**The DEPART System: A Continuous Ambulatory Blood Pressure Monitor**
(Technical Report)

**Medical Devices in the Regulatory System: Factors Contributing to the Recall Crisis**
(STS Topic)

A Thesis Prospectus in STS 4500
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Author
Kayla Prose-Craig
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Technical Project Team Members
Alex Duerre
Kiersten Paul
Elayna Render

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

Signature Kayla Prose-Craig Date 12/04/20

Approved _____ Date _____
Tsai-Hsuan Ku, Department of Engineering and Society

Approved _____ Date _____
Eugene Parker Ph.D., Barron Associates Inc.

## Background

The scientific community's need for innovation and change is a part of a tradition that stems from the early stages of the modern development of the United States. From automobiles to electricity, scientific progress is a facet of this country that many refer to as one of the reasons why American medicine is as advanced as it is today. However, as these advancements have been accelerating at an exponential rate recently, the American government has run into an issue regarding the regulation and release of medical devices to the public. The Food and Drug Administration (FDA) introduced many new laws that approached unique ways of regulating novel devices, but it was met with pushback from biomedical device companies and independent inventors. The technical portion of this prospectus will explore the medical device company's interest in FDA regulations with testing done on a medical device made by Barron Associates. The goal of this study is to contribute statistical data towards the approval of the device as one that is extensively similar to devices already on the market, but with some updates and improvements. The STS portion of this prospectus aims to investigate the socio-economic and political factors involved in the medical device approval process and recalls. This thesis will address the tensions created between innovation and regulation in the medical device industry.

## Technical Topic

In 2018, hypertension, defined as blood pressure at or above 130/80 mmHg, was listed as a primary or contributing cause to nearly 500,000 deaths since it puts patients at risk for heart disease and stroke. This condition affects 45% of the adults in the United States; however, only 24% of adults with hypertension have their condition under control. (CDC, 2020) Barron Associates has created a continuous ambulatory blood pressure monitor to address multiple

problems that occur in blood pressure measurement, including technical problems with the traditional blood pressure cuff. They determined that a self-monitoring ambulatory system will best account for these errors, as well as improve the diagnosis of hypertension. 24-hour ambulatory blood pressure is the best indicator of treatment results in hypertensive patients. In order to determine the accuracy of the Barron Associates DEPART device, a clinical study will be performed to compare the DEPART device to both the Association for the Advancement of Medical Instrumentation® (AAMI) standards, a nonprofit organization that creates standards for the medical device industry, and the Finapres Nano System. The Finapres Nano System is another ambulatory blood pressure monitor that has been previously approved and presents similarities concerning the DEPART device that we are assessing. The subjects are monitored in the traditional posture used to take blood pressure measurements, a sitting position with the patient's feet flat on the floor, and their arms by their sides. The two devices will be compared over multiple other postures, as well as during isometric hand exercises, which have been shown to increase blood pressure. (Jake Samuel et al., 2017) The DEPART device collects ECG data at two patches. The data will be processed using a machine learning algorithm that will determine the pulse transit time (PTT) by taking the difference between the pulse arrival time (PAT) at each of the two ECG patches. Heart rate variability (HRV) will also be measured and used to account for the sympathetic nervous system's effect on the PTT. The inverse of the PTT, adjusted for the HRV will give the blood pressure measurement for the patients. Statistical analysis will be performed to compare the Finapres Nano System and the DEPART system against the AAMI standards for blood pressure measurements in the traditional posture. In the other postures, equivalence testing will be used to ensure that the DEPART system is accurately measuring blood pressure in an ambulatory setting.

**Prospectus Introduction**

The Food and Drug Administration (FDA) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States as well as monitor and approve devices set to be released to the public market. The FDA's approval process requires a lot of testing for both quality and safety. However, it seems as though the number of devices being recalled has been increasing. Why is there an increase if the FDA is doing their job properly? Recipients of medical devices, especially ones that are implanted, hope that the devices prescribed to them will help them in their everyday lives and benefit their livelihoods for the foreseeable future. When these medical devices are put into the market, many factors can affect it both before and after it is released. The FDA's approval process requires a lot of testing for quality, effectiveness, and safety. However, developers are now questioning whether or not the FDA's regulations are impairing scientists' ability to create novel devices. Inventors, especially persons associated with small start-ups or companies, show concerns about expenses involved in the regulatory system. The FDA receives push-back from the public as well for 'allowing' medical devices to be cleared when they can, and do, cause harm to their recipients. Public opinion of the FDA continues to go down as more device failures occur. (Kaganov, 1980) While regulation is a must in the healthcare department, the detriment that the current FDA system presents may be less than optimal for the United States to stay ahead in terms of advancements and development. This is an essential topic that is long overdue for discussion in the American government.

