to a comparable level of the THS; however, the animal explants were not as promising as with the THS 20 weeks after implantation. The identified pros, cons, and costs of the MVU are shown on the right in Table 1.

Table 1 Estimated Pros, Cons, and Costs of THS (left) and MVU (right)

THS-Pros	*MVU-Pros*
–Develops valves to near perfection	–Inexpensive ($2,500 each) and single user devices
–Suitable for up to five sequential TEHVs	–Easy to use; short training course for surgeons (1 day)
THS-Cons	
–Expensive ($30,000 to build and $50,000/year to operate and maintain per bioreactor)	–No on-site tech needed to maintain units
–Requires highly trained personnel to operate	–Can be distributed worldwide
–Device will be 'reused' four times	*MVU-Cons*
–Will only be located in four regional centers in the US (San Francisco, Atlanta, Pittsburgh, and Dallas)	–Provides acceptable (but not ideal) tissue development –No feedback (pressure, flow)
THS-Costs	–Has not achieve results of the THS
–$30,000 for each new THS	
–$50,000 for operation/yr	*MVU-Costs*
–$1,500,000 for insurance/yr	–$2,500 for each new MVU
–4 centers with 5 units	–$100,000 for surgeon training/yr
–Each unit can be used five times	–$500,000 for insurance/yr
–Estimate that 100 children/year will have access to the device	–Estimate that 1,000 children/year will have access to the device
$3,100,000 Cost	$3,100,000 Cost
Cost x 2 (for profit) = $6,200,000	Cost × 2 (for profit) = $6,200,000
$62,000 per patient + surgeon and hospital fees	$6,200 per patient + surgeon and hospital fees
Will save 100 children/year	Will save 1,000 children/year

Other Considerations

To date, both devices have received FDA approval as Class I devices that do not require clinical trials. Clinical trials were not required as these are considered non-implanted, delivery devices (like a catheter) with all components being FDA approved biomaterials. No further approval is needed from the FDA before either product is released.

The company cannot manage the necessary overhead to support both devices. Therefore, a choice has to be made as to which will be released into the marketplace. Note that for the sake of argument one should assume that there will be equal profits from either choice (Table 1) so that the decision would not be influenced by concern for profits. Each device has its own requirements that must be addressed. THS devices require technical support, insurance, and maintenance because they will be controlled and run by the company at the regional centers. On the other hand, the MVU will be sold as a simple device that requires the purchasing surgeon to be trained for one day by PediaValve, thus less insurance is needed for

the MVU versus the THS. Hence, PediaValve is 'married' to the THS device in a much more intimate and sustained way.

Discussing the Ethical Issues (Prior to Voting)

In order to consider the possible ramifications of this decision prior to voting, it was discussed with those in attendance within the framework of two common ethical theories. Utilitarian theory and rights of persons (or liberal individualism) theory were chosen to highlight the points of consideration in this case as they are two of the most common theories from which many ethical dilemmas are argued. The comments and questions raised in the following sections were put to the students in order to try to inform the decision they were attempting to make. Additionally, questions were raised to elicit thought and dialogue.

Utilitarian Theory

Using utilitarian theory [2] to analyze this decision is useful in that it requires estimation of eventualities and probable outcomes [3, 4]. In order to clarify the good and the bad, it is useful to identify interested parties and possible outcomes. The interested parties are the patients, their families, the surgical team, and the company. The possible outcomes include life or death for the patients, and the resulting ramifications for their families and the healthcare staff. As the THS is superior to the MVU in developing TEHVs, it appears that the THS has the most likelihood to save a particular child's life. With the THS's effectiveness comes high cost that, unfortunately, would preclude the majority of the world from being able to afford the technology, including those without medical insurance and those that are not wealthy.

The MVU allows wide-spread distribution that could reach patients where there are currently few options. Though the MVU does allow for much greater distribution, it is still prohibitive to poorer patients or those without medical insurance; however, it is believed that its price is more feasible for those in lower-to-middle socio-economic levels. While distribution increases with the MVU, concerns remain about the device's efficacy in developing a competent TEHV. This concern highlights a somewhat gray area for nearly all ethical theories, that is, maintaining a distinction between morally obligatory and supererogatory (e.g. going beyond the requirements of duty) actions [3]. Is the risk of releasing the MVU acceptable if this device is considered supererogatory in light of all children worldwide having few options for heart valve replacement? Or, is PediaValve held to a professional obligation of releasing the best product possible for their patients? The THS is not considered supererogatory in this instance because it would not be released with the presupposed risks that exist for the MVU. Though this is not the typical application of these distinctions, they seem suitable on this occasion. For instance, assume that the THS did not exist; would there still be a question as to whether the MVU was worth the risk or is it

only by comparison that the MVU appears sub-par and causes concern about efficacy?

Rights of Persons or Liberal Individualism

A problem that utilitarianism typically faces is unjust distribution, permitting the majority to override the interest and rights of the minority [3, 4]. All members of this current meeting are wealthy US citizens who have medical insurance, and if they had a child receiving a TEHV, they would undoubtedly choose the THS. Therefore, if all are motivated to vote for their own interests and the THS is chosen, does this resemble unjust distribution for the uninsured or poorer patients? While all surely want the best treatment for their children, can one demand it at the cost of no treatment for other children? This can be scrutinized with Immanuel Kant's 'Categorical Imperative' [5]. While a person may 'will' that everyone's child receives the best possible treatment, this is not a possibility. If the THS were chosen, this would result in possibly 100 children per year given a treatment option, while if the MVU were chosen, this would result in possibly 1,000 children per year given a treatment option. From the aforementioned laboratory studies, equal confidence does not exist in the TEHV development capability of the two devices. So, how is one to weigh efficacy of treatment with the number of those treated?