## Research Question

The FDA itself can be influenced by both internal and external factors. In the United States, scientific progress has always been heralded as one of the reasons that the country is so advanced and developed in comparison to other countries. Does the heavy regulation by the U.S. government, namely the FDA, create a stressed relationship with the medical companies? Is it beneficial for companies to utilize the avenue in the FDA process that allows for easier approval? What is it about the relationship between the FDA, companies, and medical practitioners that contributes to a higher rate of recalls? There are pros and cons to heavy regulation as well as light regulation, and this paper will address them through the scope of three different case studies on recalled medical devices in the past few decades, possibly including a case study done through the biotech company Barron Associates with whom the technical portion of this thesis is working with.

## Literature Review

In this literature review I would like to focus on the FDA and regulatory side of the arguments, to explore the background of the regulatory process. By doing this, we can assess and better understand where tensions can arise in the relationship between medical companies and the FDA.

### *Role of Defects and Quality Evaluations*

Not only do medical device recalls occur with some frequency, but they also have serious implications for their customers, which are often doctors and their patients. As the rate of recalls has increased nearly 50% between 2002 and 2012, more thought has been put into their early

detection and prevention for the customer's safety. (G. P. Ball, Shah, & Donohue, 2018) A study done by (G. P. Ball, Shah, & Donohue, 2018) explored some of the behavior behind the use of a recall or not. They found that if a physician can detect a defect before product use, then the likelihood of a recall being issued is low. Similarly, the operations manager at a manufacturing company is tasked with juggling many responsibilities that affect the likelihood of a recall. They are the ones who can maintain a company's reputation positively or negatively with how they handle customer satisfaction, customer safety, and regulatory oversight. Managers may be influenced to look the other way if the perceived cost of a recall is high and patient harm is low. They are less likely to turn a blind eye, however, if patient harm is high, even if the perceived cost is high.

This is concisely why there is a need for the FDA to perform routine quality checks and evaluations at any medical manufacturing company. Inspections are a necessary means of enforcing quality in this high-risk field, but they are not exempt from human behavior flaws. In another study done by G. Ball (2017), they found that there is a 21% increase in the recall hazard on the second visit by the same investigator, and a 57% increase on the third visit, regardless of the inspection outcome from the investigator. This means that it is more likely for an investigator to become more comfortable or lenient with a manufacturer if the inspector has become familiar with their facilities. Repeat inspectors are not the only source of complacency at the production stage. Products resulting from lower quality manufacturing is another issue. With avenues opening via legislation to increase competition of medical drugs and devices, more general products become available on the market and prices lower. To decrease prices without changing the design, the firms often cut costs by lowering the quality of the manufacturing. This was shown in another study by G. Ball (2018) on prescription drugs rather than on medical devices,

but the concept is the same. Increasing product profits often takes a toll on product quality, which is harmful to the consumers and the reason why routine inspections are necessary.

*The Role of the 510(k) Program*

The FDA regulatory systems classify medical devices into three classes, with the first-class being the lowest risk, the second class being of medium risk, and the third class having the highest risk. For a device to be released onto the market, there are two ways that they can be reviewed, Premarket Approval (PMA) and Premarket Notification/510(k) process.

The 510(k) process allows manufacturers to update devices via incremental innovations rather than waiting to release a new product. For a device to qualify for premarket notification, the firm must prove that their device is 'substantially equivalent' to a previously approved device. (Health, 2020) This raises another question, however. What does 'substantially equivalent' mean or refer to and are there guidelines for this? The 510(k) process is different from PMA in that it does not fully approve a device but instead gives it clearance to the general market in the United States. Clearance is limited in its use and indications of the predicate device. A cleared device can only operate under the predicate device's intended use. However, this does not limit or restrict the practice of medicine by a clinician. (Beitzel et al., 2015) As good medical practice goes, the patient is to be informed of the decision to use a cleared device and the use of the product needs to be monitored and kept in records. These clinicians do not need to be supervised by the FDA. (Beitzel et al., 2015)

This lack of supervision highlights an oversight by the FDA. The 510(k) process is not required to do any safety testing at the time of the approval. As a result, most medical devices that are recalled for life-threatening or very serious hazards were originally cleared for the

market using this process. (Zuckerman et al., 2011) In a study done by Day (2016), they found that numerous orthopedic devices were cleared through 510(k). This was concerning since a device was 11.5 times more susceptible to being recalled in this way than a device that was approved via PMA. They showed that an orthopedic surgeon should be mindful of how a device was cleared to determine if it could be harmful to a patient.