Additionally, the question of individual rights is intimately tied to utilitarianism, but should be considered in more detail here. Primarily, one must be concerned with the MVU and the question of the right to decent minimum health care for the individual. Though this right is just, it is not an absolute right and must be scrutinized. As these devices provide life saving capabilities as a service to the recipients, the right of the patient is termed a 'positive right' and implies an obligation by the providers [3]. Here again, the idea of obligation arises, but now it is being correlated with rights. If the product is considered supererogatory, can it be an obligation?

Voting by Meeting Members

This case and these ethical questions were put before those in attendance for their vote. Voting members that day tallied 9 for the THS and 6 for the MVU (including the author). The overriding motive for the decision was the efficacy of the THS and reservations about the risk associated with the MVU.

Future Eventualities

As this was an exercise in bioengineering ethics and in order to assess their decisions, the meeting members were then presented with hypothetical future eventualities that might come about as a result of one or the other decision (Table 2). Obviously, hindsight is 20/20 and these outcomes could not have been

Table 2 Future *hypothetical* eventualities of choosing either the THS or MVU

If the THS was chosen	*If the MVU was chosen*
Over the next 20 years (with product improvement), 2,000 children in the US were implanted	Over the next 20 years (with product improvement), 20,000 children worldwide were implanted
• 5% surgical mortality (100 children)	• 5% surgical mortality (1000 children)
• 1% died due to acute valve failure within one year (20 children)	• 10% died due to acute valve failure within one year (2,000 children)
• 0.5% died due to chronic valve failure (next 19 years, 10 children)	• 20% died due to chronic valve failure (next 19 years, 4,000 children)
1,870 children have survived to the 20 year time point (93.5%)	13,000 children have survived to the 20 year time point (65%)
Trends indicate that 70% of the total (1,400 children) will survive to the average life expectancy without valve complications	Trends indicate that 20% of the total (4,000 children) will survive to the average life expectancy without valve complications

known at the time of voting (except by the author). From these numbers, it is clear that previous laboratory and animal studies were fairly telling, as the THS was 93% effective while the MVU was only 65% effective at the 20 year mark. The MVU would have given 12,300 children a 20-year reprieve; however, more of the 2,000 children who could have afforded the THS would have died due to the MVU. The THS had excellent success; however, it was only within a wealthy patient population of 2,000 and 18,000 children died because they lacked other options without the MVU being released.

Resolution and Conclusions

Resolution of PediaValve Case Study by Members

There was a voting consensus to release the THS, and this decision turned out to be both safe and good for wealthy patients; however, this decision excluded 18,000 children, primarily those without medical insurance or in lower socio-economic levels. The voters felt that ethically they would be doing a disservice to patients by releasing the MVU as this would result in many more deaths due to TEHV failure. Additionally, as bioengineers the voters felt that one should always use the most effective design, regardless. This was expected by the author and was intended to address concerns about design and development. How can bioengineers balance design, cost, and distribution of biomedical devices? This should be a concern on many levels that go beyond merely manufacturing questions. Ethically, the primary question is how does the design affect availability to patients in all socio-economic classes? This case study was intended to speak to this question.

Some suggestions were made by the voters to ameliorate the fact that the company would be excluding treatment to poorer patients by selecting the THS. Primarily, it was suggested that philanthropic funds should be made available from the company to aid in treating other maladies not related to valvular disease, or

medication purchased to ease the suffering of those afflicted with valvular disease. Though these are commendable suggestions, they do not address the problem that PediaValve exists to deal with. Simply directing funds to another medical problem, while perfectly legitimate, does not absolve PediaValve of their professional responsibility. Moral acts of kindness, practiced at the corporate level, cannot replace the professional responsibility of the engineer who has set about to complete a task. For instance, PediaValve could contribute to AIDS treatment in third-world countries, but the drug companies that would undoubtedly do a better job of this will be unable to develop a competent TEHV for PediaValve's target population. Hence, if PediaValve has a moral responsibility, it must be to those who would benefit from their technology and leave the pharmaceutical companies to make contributions for those who are relying directly on their technology.

Summary

While there are typically no perfect conclusions arising from ethical dilemmas, decisions must be made and consequences dealt with. Ultimately, theory cannot make decisions and deal with resulting outcomes, but it can inform the decisions of those who must decide. In this case, the majority of voters felt there were too many risks associated with the MVU, while others felt there were both scientific reasons and moral support for the MVU. Whether cases like this will be relevant in the future of bioengineering and tissue engineering remains to be seen, but all trained bioengineers (and those in training) should prepare themselves for designing with income disparities, justice and global implications in mind. While this simple case does not provide a complete framework for making ethical decisions related to design, it does raise the point that progress must be made with these ideas in mind. Ultimately, the bioengineer must learn to steer his or her research and design practice so that they are scientifically sound, yet have positive global and local impact.

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