One such device, Menaflex, a knee implant device by ReGen Biologics, was approved by the FDA commissioner despite it having failed approval twice already. The scientific experts claimed that it was not safe enough to be used in practice but the commissioner was convinced to push it through because of a petition by four congressmen to approve the device. The device proved to be faulty as it was later recalled but this issue stemmed from the misuse of the 510(k) process. If over two-thirds of devices cleared through this process end up being recalled, then there is an inherent problem with the FDA's regulation policies that need updating. (Milfred, 2012)

Another example where the need for an update to 510(k) is apparent was highlighted in a study done by Heneghan (2017). Transvaginal mesh devices used for pelvic organ prolapse also saw 61 devices whose approval ultimately relied on claimed equivalence to two predicate devices, the Mersilene Mesh and the ProteGen Sling. Even though the basis for 510(k) clearance does not involve any testing before clearance, it is expected that safety testing will occur at some point in time after its release. The FDA began to raise concerns about the safety of some transvaginal mesh products in 2011 when serious adverse events began to occur in the patients who received a mesh transplant. The FDA issued orders to have post-marketing studies done, and as a result, many manufacturers removed their devices from the market without doing any sort of testing. Given the high rate of recalls in the 510(k) category, it is clear that more testing is

needed but at what cost? Some argue that the 510(k) does its job adequately by giving the USA the ability to compete globally and that the high costs and delays in obtaining FDA approval are a hindrance to innovation. (Fargen et al., 2013)

*Conclusion*

There are many effectors in the FDA approval process and there are many issues in the system. The proposed solution by Milfred (2012) to de-emphasize the pursuit of efficiency by either tightening or discarding programs like 510(k) warrants investigation. However, the focus of my research questions is broader than just the evaluation of the 510(k) process, which is only a small factor. The FDA is not the only contributor to the tension between the government agencies and the medical device companies. What is it about this relationship between the FDA, companies, and medical practitioners that contributes to a higher rate of recalls? What is considered 'substantially equivalent' to the FDA compared to the companies? This literature and the case studies will hopefully answer these questions in the scope of my proposed STS frame.

**STS Framework and Method**

In the field of medical science, innovation is part of a "system" constituted by many subsystems and artifacts. Thus, for this particular paper, I would like to employ the framework of a large technical system (LTS) proposed by Thomas Hughes. For the case studies that I will be studying, I would like to build complex social and technical systems for each and combine them into a large hierarchical structure. Each case will have its system builders but some overarching ones will include inventors, medical device companies, regulators, medical experts, and recipients of the devices. The FDA's Center for Devices and Radiological Health (CDRH) is

responsible for regulating who manufactures, repackages, relabels, and/or imports medical devices sold in the United States. The processes used to evaluate medical devices is a complex socio-technical system in which I think the many complexities allow the LTS framework to be the most suitable frame for expansion of this topic. I would also like to try using the SCOT method to evaluate the social and technical elements involved in the interactions between the companies and the government. In this scope, I would like to include my technical project as a possible case study. This would involve inspecting the process of gaining approval from the medical companies' side of the process via interviews. By doing this, we can aim to see how the 510(k) process is interpreted by different stakeholders.

**Methods for Data Collection:**

I posit that a few case studies be evaluated in the context of the research question and be evaluated to determine the validity of either side's argument. Through these case studies revolving around a recalled device, the issue of innovation versus regulation can be addressed from various viewpoints of different stakeholders. The case studies can be reviewed through scientific journals, published articles by magazines or newsprint, public interviews, statements by politicians, as well as any testimonies given by doctors and patients. The nature of these sources is mostly qualitative.

In this thesis, I would like to present the material in an unbiased way but it is impossible to be truly neutral. As the argument being explored is fairly polarized, there will be bias from both sides on how regulation should be addressed. To evaluate the cases from multiple perspectives and put them side by side, I believe this is the most optimal way to be unbiased.

**Timeline**

I would like to have my research done on my case studies done within the first two months of next year, in other words before March of 2021. If this is the case, I can focus my efforts on writing and synthesizing data acquired over many different sources. I would like to complete my synthesizing in March of 2021. The goal of this prospectus is to highlight the struggles of both sides of the innovation vs. regulation argument and present them for evaluation without bias. In the end, I will present my own opinion in a "discussion" section and address the core of the issues in the regulation facilities in the United States' healthcare system. I think this is an important topic to discuss as recall rates have been increasing, in part due to the 510(k) process, so I hope that this thesis will be an easy source for others to develop an opinion and then contact the regulator to make a change, for worse or for better on either side.

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